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Disease-specific health-related quality of life questionnaires for heart failure: a systematic review with meta-analyses

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Abstract
Background Heart failure (HF) is an increasingly common condition affecting patients' health-related quality of life (HRQL). However, there is little literature comparing HF-specific instruments. Our aim was to evaluate and compare data on the conceptual model and metric properties (reliability, validity and responsiveness) of HF-specific HRQL instruments, by performing a systematic review with meta-analyses.
Methods and results Of 2,541 articles initially identified, 421 were full-text reviewed. Ninety-four reported data on five questionnaires: Minnesota Living with Heart Failure Questionnaire (MLHFQ), Chronic Heart Failure Questionnaire (CHFQ), Quality of Life Questionnaire for Severe Heart Failure (QLQ-SHF), Kansas City Cardiomyopathy Questionnaire (KCCQ) and Left Ventricular Dysfunction (LVD-36) questionnaire. Metric properties (reliability, validity and responsiveness) were summarised using meta-analysis for pools above five estimates. Cronbach's alpha coefficients were generally high (0.83–0.95) for overall scores and scales measuring physical health. Associations with four validity criteria (New York Heart Association [NYHA] class, six-minute walk test [6MWT] and short form-36 [SF-36] 'Physical' and 'Social Functioning') were moderate to strong (0.41–0.84), except for those between two CHFQ domains (fatigue and dyspnoea) and the NYHA (0.19 and 0.22). Pooled estimates of change from eight meta-analyses showed the MLHFQ to be highly responsive, with changes in overall score ranging from −9.6 (95% confidence interval [CI]: −4.1; −15.2) for placebo to −17.7 (95% CI: −15.3; −20.2) for

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pacing devices. The CHFQ and KCCQ also showed good sensitivity to change.

Conclusions Most of the questionnaires studied met minimum psychometric criteria, though current evidence would primarily support the use of the MLHFQ, followed by the KCCQ and CHFQ.

Keywords Congestive heart failure · Meta-analysis · Psychometrics · Quality of life · Review (publication type)

Abbreviations

ACEI	Angiotensin-converting enzyme inhibitor
CHFQ	Chronic Heart Failure Questionnaire
ES	Effect size
HRQL	Health-related quality of life
HF	Heart failure
ICC	Intra-class correlation coefficient
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVD-36	Left Ventricular Dysfunction-36 questionnaire
MLHFQ	Minnesota Living with Heart Failure Questionnaire
NYHA	New York Heart Association
QLQ-SHF	Quality of Life Questionnaire for Severe Heart Failure
6MWT	Six-minute walk test

Introduction

Heart failure (HF) is a serious, costly and increasingly common condition in developed countries. The prevalence of HF increases with age and the condition affects about 6–10% of the elderly. It is the most frequent cause of hospitalisation amongst people aged 65 years and over, and is responsible for 5% of all admissions [1].

HF has a significant impact on health-related quality of life (HRQL) [2], comparable to or greater than conditions such as diabetes and arthritis [3, 4]. Furthermore, as treatment goals in HF are mainly symptomatic, the interest in assessing HRQL in HF patients has increased in recent years. To this end, several HF-specific HRQL instruments have been developed [5]. These instruments have been increasingly used to assess the burden of the condition, as well as being used as outcome measures in clinical trials and practice.

However, HRQL measures have a number of limitations that must be considered in order to optimise their use [6]. Clinicians have only recently begun to use these instruments, and, therefore, may not yet be completely au fait with the criteria for selecting the most appropriate instrument and the interpretation of scores. In addition, literature evaluating similarities and differences between the various instruments is still scarce. Generally speaking, the development and validation process is studied only in research appearing shortly after a new HRQL instrument has been introduced. This is unfortunate, since the evaluation of an instrument and a gauging of its usefulness is an ongoing process which incorporates all of the accumulated data [7]. Both observational studies investigating the burden of disease and its determinants, and trials assessing the efficacy of new interventions can be important sources of data on validity and sensitivity to change. A comprehensive summary of the evidence could better describe each instrument and, thereby, help clinicians, researchers and policy-makers to select the most appropriate instrument for any given purpose.

The aim of the present study was to identify all of the available disease-specific questionnaires to measure the HRQL of HF patients and to evaluate and compare the available data on the underlying conceptual model and metric properties (reliability, validity and sensitivity to change) for the questionnaires identified.

Materials and methods

Search strategy and data identification

In order to identify existing HF-specific HRQL instruments, as well as any studies in which they had been used, a broad search was conducted in NLM Gateway PubMed (from 1966 to early 2006), using "heart failure" and "quality of life" as MeSH terms and free text. Citation tracking with references from each article was also performed. The cardiovascular section of the PROQOLID database was also consulted.

To be eligible, studies had to meet at least one of the following criteria: (a) methodological manuscripts reporting the development and validation of HF-specific HRQL instruments; (b) studies of the determinants of health or burden of disease; (c) longitudinal, evaluative studies. We only included articles published in English, Spanish, French, German or Russian. Identified articles were full-text reviewed to select and extract data on: (i) conceptual and measurement models; (ii) instrument reliability, including internal consistency and reproducibility; (iii) construct validity; and/or (iv) responsiveness or sensitivity to change.

Standardised forms were designed to facilitate the homogeneous extraction of relevant information. Each step in the systematic review was conducted separately by two reviewers (OG and AP, or OG and AK). Disagreements were resolved by consensus or with the involvement of a third researcher (MF).

Analytic strategy

The instrument review criteria of the Medical Outcomes Trust [8] were used as a guideline to evaluate the extracted data on conceptual models, reliability, construct validity and responsiveness. The conceptual and measurement model underlying each instrument was evaluated qualitatively by considering the adequacy of the following aspects: (a) methods for generating items and for combining them into single or multiple scales; (b) concepts covered and items contained in each scale; and (c) procedures for deriving scores.

Two types of reliability were assessed: (i) internal consistency [9] was evaluated by examining Cronbach's alpha or Kuder–Richardson (for dichotomous variables) coefficients for scale scores; and (ii) test–retest reliability or stability over time [8] was assessed by examining intra-class correlation coefficients (ICC) [10] for scale scores or Pearson or Spearman coefficients when ICCs were not provided.

In the absence of a gold standard in the area of HRQL [11], construct validity was assessed by testing a priori hypotheses regarding correlations with other measures. The other measures used are usually previously validated, often generic HRQL questionnaires, such as the SF-36 health survey [12], and clinical variables, such as the New York Heart Association (NYHA) classification [13] or the six-minute walk test (6MWT) [14].

A further property examined for all questionnaires identified was that of *responsiveness*. Responsiveness (or sensitivity to change) is often expressed using estimates of the magnitude of change, such as the effect size (ES) [8], which is computed by dividing the difference between pre- and post- mean scores by the standard deviation (SD) at baseline. ESs are usually classified as 'low' (ES = 0.2), 'moderate' (ES = 0.5) or 'large' (ES = 0.8) [15], and depend not only on the questionnaire's sensitivity to change but also on an intervention's ability to impact on patients' HRQL. For that reason, when evaluating an HRQL questionnaire, it is necessary to have some form of external benchmark for the magnitude of change. In the present review, two different approaches to estimating the magnitude of change were used: (a) we examined whether additional, supplementary measures of change, such as patients' global rating of change and/or clinical assessment, were used alongside the HRQL instrument being evaluated; and (b) we developed a series of hypotheses regarding the likely, expected magnitude of change on HRQL for five common HF interventions with well-known efficacy. The five interventions were exercise programmes and beta-blockers, which were expected to produce moderate ES, and angiotensin-converting enzyme inhibitors (ACEIs), special management programmes and pacing devices, which were expected to produce large ESs.

To summarise information, a meta-analysis was conducted for each metric property, where a pool of at least five estimates was obtained. Otherwise, the range of estimates was recorded. In order to conduct the meta-analysis of Cronbach's alpha values, the coefficient was needed, together with its associated error, which was calculated using the sample size and number of items in the relevant domain [16]. When conducting responsiveness meta-analyses for each intervention, the required data was the change in score, the SD of the change and the sample size. When the SD of change was not reported, but baseline and final SDs were known, the SD was computed using the formula described by Deeks et al. [17]. If a study included more than one follow-up visit, data for change between the first and the last visit was used.

Heterogeneity amongst study estimators was assessed using the X2 statistic and Galbraith plots. For the meta-analyses, summary estimates were computed using the DerSimonian and Laird random effects model because the X2 *P*-values were <0.10 [18]. This level was used instead of the conventional level of 0.05 due to the low sensitivity of the X2 test. Moreover, meta-regression models were constructed to evaluate the heterogeneity explained by the NYHA class of the study's patients, follow-up days and study design (clinical trial vs. observational).

Results

Search results

Of a total of 2,541 articles identified, 1,395 were excluded after title review and abstracts were reviewed for the remaining 1,146 articles, leading to a further 725 exclusions. Articles were excluded in these initial stages mainly because they were editorials, letters or protocols without new primary data, because they focussed on other diseases (not HF) or because they were published in Japanese, Italian or other non-eligible languages. Full-text reviews were, therefore, performed for 421 studies. Of these, 94 articles [2, 19–111] met the inclusion criteria and were considered eligible for data extraction. The rest were excluded for the following reasons: 20.3% did not include HRQL data on HF patients (methodological studies, clinical studies without HRQL evaluation etc.), 27.4% used a generic or cardiovascular-specific measure but not an HF-specific instrument and 52.3% used a specific instrument but did not provide relevant information on the metric properties of HF-specific instruments. Only three of the articles reviewed contained data from more than one disease-specific questionnaire [2, 46, 81].

The search identified five HF-specific questionnaires: the Minnesota Living with Heart Failure Questionnaire

(MLHFQ) [89], the Chronic Heart Failure Questionnaire (CHFQ) [49], the Quality of Life Questionnaire for Severe Heart Failure (QLQ-SHF) [105], the Kansas City Cardiomyopathy Questionnaire (KCCQ) [46] and the Left Ventricular Dysfunction (LVD-36) questionnaire [81] (Table 1). Of these, by far the most widely used is the MLHFQ, followed by the CHFQ. For the MLHFQ, 39 studies were conducted in the USA, 15 in other English-speaking countries and 37 were conducted in 11 non-English speaking countries (Germany, Austria, the Netherlands, Sweden, Russia, Hungary, France, Italy, Greece, Brazil and China). Other language versions of the CHFQ and KCCQ were only used in one study each per instrument, and both of those were validation studies (Chinese and Norwegian, respectively). For the QLQ-SHF, two studies were conducted in Sweden, where the instrument was developed, and two were conducted in other countries (the Nordic countries and the Netherlands). In the case of the LVD-36, the only study included was the initial development performed in the United Kingdom.

Conceptual model

All questionnaires were specifically developed to assess the HRQL of patients with HF, except for the LVD-36, which was developed for patients with left ventricular dysfunction [81]. Three of the questionnaires were developed in the late 1980s and the other two appeared more than 10 years later (Table 1). Literature reviews and generic HRQL instruments were cited by all developers as sources for items. Patient and expert panels were only used to generate items in the two most recent instruments, the KCCQ and LVD-36. Item reduction was based on either factor analysis (MLHFQ, QLQ-SHF and LVD-36) or on patient-rated clinical impact (CHFQ and KCCQ). All questionnaires are multi-dimensional, except the LVD-36, which is uni-dimensional. The number of domains covered ranged from two (MLHFQ) to five (KCCQ). All of the multi-dimensional questionnaires included a 'Physical' domain, which measures the limitations of activities (walking, house-work etc.). In the CHFQ, this aspect is measured by the 'Dyspnoea' domain, which asks patients to assess their shortness of breath when doing the five daily life activities which are most important to them. All questionnaires except the MLHFQ also included a 'Symptoms' domain. The QLQ-SHF somatic symptoms domain covers the widest range of symptoms (chest pain, fatigue, dullness etc.). In the KCCQ, the symptoms covered include frequency and intensity of shortness of breath, swelling and fatigue, while the CHFQ symptoms domain focuses on fatigue. Only the KCCQ and QLQ-SHF include a specific domain on life satisfaction; these are titled 'quality of life' and 'life dissatisfaction,' respectively. All questionnaires included a domain assessing 'Emotional/Psychological' aspects of quality of life, except the KCCQ. The latter did, however, include items on emotional issues in its quality of life domain. Social limitations and self-efficacy-specific domains were only included in the KCCQ.

The majority of instruments use Likert-type response scales (6–7 response options) and are all self-administered, except for the CHFQ, which is interviewer-administered.

Reliability

Most of the instruments had fewer than five reliability estimates available, and it was only possible to calculate a summary estimate of Cronbach's alpha using meta-analysis for the MLHFQ scores (Table 2). Overall scores and scores on the physical dimension showed the highest Cronbach's alpha coefficients (range from 0.81 to 0.95) on most of the questionnaires. Reported ICCs were high and similar across questionnaires and domains (ranging from 0.78 to 0.95), except for the 'self-efficacy' and 'quality of life' domains of the KCCQ (0.41–0.57). For the QLQ-SHF, only test–retest correlation coefficients were reported.

Validity

Tables 3 and 4 show the correlations between domains on the questionnaires assessed with other scales or instruments with which they were expected to be related. The SF-36 'Physical Functioning' dimension was strongly associated with the physical domains of the MLHFQ and the KCCQ, and with the total score of the LVD-36 ($r = 0.65-0.84$). The total scores of the MLHFQ and LVD-36 presented the highest correlations with the 'Social Functioning' dimension of the SF-36 ($r = 0.70$). The CHFQ showed the highest correlations with the 6MWT (0.6–0.7). The KCCQ physical domain had the highest correlation with NYHA class (0.65), and the CHFQ domains of fatigue and dyspnoea had the lowest correlations with this functional capacity classification (0.19 and 0.22, respectively).

Validity criteria used in the QLQ-SHF evaluation had limited comparability with those of the other questionnaires. It showed moderate correlations with dimensions of the Sickness Impact Profile and a high correlation with the Mood Adjective Check List [105] (0.43–0.68 and 0.59–0.72, respectively).

Responsiveness

A total of 86 change estimates were included in five meta-analyses conducted with MLHFQ scores for the different interventions. Figure 1 shows the MLHFQ total change score according to the hypothesised magnitude of effect for the intervention on quality of life (moderate and large

Table 1 Characteristics of the disease-specific health-related quality of life (HRQL) questionnaires for heart failure (HF) patients and the number of manuscripts included in the systematic review for each

Questionnaire	Acronyms	Authors (year of publication)	Response options	Domains (no. of items)	Range of scores	Administration	Number of manuscripts
Minnesota Living with Heart Failure Questionnaire	MLHFQ LHFQ MQOL MLWHFQ	Rector et al. (1987)	6p Likert scale (0–5)	Physical (8) Emotional (5) Total (21)	0–105 Best to worst	Self-administered	81
Chronic Heart Failure Questionnaire	CHFQ CHQ	Guyatt et al. (1989)	7p Likert scale (1–7)	Dyspnoea (5) Fatigue (4) Emotional (7) Total (16)	16–112 Worst to best	Interviewer-administered	9
Quality of Life Questionnaire for Severe Heart Failure	QLQ-SHF	Wiklund et al. (1987)	VAS 6p Likert scale	Psychological (7) Physical activity (7) Life-dissatisfaction (5) Somatic symptoms (7) Total (26)	0–130 Best to worst	Self-administered	4
Kansas City Cardiomyopathy Questionnaire	KCCQ	Spertus et al. (1999)	5–6–7p Likert scale (1–5/6/7)	Physical limitation (6) Symptoms (8) Self-efficacy (2) Social limitation (4) Quality of Life (3) Total (23)	0–100 Worst to best	Self-administered	2
Left Ventricular Dysfunction Questionnaire-36	LVD-36	O'Learly et al. (1998)	Dichotomous (true, false)	Total (36)	0–100 Worst to best	Self-administered	1

Table 2 Reliability data (internal consistency and test–retest reproducibility)

Estimator	Questionnaire	Domains				
		Physical	Emotional/psychological/social	Symptoms	Self-efficacy	Total
Internal consistency (Cronbach's alpha)[a]	MLHFQ	0.92 [95% CI: 0.89–0.93]	0.87 [95% CI: 0.83–0.89]			0.94 [95% CI: 0.91–0.95]
	CHFQ	0.86–0.90	0.82–0.92	0.85–0.89		0.83–0.95
	QLQ-SHF					0.88
	KCCQ	0.90–0.91	(Quality of life) 0.78–0.84 (Social limitation) 0.86–0.90	0.86–0.88	0.62–0.66	
	LVD-36					0.95[a]
Test-retest reproducibility (ICC)[b]	MLHFQ	0.91	0.92			0.84
	CHFQ	0.75–0.83	0.78–0.84	0.75		0.75–0.83
	QLQ-SHF	0.85[b]	(Psychological) 0.79[b] (Life dissatisfaction) 0.75[b]	0.82[b]		0.82[b]
	KCCQ	0.79	(Quality of life) 0.57 (Social limitation) 0.73	0.78 (stability 0.60)	0.41	
	LVD-36					0.95

Specific point estimates or ranges are shown for all instruments, except Cronbach's alpha coefficients for the MLHFQ, which are summary estimates from the meta-analysis [95% CI]

[a] Kuder-Richardson coefficients for dichotomous variables

[b] Spearman or Pearson correlations

expected changes in Figs. 1 and 2, respectively). Negative changes represent improvement and the studies are listed according to the length of the follow-up period (from long at the top to short at the bottom). For exercise programmes and beta-blockers, which were expected to generate moderate improvement, the meta-analysis produced summary estimates of change of −9.6 (95% CI: −4.1, −15.2) and −10.03 (95% CI: −6.7, −13.3), respectively. In the case of the three interventions which were expected to produce large improvements, the meta-analysis produced summary estimates of change of −12.7 (95% CI: −8.4, −17.0) for special management, −16.4 (95% CI: −7.5, −25.3) for ACEIs and −17.7 (95% CI: −15.3, −20.2) for pacing devices.

Table 5 shows the responsiveness coefficients (ES) for the individual domains of the questionnaires studied, according to the type of intervention. In general, the ES summary estimates provided by the meta-analysis of MLHFQ change scores were within the expected range. In other words, exercise programmes and treatment with beta-blockers produced an ES close to 0.5 (a moderate ES), and special management programmes, ACEI and pacing devices produced ESs of approximately 0.8 (a large ES). The coefficients shown by the physical and emotional domains in the special management groups were quite lower (0.3–0.2). Change scores on the CHFQ also produced ESs which were in the expected range, according to the interventions studied. In addition, the highest ES (from 1.2 to 1.9) were observed in outpatients who rated their overall health as "very much better" after the intervention. The single longitudinal study using the KCCQ, which was

Table 3 Pearson or Spearman correlation coefficients between selected dimensions of the HF-specific questionnaires and generic and clinical outcomes used in HF patients

Questionnaire	Domain	SF-36 physical functioning	6MWT	NYHA class
MLHFQ	Physical	0.72	0.41	0.58
	Total	0.74	0.51	0.6
CHFQ	Dyspnoea	0.52	0.6	0.22
	Fatigue	0.55	0.58	0.19
	Total		0.7	
LVD-36		0.74		
KCCQ	Physical limitations	0.79–0.84	0.48	0.65

Table 4 Pearson or Spearman correlation coefficients between the SF-36 social functioning scale and similar dimensions on the disease-specific questionnaires

Questionnaire	Domain	SF-36 social functioning
MLHFQ	Total	0.7
CHFQ	Emotional	0.63
LVD-36		0.7
KCCQ	Social limitations	0.59–0.62

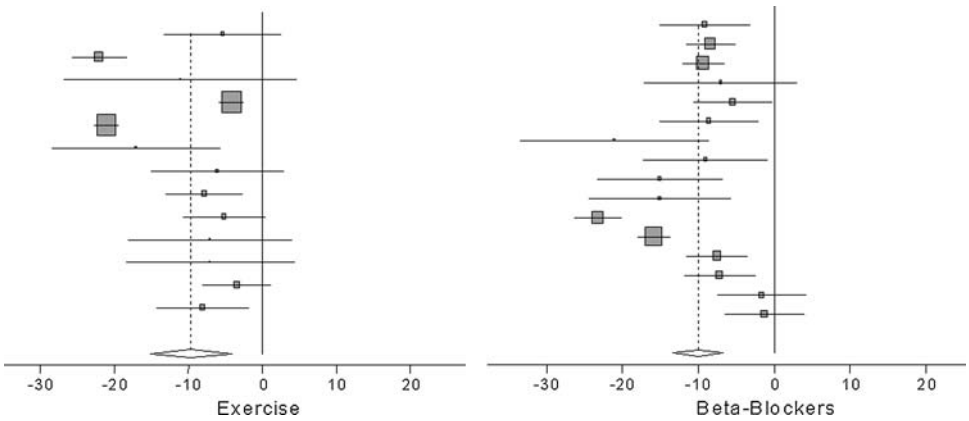

Fig. 1 Interventions hypothesised as having a moderate effect: exercise and beta-blockers. Thirteen estimates were included in the exercise meta-analysis: Harris 2003 [50], Parnell 2002 [84], Levinger 2005 [66], Laoutaris 2004 [61], Dall'Ago 2006 [35], Yeh 2004 [110], van der Berg-Emons 2004 [99], Haykowsky 2005 [52], Keteyian 1999 [56], Gottlieb 1999 [44], McKelvie 2002 [71], Belardinelli 1999 [24]. Sixteen estimates were included in the beta-blockers meta-analysis: Sanderson 1999 (metoprolol/carvedilol) [94], Fung 2002 (two different beta-blockers) [41], Sanderson 1998 (metoprolol/celiprolol) [93], Pollock 1990 (bucindolol) [86], Metra 1994 (carvedilol) [72], Kukin 1999 (carvedilol/metoprolol) [60], Edes 2005 (nebivolol) [40], González-Juanatey 2003 (bisoprolol) [42], Metra 2000 (metoprolol/carvedilol) [73], Di Lenarda 1999 (metoprolol/carvedilol) [38]

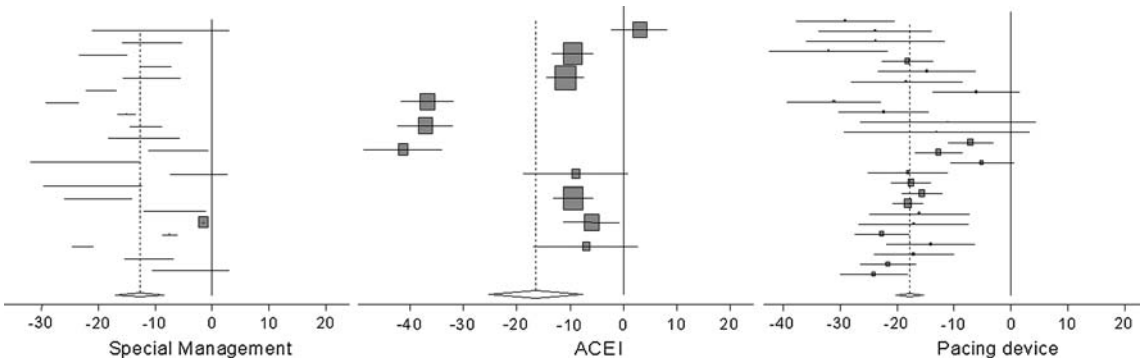

Fig. 2 Interventions hypothesised as having a large effect: special management, angiotensin-converting enzyme inhibitors (ACEIs) and pacing device groups. Twenty-one estimates were included in the special management meta-analysis: Klaus 2000 [58], Meyer 2002 [74], Harrison 2002 [51], Delgado 2003 [37], Ni 2000 [79], Benatar 2003 (home visit/telemonitoring) [25], Prasum 2005 [87], Curiati 2005 [33], Smart 2005 [96], Kuehneman 2002 [59], Smith 1997 [97], Bouvy 2003 [28], Holst 2001 [55], Doughty 2002 [39], Hershberger 2005 [53], Ojeda 2005 [82], Vavouranakis 2003 [102], Atienza 2004 [20], Varma 1999 [101], Shively 2005 [95]. Ten estimates were included in the ACEIs meta-analysis (specific drug in brackets): Rector 1993 (enalapril) [91]; Cowley 2000 (losartan and captopril) [34], Vizir 2002 (enalapril, losartan, and both) [103], van den Broek 1997 (spirapril and captopril) [100], Little 2004 (candesartan) [68], Warner 1999 (losartan) [104]. Twenty-six estimates were included in the pacing device meta-analysis: Twidale 1998 (two different groups) [98], Miller 2004 [76], Lupi 2000 [70], Austin 2005 [22], Cazeau 2001 (cross-over) [31], Wilson 1996 [107], Baker 2002 [23], Livanis 2003 [69], Lau 2000 [62], Artinian 2003 [19], Higgins 2003 [54], Molhoek 2002 [77], Auricchio 2003 (cross-over) [21], Young 2003 [111], Kiès 2006 [57], Molhoek 2005 [78], Lenom 2005 [65], Braunschweig 2000 [29], Gras 2002 [45], Linde 2002 (two different groups) [67], Leclercq 2004 (two different groups) [63]

carried out in inpatients followed for three months after discharge, also produced very large ESs (from 0.6 to 3.2), whilst the QLQ-SHF produced low and similar ESs for beta-blockers and ACEIs (estimates between −0.1 and 0.3).

In the meta-regression models (data not shown), none of the three variables studied (NYHA class of the study patients, follow-up days and study design) were statistically significant, except for NYHA class in the ACEI group.

Discussion

The availability of five different disease-specific HRQL questionnaires for patients with HF, together with the increasing rate of publications related to the development or use of these instruments (almost 67% of the selected articles appeared after 1999), confirms the growing interest in measuring the quality of life of HF patients. The current systematic review indicates that all five questionnaires have adequate metric properties, though there are some

Table 5 Responsiveness coefficients (effect size, ES) of the questionnaires for interventions with a hypothesised moderate or large effect

Questionnaires	Domains	Hypothesised moderate effect, ES = [0.5-0.79]		Hypothesised large effect, ES ≥ 0.8			
		B-blockers	Exercise	Special management	ACEIs	Pacing device	Measured change Much better improvement
MLHFQ	Physical			0.3 ($n = 11$) [95% CI: 0.1–0.6]			0.5[a] ($n = 1$)
	Emotional			0.2 ($n = 11$) [95% CI: 0–0.3]			0.6[a] ($n = 1$)
	Total	0.6 ($n = 16$) [95% CI: 0.4–0.8]	0.6 ($n = 13$) [95% CI: 0.2–0.9]	0.9 ($n = 21$) [95% CI: 0.6–1.2]	0.8 ($n = 10$) [95% CI: 0.4–1.2]	0.9 ($n = 26$) [95% CI: 0.8–1]	0.9[b] ($n = 1$) 0.7[a] ($n = 1$)
CHFQ	Dyspnoea		1.1 ($n = 1$)	0.6, 0.9 ($n = 2$)			1.7[b] ($n = 1$)
	Fatigue		0.5 ($n = 1$)	0.3, 1.0 ($n = 2$)			1.2[b] ($n = 1$)
	Emotional		0.7 ($n = 1$)	0.1, 0.8 ($n = 2$)			1.3[b] ($n = 1$)
	Total		0.15 ($n = 1$)[c]	0.4, 1.4 ($n = 2$)			1.9[b] ($n = 1$)
QLQ-SHF	Somatic	0.2 ($n = 1$)			0.3 $n = 1$)		
	Psychological	0.3 ($n = 1$)			0.2 ($n = 1$)		
	Life-dissatisfaction	0.0 ($n = 1$)					
	Physical	0.3 ($n = 1$)			0.3 ($n = 1$)		
	Total				0.2, 0.3 ($n = 2$)		
KCCQ	Physical limitation						1.5[a] ($n = 1$)
	Social limitation						0.6[a] ($n = 1$)
	Symptoms						3.2[a] ($n = 1$)
	Quality of life						0.9[a] ($n = 1$)
	Self-efficacy						0.8[a] ($n = 1$)
LVD-36							1.0[b] ($n = 1$)

ES for the MLFHQ are summary estimates [95% CI] from the meta-analysis. ES for the other instruments are point values or ranges. The number of studies providing information on ES are shown in brackets

[a] Patients who improved 3 months after hospital admission; responsiveness statistic coefficient (change/SD of stable patients) was used instead of ES [102]

[b] Outpatients who answered "very much better" to the global rating of change question in follow-up studies

[c] Patients over 70 years old

concerns relating to the construct validity of the CHFQ and the responsiveness of the QLQ-SHF. Nonetheless, there were considerable differences between questionnaires in terms of the amount of evidence available on their metric properties. This was particularly true for responsiveness. The widespread use of the MLHFQ was noteworthy, and the largest amount of data was available for this instrument.

Selection of specific questionnaires and eligible studies

Although the LVD-36 was developed for patients with left ventricular dysfunction [81], we felt that it was appropriate to include this questionnaire in view of the considerable overlap between this condition and HF. Two other HF-specific HRQL questionnaires [112, 113] were excluded from this evaluation, as no information was available on either the conceptual model used or the instruments' metric properties.

Since all of the HRQL instruments included, except the QLQ-SHF, were developed in English-speaking countries, a number of other language versions had been developed. For that reason, we included articles using adapted versions in our review (32.4%). Most of these related to the MLHFQ, which, undoubtedly, contributed to the robustness of the study results and the conclusions regarding this instrument's metric properties. However, proper assessment of linguistically adapted versions requires the demonstration of their equivalence with the original [8, 114]. Validation studies were only identified for three adapted versions of the MLHFQ (French, German and Dutch). This finding highlights the need for further cross-cultural research into the equivalence of different language versions of instruments used in international studies.

Conceptual model

All of the multi-dimensional questionnaires covered both physical and emotional health, though the number and focus of the domains measuring these aspects varied among the questionnaires. The KCCQ was the only instrument that included domains intended to measure patient 'self-efficacy' and 'social limitation.' In this instrument, emotional issues were not included in a specific domain, though the 'quality of life' domain includes some items on emotional well-being. The KCCQ also has two summary scores to facilitate interpretation (functional status and clinical), and which have shown similar properties to the domains (data not shown). Content differences between questionnaires should be taken into account when selecting an instrument, particularly when changes are expected in a specific domain.

Reliability

Almost all of the domains from the five questionnaires can be used to measure and compare HRQL across groups of patients, as reliability was above the standard of 0.7 recommended for this purpose. Furthermore, the overall score and some domain scores of the MLHFQ and the CHFQ achieved Cronbach's alpha values of 0.9 [8], the highest recommended standard for reliability coefficients.

Validity and responsiveness

Comparing data on validity across questionnaires proved difficult, as many different reference criteria were found; however, the four most frequently used criteria (NYHA class, 6MWT, SF-36 'Physical' and 'Social Functioning' dimensions) seemed particularly suitable for this purpose. Correlations between the disease-specific instruments and these clinical and generic measures followed the hypothesised pattern, with the exception of the low correlations (around 0.2) between the CHFQ and the NYHA. The KCCQ's results in terms of construct validity are particularly noteworthy, with strong associations with the SF-36 physical and social functioning domains and with NYHA class. Since only the CHFQ correlated highly with the 6MWT, the moderate correlations for the other questionnaires might appear low. However, associations between disease-specific HRQL questionnaires and functional outcomes in general are usually only low to moderate. For example, correlations between chronic obstructive pulmonary disease (COPD)-specific HRQL measures and FEV1 (a well-established indicator of severity in COPD) were lower than 0.5 [115].

Both the MLHFQ and the CHFQ were able to detect a reasonably broad spectrum of improvement in HRQL according to the magnitude of change, with ACEIs, special management programmes and pacing devices producing large ESs of 0.8 or greater and beta-blockers and exercise programmes producing moderate ESs higher or equal to 0.5. To put these results into context, laparoscopic surgery for inguinal hernias has been found to produce an ES of 0.44 [116], which is similar to that produced by C-PAP (continuous positive airway pressure) in the treatment of sleep apnoea [117]. Our use of external criteria as benchmarks for the magnitude of change (patient global ratings of change and hypothesised size of change for specific interventions) helps to support the claim that the instruments studied adequately reflect change over time in health status.

Because the MLHFQ is the most commonly used instrument in clinical trials, there was extensive evidence supporting its responsiveness and its capacity to discriminate between different magnitudes of change in patients' HRQL. Surprisingly, the physical and emotional domains of the MLHFQ showed smaller ESs than the total score in the special management groups. However, it is important to note that different primary studies were included in the meta-analyses of domain scores ($n = 11$) and the overall score ($n = 21$). Of the 11 estimators included in the meta-analysis of physical and emotional domain scores, the lowest were from studies with no overall score data. These differences could explain the apparent discrepancies regarding the sensitivity to change of MLHFQ scores for these interventions.

Although compared with the MLHFQ there was less data available for the CHFQ, it was sufficient to indicate that the instrument is responsive to change and is able to differentiate between interventions. This is an important property and can probably be explained by the fact that the CHFQ offers patients the possibility to select individualised activities. The KCCQ seems to have similar levels of responsiveness to the CHFQ, but a lack of data hampered the evaluation of its ability to distinguish between magnitudes of change. The same is true for the LVD-36, which, in the only longitudinal study performed with the instrument to date, demonstrated similar responsiveness to the MLHFQ. The instrument which fares worst in terms of responsiveness is the QLQ-SHF.

Limitations

Our study has some limitations which merit discussion, beginning with those common to systematic reviews. In this case, reviewer selection bias was minimised by the title, abstract and full-text review being performed independently by two researchers and by using standardised forms to homogenise data extraction. PubMed was the only biomedical journal database used as a source for articles.

PROQOLID, one of the main HRQL-specific databases, was also searched, but no additional instruments or manuscripts were identified. The effect of publication bias was probably less important in this study than in other meta-analyses, since we were primarily interested in assessing HF-specific questionnaires, and not the efficacy of particular treatments. Regarding the metric properties evaluated in this review, it should be noted that certain characteristics, such as interpretability or respondent and administrative burden, which have been included in recent guidelines on the assessment of patient-reported outcome instruments [114, 118], were not addressed. However, reliability, validity and responsiveness can be considered as the traditional and fundamental attributes which should be assessed.

Finally, differences in study characteristics might call some of the summary estimators obtained in the meta-analyses into question. We investigated whether the NYHA class of study patients, follow-up period or study design were potential sources of heterogeneity, but were unable to identify any significant heterogeneity in meta-regression analyses. Although other variables might produce heterogeneity, those selected were previously hypothesised to be the most likely causes. In order to rule out the effect of the study design on estimators, a direct comparison of instruments in head-to-head studies would be recommendable.

Applicability

On the whole, our data suggests that the metric properties of four of the questionnaires meet the minimum criteria for use in assessing HRQL in patients with HF (the QLQ-SHF presented particularly poor responsiveness). Data for the LVD-36 is, however, scarce and, whilst the KCCQ appears to have excellent metric and applicability properties, they have only been assessed in three studies. Further evaluation and use of these instruments in different settings would be helpful. The CHFQ seems to show the highest responsiveness, but its use has been fairly limited, perhaps because it is interview-administered. Finally, the MLHFQ has good metric properties that have been demonstrated consistently in a large number of studies. It is, by far, the most widely used instrument, which may, in part, be due to its simple structure and ease and speed of administration. Based on the quality and quantity of evidence regarding metric properties, the MLHFQ appears to be the most recommendable instrument. Although the MLHFQ represents a safe choice, the KCCQ and CHFQ should not be discounted and may function better than the MLHFQ in some areas, though further evidence of their metric properties in a wider range of settings is required. Potential users of any of these questionnaires should also take into account differences in content and choose the questionnaire which appears to be the most suitable for their particular purpose.

The use of meta-analysis on pooled responsiveness data is also important, as this information provides useful summary estimates on the expected impact of several different interventions on HRQL which may be helpful in calculating sample size studies in HF patients.

In conclusion, it is hoped that the information provided here will help clinicians and researchers make an informed choice of questionnaire: (1) for patients with left ventricular dysfunction, the LVD-36 may be the most suitable instrument, even though its sensitivity to change has not yet been tested; (2) in certain settings, self-administration might be preferred, so the choice would be between the MLHFQ and the KCCQ; (3) for use in longitudinal studies or daily clinical practice, where responsiveness is an issue, the MLHFQ and the CHFQ would be adequate; and (4) although all instruments were specifically developed for HF, some of them address specific dimensions (such as ‘self efficacy’ or ‘social limitation’ in the KCCQ) that may be of particular interest in some studies. Further research involving head-to-head studies between the different questionnaires is needed to gain a better understanding of their respective advantages and limitations.

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