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POSITION PAPER

Quality of life in heart failure. The heart of the matter. A scientific statement of the Heart Failure Association and the European Association of Preventive Cardiology of the European Society of Cardiology

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For most patients with chronic, progressive illnesses, maintaining good quality of life (QoL), with preserved functional capacity, is just as crucial as prolonging survival. Patients with heart failure (HF) experience much worse QoL and effort intolerance than both the general population and people with other chronic conditions, since they present a range of physical and psychological symptoms, including shortness of breath, chest discomfort, fatigue, fluid congestion, trouble with sleeping, and depression. These symptoms reduce patients' capacity for daily social and physical activity. Usual endpoints of large-scale trials in chronic HF have mostly been defined to evaluate treatments regarding hospitalizations and mortality, but more recently, patients' priorities

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[Correction added on 5 June 2025, after first online publication: Additional affiliations have been included for Maurizio Volterrani and Giuseppe Rosano in this version, and the affiliation numbers have been adjusted accordingly.]

and needs expressed with QoL are gaining more awareness and are being more extensively evaluated. This scientific statement aims at discussing the importance of QoL in HF, summarizing the most largely adopted questionnaires in HF care, and providing an overview on their application in trials and the potential for their transition to clinical practice. Finally, by discussing the reasons limiting their application in daily clinical routine and the strategies that may promote their implementation, this statement aims at fostering the systematic integration of the patient's standpoint in HF care.

Keywords Aging • Chronic disease • Exercise tolerance • Functional capacity • Frailty • Heart failure • Physical activity • Quality of life

Introduction

Maintaining a high quality of life (QoL) for the majority of patients with progressive, chronic illnesses is equally as important as assuring their survival.[1] In particular, patients with heart failure (HF) tend to have a lower QoL and more exercise intolerance than subjects with chronic conditions: they experience a variety of physical and psychological symptoms, including dyspnoea, chest discomfort, fatigue, oedema, difficulty with sleeping, and depression.[2,3]

In the Echocardiographic Heart of England Screening (ECHOES) study, enrolling 6162 people in the community screened with echocardiographic assessment in England and estimating the prevalence of left ventricular systolic dysfunction, patients with HF had significant impairment of all measured aspects of physical and mental health together with reduced physical function, as measured through the health status questionnaire, with significantly worse impairment with more severe New York Heart Association (NYHA) functional class.[4]

Furthermore, in more than 1 million hospital cases in Sweden between 1988 and 2004, the impact of HF on QoL was higher than other disabling conditions, such as prostate, colorectal, lung, and bladder cancer.[5] These symptoms make it harder for patients to engage in daily social and physical activity. Moreover, the progression and prognosis in HF are unpredictable, which may also have a negative impact on patients' QoL.[6]

Numerous studies have shown that QoL plays a part in predicting both the utilization of healthcare services and mortality.[3]

The importance of QoL for patients with HF is highlighted in a survey showing that 61% attached more weight to QoL over longevity, with 9% and 14% willing to trade 6 and 12 months, respectively, for perfect health and better QoL.[7]

The crucial role of patient-reported outcome (PRO) questionnaires has been recently underlined and their role in shared clinical decision- making, quality monitoring and improvement, clinical trials, regulatory and reimbursement decisions, and the digital health arena revised.[8]

This scientific statement of the Heart Failure Association and the European Association of Preventive Cardiology of the European Society of Cardiology (ESC) aims at discussing the importance QoL in HF, summarizing the most largely adopted questionnaires, and providing an overview on their application in trials and the potential for their transition to clinical practice. By discussing the reasons limiting their application in daily clinical routine and the strategies that may promote their implementation, this statement aims at fostering the systematic integration of the patient's standpoint in HF care.

Definitions and assessment of quality of life in heart failure patients

The definition and assessment of QoL are poorly described. The terms QoL and health-related QoL (HRQoL) are frequently used inter changeably, and some definitions fail to differentiate between the two. In fact, it is difficult to conceive of significant aspects of QoL that are not at least partially influenced by health, especially when indirect effects are taken into account (e.g. health influences income and, consequently, housing, education).[9]

However, apart from the definitions used, the concept of QoL is subjective and multidimensional, encompassing physical and occupational function, psychological state, social interaction, and somatic sensation.[10]

In this document, the definition of QoL includes three components: (i) the ability to carry out activities (physical and social), (ii) the ability to maintain happiness, and (iii) the ability to engage in fulfilling relationships with others. All these components are influenced by important factors, such as social factors, general health status, economic status, self-care behaviour, and psychological factors (*Figure 1*).

Several QoL questionnaires have been used in HF, some of these are disease-specific for HF, and others are non–disease-specific. Several reasons have limited their implementation such as the lack of a clear role as prognosticator, the limited coverage of symptom expression, limited feasibility and interpretability, language barriers, content validity, and the limited availability of validation studies. *Table 1* summarizes the most common questionnaires, classified in HF disease-specific and non-disease-specific highlighting the specific domains measured, country and year of development, score range, and modality of administration.

Disease-specific questionnaires

Among the disease-specific questionnaires, the Minnesota Living with Heart Failure Questionnaire (MLHFQ) and the Kansas City Cardiomyopathy Questionnaire (KCCQ) have been qualified as

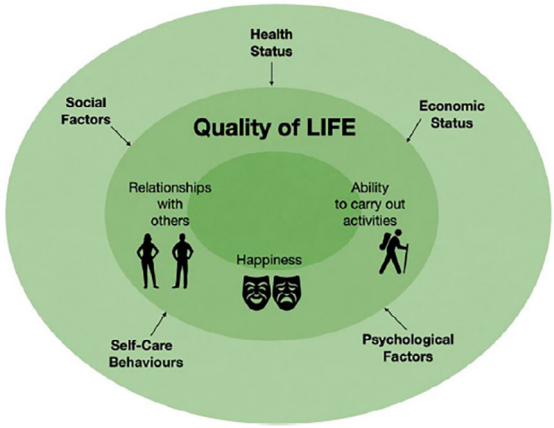

Figure 1 Components influencing the quality of life.

Medical Device Development Tools by the Food and Drug Administration (FDA) Center for Devices and Radiological Health, with KCCQ also qualifying as Clinical Outcome Assessment by the FDA Center for Drug Evaluation and Research for cardiovascular trials.[21,22]

The KCCQ includes 23 items that capture the impact of HF on 7 different domains within a 2-week recall period. These domains include symptom frequency, stability, and burden, as well as physical and social limitations, QoL, and self-efficacy (i.e. the patients' understanding of their HF management).[11]

To increase the feasibility of its use, its 23 items (KCCQ-23) were reduced to 12 items, while maintaining the reliability, validity, and prognostic properties of the full instrument.[23]

Although KCCQ-12 might be the best choice for clinical purposes, the full version is preferred for use in clinical trials because it has been qualified as clinical outcome by the FDA to support labelling.

In a prospective cohort of 476 HF outpatients, KCCQ accurately reflected clinical changes compared with 6-min walking distances (6MWD) and NYHA class, with higher sensitivity in the identification of small clinical deteriorations that were not discriminated by the two other measures.[24]

The KCCQ and NYHA class provide similar assessment of functional capacity as measured by peak exercise oxygen consumption (pVO_2).[25] Changes in KCCQ scores have been shown to correlate with changes in functional capacity, as measured by the 6MWD and cardiopulmonary exercise test. A 5-point overall change in the KCCQ score corresponded to a 1.4 mL/min/kg change in pVO_2 at the cardiopulmonary exercise test and to a 49.7 m change in distance walked at the 6MWD.[26]

The MLHFQ includes 21 items mapping physical and emotional domains within a 4-week recall period. Eight items are not included in these domains but are considered for the calculation of the total score. The total score ranges between 0 and 105, with lower scores indicating better health status.[12]

Previous data suggest a strong correlation between MLHFQ and exercise capacity measured as 6MWD, particularly in HF with preserved ejection fraction (HFpEF).

Although the MLHFQ has been shown to be associated with pVO_2, it was not associated with minute ventilation/carbon dioxide production (VE/VCO_2), which is independent of the subject's effort and therefore not influenced by early exercise termination due to symptom perception.[27]

The MLHFQ has been shown to correlate with NYHA class and to be an independent predictor of mortality/HF hospitalization in both outpatients and inpatients, regardless of left ventricular ejection fraction (LVEF). Comparisons between these two questionnaires are limited.[28,29] In HFpEF, MLHFQ and KCCQ were both reliable and valid tools for assessing health-related QoL, but KCCQ was more strongly associated with baseline functional status, whereas MLHFQ was more sensitive in detecting improvements in 6MWD.[30]

In a combined cohort of HFpEF and HF with reduced ejection fraction (HFrEF), KCCQ was more prognostic of death, transplant, left ventricular assist device (LVAD), and hospitalization than MLHFQ, suggesting that KCCQ might be the preferred tool if the goal is prognostication.[31]

Notably, improvement in NYHA class was not associated with clinical outcomes, whereas an improvement of ≥5 points in KCCQ predicted a 51% lower risk of mortality and a 27% lower risk of mortality/HF hospitalization.[32]

The KCCQ and MLHFQ cover many important HF symptoms, with some of them considered by only one of these tools, some others covered by both, and some others not considered by neither (*Table 2*).

It is important to highlight that it is not questionnaire's aim to evaluate symptoms/signs, but they rather aim to efficiently capture the total burden of HF (in particular chronic symptoms) on the overall patient's health status by taking into consideration several domains, e.g. mental, social, and physical.

Other disease-specific questionnaires are available in HF, including the Chronic Heart Failure Questionnaire (CHFQ), the Quality of Life Questionnaire for Severe Heart Failure (QLQ-SHF), the Left Ventricular Dysfunction Questionnaire (LVDQ), and the Chronic Heart Failure Assessment Tool (CHAT) (*Table 1*).[15,16,33,34]

Several reasons have limited their implementation as compared with the more widely adopted KCCQ and MLHFQ which received qualification by the FDA, and among these there are the lack of a clear role as prognosticator, the limited coverage of symptom expression, limited feasibility and interpretability, language barriers, content validity, and the limited availability of validation studies.

Non-disease-specific questionnaires

The information from global clinical assessment derived from non-disease-specific questionnaires provide important additional information.

For example, these questionnaires might be useful for investigating HF interventions when the treatment might also cause major complications whose impact could be neglected when using

Table 1 Questionnaires to measure quality of life in heart failure

Instrument	Aim: To measure	Country and year of development	Specific domains	Score range	Mode of administration
Disease-specific questionnaires					
Kansas City Cardiomyopathy Questionnaire (KCCQ)[11]	QoL in HF	USA, 1999	• Physical limitation • Symptoms • Self-efficacy • Social limitation • QoL	0–100 (worst to best)	Self-administered (telephone)
Minnesota Living with Heart Failure Questionnaire (MLHFQ)[12]	The extent to which HF prevents patients from living the way they would want to	USA, 1987	• Physical • Emotional	0–105 (best to worst)	Self-administered (telephone)
Cardiac Health Profile congestive heart failure (CHPchf)[13]	How HF influences subjective perceptions of physical, psychological, and social well-being	Sweden, 2007	• Symptoms • Activity levels • Psycho-social emotions	Visual Analogue Scales	Self-administered
Chronic Heart Failure Questionnaire (CHFQ)[14]	Longitudinal change over time within persons with HF	Canada, 1989	• Dyspnoea • Fatigue • Emotional	16–112 (worst to best)	Interview administered (telephone)
Chronic Heart Failure Assessment Tool (CHAT)[15]	QoL from the patient perspective	UK, 2007	• Symptoms • Activity levels • Psycho-social emotions	A variety of Response scales are used	Self-administered
Left Ventricular Dysfunction Questionnaire (LVD-36)[16]	The impact of left ventricular dysfunction daily life and well-being	UK, 1998	• Activity levels • Psycho-social status	0–100 (worst to best)	Self-administered (telephone)
Quality of Life Questionnaire in Severe Heart Failure (QLQ-SHF)[17]	Self-assessment of health-related quality of life in severe HF	Sweden, 1987	• Psychological • Physical activity • Life dissatisfaction • Somatic symptoms	0–130 (best to worst)	Self-administered
Non-disease-specific questionnaires					
EuroQol five-dimensional questionnaire (EQ-5D)[18]	Generic measure widely used for the assessment of health status	EuroQol Group, 1987	• Mobility • Self-care • Usual activities • Pain/discomfort • Anxiety/ depression	−0.594–1.000 (worst to best)	Self-administered
The MOS 36-item and the Short-Form Health Survey (SF-36 and SF-12)[19]	Multi-item scale to assess health status	Medical Outcomes Study, 1992	• Physical activities • Social activities • Usual role • Bodily pain • Mental health • Emotional problems • Vitality (energy and fatigue) • General health	0–100 (worst to best)	Self-administered (in person or by phone)
HeartQoL[20]	A health-related QoL questionnaire, originally developed in ischaemic heart disease	European Association of Preventive Cardiology, 2014	• Ten-item physical • Four-item emotional	Each item is scored from 0 to 3 (worst to best)	Self-administered

HF, heart failure; QoL, quality of life.

Table 2 Questionnaire content coverage by Kansas City Cardiomyopathy Questionnaire (KCCQ), Minnesota Living with Heart Failure Questionnaire (MLHFQ), and missing items

KCCQ and MLHFQ	Shortness of breath, fatigue, swelling (oedema) in the feet and ankles, sleeping problems, depression/anxiety, and limitations in working, recreational, and social activities and in intimate/sexual relationship
KCCQ	Exercise limitation, life satisfaction pleasure, and enjoyment of life
MLHFQ	Difficulties in concentrating, eating/drinking disorders, and feeling inadequate, worthless, and a burden to caregivers
Missing items	Swelling in the abdomen; feeling restless and tense; weight gain; lack of appetite, nausea, and chest pain; palpitation and dizziness; and persistent cough or wheezing

disease-specific questionnaires. For example, LVAD improves dyspnoea but might lead to stroke.

The KCCQ or MLHFQ, which focus on HF aspects, might underemphasize the impairment of QoL related to the complication, in turn overemphasizing the improvement in HF-related QoL. Global questionnaires such as the EuroQol-5d Questionnaire (EQ-5D) or the Short-Form Health Survey (SF-36) might be particularly useful for the assessment of older patients with multiple chronic diseases, a situation in which HF is not the only contributor to explain patient's health-related QoL, and can facilitate comparisons among patients with different conditions (*Table 1*).

In particular, EQ-5D has been often used to estimate QoL in HF populations. It assesses five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. It is commonly used to assess health state utilities, to support cost-effectiveness analyses.[35]

Application of quality of life questionnaires in clinical practice

The application of QoL questionnaires in HF has been reviewed and divided into settings of pharmacological interventions in HF with reduced (HFrEF) and preserved (HFpEF) LVEF (principally assessed by KCCQ and MLHFQ) (*Table 3*) and non-pharmacological strategies (*Table 4*).

Pharmacological intervention in heart failure with reduced ejection fraction

In previous studies evaluating guideline-directed medical therapies (GDMT), there is limited evidence of positive effects of pharmacologic interventions using angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and mineralocorticoid receptor antagonists (MRAs) on exercise capacity and QoL.[71]

In a randomized controlled trial involving 1050 African–American patients, the fixed combination of isosorbide dinitrate/hydralazine was associated with improvements in MLHFQ at all times during 18-month follow-up period.[36]

Ivabradine has also been linked to benefits in functional capacity and QoL, although their quantitative clinical relevance is limited.[37]

Regarding the most recent treatments for HFrEF, the benefit in terms of QoL was demonstrated by all pharmacological intervention. For example, a sub-analysis of the PARADIGM-HF trial conducted on 7623 patients, which completed the KCCQ, reported a significant score improvement in treated patients.[39] At 8 months, sacubitril/valsartan improved both KCCQ clinical summary score (CSS) (+0.64 vs. −0.29; $p < 0.01$) and KCCQ overall summary score (KCCQ-OSS) (+1.13 vs. −0.14; $p < 0.001$) compared with enalapril group and significantly less proportion of patients showed a score deterioration (27% vs. 31%; $p = 0.01$). However, 12-week sacubitril/valsartan therapy did not significantly improve functional capacity.[72,73]

For sodium–glucose cotransporter 2 inhibitor (SGLT2i), an analysis of the DAPA-HF trial investigated the effects of dapagliflozin on QoL, assessed by KCCQ total symptom score (KCCQ-TSS), in 4443 patients at randomization, 4 months, and 8 months.

At 8 months, patients on dapagliflozin showed a greater improvement in mean KCCQ-TSS, KCCQ-CSS, and KCCQ-OSS (respectively 2.8, 2.5, and 2.3 points higher vs. placebo; $p < 0.0001$ for all) and lower rates of score deterioration in KCCQ-TSS [odd ratio (OR) 0.84, 95% confidence interval (CI) 0.78–0.90; $p < 0.0001$].

The effects of dapagliflozin in reducing cardiovascular death or worsening HF were consistent across the range of baseline KCCQ-TSS.[40] Empagliflozin improved KCCQ-CSS and KCCQ-TSS at 3, 8, and 12 months in the EMPEROR-Reduced trial.[41]

Also after an acute event, empagliflozin improved KCCQ-TSS at 15, 30, and 90 days in the EMPULSE trial[43] Only in the small EMPERIAL trial empagliflozin failed to improve significantly QoL.[50]

Collectively, these data consistently demonstrate a beneficial effect of novel HF drugs on health condition, further supporting their use in clinical practice to impact on major cardiovascular outcomes and wellbeing status.

Pharmacological intervention in heart failure with preserved ejection fraction

Patients with HFpEF tend to be older with multiple comorbidities, in whom reduced exercise tolerance and dyspnoea are key manifestations.[74] These symptoms, along with frequent hospitalizations, pervade all aspects of daily life, eventually impairing function and independence, two commonly most important limitations in older adults. Indeed, from a trial design perspective, QoL primary endpoints are considered important, as the non-cardiovascular comorbid burden and older age play a major role with respect to prognosis in patients with HFpEF. Patients with HFpEF from PARAGON-HF had lower KCCQ scores in nearly all domains than those with HFrEF from PARADIGM-HF.[48,75,77]

Table 3 Pharmacological interventions on heart failure affecting quality of life

	Study	Study population	Characteristics of the study population	Tool to measure QoL	Results
Heart failure with reduced ejection fraction					
Isosorbide dinitrate/hydralazine	A-HeFT[36]	1050 African–American	60% male; 56 ± 13 years, 24% LVEF	MLHFQ every 3 months till 18 months	Improvements at all times by average of 3.6 points ($p < 0.001$)
Ivabradine	APULIA study[37]	221: 110 ivabradine; 111 β-blockers	49% male; 64 ± 6 years, 44% LVEF	SF-36 (at baseline and 1 month)	Improvements of physical functioning, physical role functioning, emotional role functioning, and mental health scales vs. β-blockers ($p < 0.001$)
	SHIFT[38]	1944 patients: 968 ivabradine, 976 placebo	76% male; 60 ± 11 years, 28% LVEF	KCCQ at randomization and 4, 8, and 12 months	Improvements in KCCQ by 2.4 OSS and by 1.8 CSS vs. placebo ($p < 0.05$)
Sacubitril/valsartan	PARADIGM-HF (sub-analysis)[39]	7623	79% male; 64 ± 11 years, 30% LVEF	KCCQ at randomization, 4 months, 8 months, and annual visits	At 8 months, sacubitril/valsartan group improved both KCCQ-CSS (+0.64 vs. −0.29; $p = 0.008$) and KCCQ-OSS (+1.13 vs. −0.14; $p < 0.001$) vs. enalapril
Dapagliflozin	DAPA-HF (sub-analysis)[40]	4443	77% male; 66 ± 10 years, 31% LVEF	KCCQ at randomization and 4 and 8 months	Dapagliflozin improved mean KCCQ-TSS, KCCQ-CSS, and KCCQ-OSS at 8 months (2.8, 2.5, and 2.3 points higher vs. placebo; $p < 0.0001$ for all)
Empagliflozin	EMPEROR-Reduced (sub-analysis)[41]	3705	76% male; 67 years 27% LVEF	KCCQ at baseline and 3, 8, and 12 months	Empagliflozin improved KCCQ-CSS, KCCQ-OSS, and KCCQ-TSS at 3, 8, and 12 months ($p < 0.01$)
	EMPERIAL Reduced[42]	312	75% male; 69 ± 10 years, 30% LVEF	KCCQ-TSS score at baseline and Week 12	Empagliflozin did not significantly improve KCCQ-TSS
	EMPULSE (sub-analysis)[43]	530 hospitalized for acute HF	66% male; 68 ± 13 years, 31% LVEF	KCCQ at baseline and 15, 30, and 90 days	At 90 days improvement in KCCQ-TSS: (+4.5 points) for the empagliflozin group vs. placebo ($p = 0.035$)
Sotagliflozin	SOLOIST-WHF[44]	1222 with diabetes	71% male; 69 years 35% LVEF	KCCQ at 4 months	Sotagliflozin improved KCCQ-CSS (+4.1, $p < 0.05$)
Ferric carboxymaltose	FAIR-HF[45]	459	47% male; 67 ± 10 years, 31% LVEF	KCCQ and EQ-5D Visual Analogue Scale at baseline and weeks 4, 12, and 24	KCCQ +7 ($p < 0.001$) EQ-5D +7 ($p < 0.001$)
Omecamtiv mecarbil	GALACTIC-HF[46]	8256	78%male; 64 ± 11 years, 26% LVEF	KCCQ at 24 weeks	No improvements
Heart failure with preserved ejection fraction					
Irbesartan	I-PRESERVE[47]	3605	39%male; 71 ± 7 years	MLHFQ at randomization and 6, 14, and 56 months	No significant improvement in QoL
Sacubitril/valsartan	PARAGON-HF[48]	4822	49%male; 72 ± 8 years	KCCQ at randomization and 8 months	Sacubitril/valsartan improved the KCCQ-CSS by ≥5 points in a higher percentage of patients vs. valsartan (33% vs. 29%; OR 1.3; 95% CI 1.04–1.61)
	PARALLAX[39]	2572	49% male; 72 ± 8 years	KCCQ at baseline and 12 and 24 weeks	No between-group difference in the mean change in the KCCQ (12.3 vs. 11.8; OR 0.52; 95% CI −0.9 to 2.0)
Dapagliflozin	DELIVER[49]	6263	56%male; 71 ± 9 years	KCCQ at 8 months	Dapagliflozin improved KCCQ-TSS (+2.4; $p < 0.05$)
	PRESERVED-HF[50]	324	43%male; 69 years	KCCQ at 12 weeks	Dapagliflozin improved KCCQ-CSS (+5.8) and KCCQ-OSS (+4.5) ($P < 0.05$)
	DEFINE-HF[51]	263	72% male; 62 ± 11 years	KCCQ 12 weeks	Dapagliflozin improved mean KCCQ-CSS and KCCQ-OSS at 12 weeks (4.6 and 3.7 points higher vs. placebo; $p < 0.0001$ for all)
Empagliflozin	EMPEROR-Preserved (sub-analysis)[52]	5988	55%male; 72 years	KCCQ at baseline and 12, 32, and 52 weeks	Empagliflozin improved KCCQ-CSS (+1.03, +1.24, and +1.50 at 12, 32, and 52 weeks, respectively; $p < 0.01$)
	EMPERIAL[42]	315	75% male; 69 ± 10 years	KCCQ-TSS at baseline and Week 12	Empagliflozin did not improve KCCQ-TSS
Spironolactone	TOPCAT (sub-analysis)[53]	3445	48% male; 69 years	KCCQ and EQ-5D Visual Analogue Scale at baseline, 4–12 months, and annually after	Improvement in KCCQ in the spironolactone vs. the placebo group at 4- (1.54; $p = 0.002$), 12- (1.35; $p = 0.02$), and 36-month (1.86; $p = 0.02$) visits
Isosorbide mononitrate	NEAT-HFpEF[54]	110	43% male; 69 years	MLHFQ and KCCQ at baseline and 6 weeks	No effect between isosorbide mononitrate 120 mg vs. placebo in KCCQ (−1.91; $p = 0.16$) and MLHFQ (+1.62; $p = 0.37$)
Inhaled nebulized inorganic nitrite	INDIE-HFpEF[55]	105	44% male; 68 years	KCCQ at baseline and 4 weeks	No difference in KCCQ (62.6 vs. 61.9; $p = 0.39$)
Praliciguat	CAPACITY-HF[56]	196	56% male; 70 ± 9 years	KCCQ at baseline and 12 weeks	No difference (defined as having ≥5-point improvement from baseline) vs. placebo
Vericiguat	VITALITY-HFpEF[57]	789	51% male; 72 ± 9 years	KCCQ at baseline and 14 weeks	No difference in KCCQ (5.5 points in 15 mg/d vericiguat group, 6.5 points in the 10 mg/d vericiguat group, and 6.9 points in the placebo group)

CI, confidence interval; CSS, clinical summary score; LVEF, left ventricular ejection fraction; OR, odd ratio; OSS, overall summary score; QoL, quality of life; TSS, total summary score; years: mean age. For remaining abbreviations, refer to *Tables 1* and *2*.

Table 4 Cardiac devices and structural interventions on heart failure affecting quality of life

	Study	Study population	Characteristics of the study population	Tool to measure QoL	Results
Cardiac resynchronization therapy	ANXIETY CHF[58]	132 HFrEF patients	71% male; 61 ± 14 years	MLHFQ at baseline and 5, 12, and 24 months	MLHFQ improved after implantation (−6.74, $p < 0.001$)
	MUSTIC[59]	58 HFrEF	77% male; 64 ± 9 years, 23% LVEF	MLHFQ at 12 and 24 weeks	MLHFQ improved after implantation (−4 vs. ±1 points, $p < 0.001$)
	MIRACLE[60]	453 HFrEF (225 vs. 228)	68% male; 64 ± 10 years, 21% LVEF	MLHFQ at 6 months	MLHFQ improved after implantation (−18 vs. −9 points, $p < 0.001$)
	MIRACLE-ICD[61]	369 HFrEF (182 vs. 187)	77% male; 67 ± 9 years, 23% LVEF	MLHFQ at 6 months	MLHFQ improved after implantation (−17 vs. −11 points, $p = 0.02$)
	COMPANION[62]	1520	69% male; 68 years, 22% LVEF	MLHFQ at 3.6 months	MLHFQ improved after implantation (−24 and −26 vs. −9 and −12 points in placebo; $p < 0.001$)
	CARE-HF[63]	813	73% male; 66 years, 25% LVEF	MLHFQ and EQ-5D at 3 months	MLHFQ: −10 points ($p < 0.001$); EQ-5D: +0.8 points ($p < 0.001$)
Cardiac contractility modulation (CCM)	FIX-HF-5[64] (sub-group analysis)	53 HFrEF	70% male; 62 ± 1 years, 42% LVEF	MLHFQ at baseline and 6 months	MLHFQ did not significantly improve after implantation (−13.1 ± 21.0, $p = 0.10$)
Carotid baroreflex activation therapy (BAROSTIM)	BEAT-HF[65]	408 HFrEF	79% male; 63 years, 27% LVEF	MLHFQ at baseline and 6 months	MLHFQ improved after implantation (−14.1; 95%, $p < 0.001$)
Transcatheter interatrial shunt devices (IASD)	Systematic review and meta-analysis[66]	226 HF patients	44%–92% male; 66–70 years	KCCQ at baseline and 12 months	KCCQ improved by 17.7 points (95% CI 10.8–24.6, $p < 0.001$)
Transcatheter mitral valve repair	COAPT[67]	614 HFrEF (302 vs. 312)	66% male; 71 ± 11 years, 31% LVEF	KCCQ and SF-36 at 1, 6, 12, and 24 months	KCCQ +15.9, 15.3, 14.5, and 12.8 at 1, 6, 12, and 24 months, respectively; SF-36 + 5.3, 4.9, 4.5, and 3.6 at 1, 6, 12, and 24 months, respectively
Ventricular assist devices (VAD)	Continuous (CF) vs. pulsatile flow (PF) VAD[68]	200 (134 CF vs. 66 PF VAD)	81% (CF) and 90% (PF) male; 64 years, 17% LVEF	MLHFQ and KCCQ at 3, 12, and 24 months	MLHFQ improved by −41 and − 31 in CF and PF vs. baseline at 12 months ($p < 0.001$); KCCQ-OSS improved by +38 and +32 in CF and PF at 12 months ($p < 0.001$); KCCQ-CSS improved by +37 and +29 in CF and PF vs. baseline at 12 months ($p < 0.001$)
	HeartMate II Continuous flow LVAD[69]	655 (281 BTT; 374 DT)	75% male; 50 years in BTT and 63 years in DT, 16% LVEF	MLHFQ, KCCQ-OSS, and KCCQ-CSS at 6 months in BTT and 24 months in DT	MLHFQ improved in BTT (by −28 at 6 months) and in DT (by −41 at 24 months) ($p < 0.001$); KCCQ-OSS improved in BTT (by 27 at 6 months) and in DT (by 42 at 24 months) ($p < 0.001$); KCCQ-CSS improved in BTT (by 25 at 6 months) and in DT (by 38 at 24 months) ($p < 0.001$)
Pulmonary vein isolation (PVI) in atrial fibrillation	PABA-CHF[70]	41 (PVI) vs. 40 (AVNA)	95% male in PVI and 81% male in AVNA, 60 years, 27% LVEF	MLHFQ at 6 months	MLHFQ improved by −29 vs. −7 in PVI vs. AVNA ($p < 0.01$)

AVNA, atrio-ventricular node ablation; BTT, bridge to transplant; DT, destination therapy; HFrEF, heart failure with reduced ejection fraction; LVAD, left ventricular assist device. For remaining abbreviations, refer to *Tables 1–3*.

The 2021 ESC HF guidelines suggest reducing body weight in obese patients, increasing physical activity, and promoting regular exercise for improved QoL.[77,78]

Several trials have investigated the possibility of pharmacological therapy in improving QoL in patients with HFpEF, with inconsistent results (*Table 3*).

In the I-PRESERVE trial, irbesartan was unable to change MLHFQ as well as prognostic indicators.[47]

Among the most novel treatment, sacubitril/valsartan showed inconsistent findings. In the PARAGON-HF, the mean change in the KCCQ-CSS at 8 months was higher in the sacubitril/valsartan group compared with the valsartan-alone group.[48] Yet, results of PARAGON-HF contrast with that of the PARALLAX trial, where, among patients with HF and LVEF >40%, sacubitril/valsartan treatment did not result in greater improvement of KCCQ-CSS at 24 weeks, despite a greater decrease in plasma N-terminal pro-brain natriuretic peptide levels at 12 weeks.[39] Reasons for the lack of improvement in QoL or exercise performance despite the potent biological effect on natriuretic peptides remain unclear.

More consistent positive findings are available for SGLT2i drugs. In particular, dapagliflozin improved QoL, physical limitations, and exercise function in the PRESERVED-HF trial and in pre-specific analysis of the Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure (deliver) trial.[49–51] Patients treated with empagliflozin exhibited a mean KCCQ improvement in the EMPEROR-Preserved trial; this effect manifested early and persisted for a minimum of 1 year, in contrast to the EMPERIAL trial, which failed to observe such a benefit[42,52]

The reasons for the discrepant results are unclear but may relate to differences in baseline characteristics (less obese and less likely to be women in EMPERIAL compared with PRESERVED-HF).

Finally, in the abovementioned EMPULSE trial, which included patients with acute HF and LVEF > 40%, initiation of empagliflozin in patients hospitalized for acute HF improved all components of KCCQ, with benefits seen as early as 15 days and maintained through 90 days.[43]

Regarding MRA drug, spironolactone treatment led to improvement in KCCQ in the TOPCAT trial.[53]

However, there was no change in generic EQ-5D scale or McMaster Overall Treatment Evaluation, suggesting that non-HF-related QoL was not influenced. TOPCAT also showed that older age, obesity, current smoking habit, NYHA class III/IV, and comorbidities were associated with declines in KCCQ in HFpEF.

Notably, trials targeting the nitric oxide-cyclic guanosine monophosphate pathway failed to improve exercise capacity or QoL in HFpEF, e.g. NEAT-HFpEF, INDIE-HFpEF, VITALITY-HFpEF, and CAPACITY- HF.[54–57] It is worthwhile to observe that these latter studies presented limited sized study populations which may have played a role.

In conclusion, improving QoL is a key therapy target for HFpEF patients, who value autonomy and activity. There is evidence that some GDMT (in particular sacubitril/valsartan, SGLT2i, and MRA) may improve patient-reported clinical outcomes, but further studies are needed.

Cardiac devices and structural interventions

Table 4 present results from randomized clinical trial ls evaluating the effect of non-pharmacological interventions on QoL measures, principally assessed by KCCQ and MLHFQ. Overall, the magnitude of the improvement in QoL measures with treatment vs. control was larger and more homogeneous for studies on devices, which might also be explained by an unfeasible blinding.

For instance, in the COAPT trial, transcatheter mitral valve repair determined a 1-month mean between-group difference of 15.9 points in KCCQ-OSS which was sustained over time.[79]

In most pharmacologic trials, including the more recent trials on SGLT2i, the average treatment effect on KCCQ was <5 points.

Implantable cardioverter defibrillator and cardiac resynchronization therapy

In patients with arrhythmias and HF, implantation of a cardiac device is associated with a significant survival benefit and improvement in functional capacity, depending on the type of device. Because of technological advancements over the last two decades, there is a wide range of implantable cardiac device alternatives for a wide range of clinical conditions and indications.[80]

In general, all old trials on implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy (CRT) are consistently showing an improvement in MLHFQ after implantation. More specifically, the ANXIETY-CHF study investigated heart-focused anxiety, general anxiety, depression, and QoL in patients with HF.[58]

Psychological measures were assessed before and up to 2 years after the implantation of an ICD.

In this interesting report, total anxiety and related fear and attention and QoL improved significantly after device implantation. On the contrary, depression and HF-related avoidance of physical activity remained unchanged. As expected, HF-related anxiety seems to be more pronounced after defibrillator interventions and, therefore, psychological counselling in these patients is required not only to reduce anxiety but, also, to increase physical activity.

Cardiac contractility modulation

Cardiac contractility modulation (CCM), consisting of non-excitatory electrical signals delivered to the heart during the absolute refractory period, is considered safe, improves exercise tolerance but not QoL (MLHFQ) in patients with NYHA functional class III or IV, QRS duration <130 ms and LVEF ≥25% and ≤45%.[64]

Cardiac contractility modulation is delivered by a two-lead system allowing CCM therapy even in patients with atrial fibrillation,[81] and it seems to exert more favourable effects on exercise tolerance in patients with mildly reduced LVEF with an adequate safety profile with respect to more severe left ventricular function.[82]

Carotid baroreflex activation therapy

Baroreflex activation therapy (BAT) represents a promising therapeutic modality, offering better functional capacity, better QoL,

and lower natriuretic peptide levels according to the multicentre, prospective, randomized, controlled BeAT-HF trial.[65]

But, again, well-powered studies with longer follow-up and diverse populations are needed before BAT can be incorporated in the HF guidelines and, therefore, in routine clinical practice.

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Pulmonary vein isolation in atrial fibrillation

A small randomized trial evaluating the effect pulmonary vein isolation vs. atrioventricular ablation with pacing in symptomatic HF patients with permanent atrial fibrillation showed an improvement in MLHFQ at 6 months.

Transcatheter interatrial shunt devices

An encouraging meta-analysis of transcatheter interatrial shunt devices for improvement in functional capacity (measured by 6-min walking test) and QoL (assessed by MLHFQ or KCCQ questionnaires), as well as for reductions in pulmonary capillary wedge pressure, regardless of LVEF, was recently published.[66]

However, in a well-organized, randomized controlled multicentre study, atrial shunt device in 626 patients with LVEF ≥40% offered no benefit in the total rate of HF events or in the health status.[83]

Transcatheter mitral valve repair

Evaluation of clinical status and QoL in a HF patient with functional mitral regurgitation candidate for percutaneous mitral valve repair is of paramount importance.

The patient who fulfils all the criteria for a Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT)-like profile has a lot better prognosis compared with the non-COAPT-like profile patient together with improved QoL at 24-month follow-up.[84]

The criteria to be considered are absence of severe left ventricular dysfunction (LVEF <20%), absence of severe non-reversible pulmonary hypertension, and absence of severe right ventricular dysfunction.

Furthermore, mitral valve repair might enable us to 'buy' time in candidates for heart transplantation (HTx) either listed or bridged to decision.

Interestingly, in the MitraBridge Registry, two-thirds of the MitraClip patients were free from HTx or ventricular assist device (VAD) implantation or HF hospitalization and one out of four had no more indication for HTx because of functional improvement.[85]

Ventricular assist devices

In addition to survival benefits, important improvement in functional capacity and HF-related QoL is noted in the first 3 months and is maintained out to at least 24 months post-implant with ~80% of the queried patients to express their satisfaction with their consensus to have VAD therapy, at least during the first 2 years post implantation.[86,87]

Long-term VAD-supported patients, however, had still impaired QoL and sexual function at follow-up, despite an improvement in the frequency of HF symptoms, social interactions, and independency.[88]

Therefore, consultation and education of both patient and caregiver, capturing the whole spectrum of 'living with an VAD' including social interactions, driving, and sexual function, should be integrated into the pre-VAD implantation assessment and preparation to facilitate the way for further improvement in the well-being of the VAD patient.

Physical activity and exercise-based cardiac rehabilitation

In contrast with the pharmacological interventions or device implantations in HF, physical training and exercise-based cardiac rehabilitation have consistently shown very positive and undisputable effects on QoL, whatever the level of LVEF. Consequently, the 2021 ESC HF guidelines recommend physical training to improve QoL for all HF patients.[78] In HFrEF, this recommendation is based on the evidence of the HF-ACTION trial, the largest trial conducted with physical training.[26] The more recent EXTRAMATCH 2 meta-analysis[89] confirmed the benefit independently of LVEF or the type of rehabilitation (aerobic or aerobic plus resistive).

Regarding HFpEF patients, studies are clearly less numerous but a similar beneficial effect was found. For example, the OptimEX-CLIN study[90] showed improved QoL domains in moderate continuous training compared with control [11 (95% CI 2–19)].

Also in more fragile old patients recently discharged from HF decompensation, there is evidence of improvement in QoL by physical rehabilitation.[91] Resistance training also improves QoL, although to a lesser extent generally.[92] There is also a dose/effect relationship of physical training on QoL, although less obvious in usual aerobic exercise than in HIIT in HFpEF.[93] Interesting, in older overweight/obese patients with HFpEF, where both caloric restriction diet and aerobic exercise training increased pVO_2, only diet had a significant effect on QoL,[94] which was consistent with previous study showing poor acceptance of exercise training by older obese individuals[95] (*Table 5*).

Holistic approach

Under this category, interventions aiming at providing support that looks at the whole person are presented. In general, evidences are based on small trials and few prospectively randomized, and consequently difficult to analyse, with inconsistent findings (*Table 5*).

Self-care can be defined as a process of health promoting and preventive practices with patients and their relatives' engagement. Heart failure education is considered as a part of self-care process, focused on symptoms and signs, medical treatment, and behavioural changes. Randomized controlled studies of HF programmes that include selfcare demonstrate improved outcomes and hospital readmission due to HF worsening but non-consistent data on QoL.[97–99]

Table 5 Exercise-based cardiac rehabilitation and holistic approach interventions on heart failure affecting quality of life

	Study	Study population	Characteristics of the study population	Tool to measure QoL	Results
Exercise-based cardiac rehabilitation	HF-ACTION[26]	2331 HFrEF	71% male, 59 years, 24% LVEF	KCCQ at baseline and every 3 months for 12 months and annually thereafter for up to 4 years KCCQ-OSS improved by 5.2 points in the exercise vs. 3.3 points in the control group ($p < 0.01$)	KCCQ-OSS improved by 5.2 points in the exercise vs. 3.3 points in the control group ($p < 0.01$)
	EXTRAMATCH 2 (IPD meta-analysis)[96]	3990 HFrEF	73% male, 61 years, 27% LVEF	MLHFQ at baseline and 12 months	MLHFQ improved significantly (mean score −5.8 points, 95% CI: −9.2 to −2.4 points)
	OptimEX-CLIN[90]	180 HFpEF	43% male, 67 years, >50% LVEF	KCCQ at baseline, 3 and 12 months	KCCQ did not significantly differ between groups after 3 months of exercise intervention. At 12 months, the QoL improved in moderate continuous training vs. control (11, 95% CI 2–19)
	REHAB HF study[91]	349 HFrEF	48% male, 73 years, >45% LVEF in 93%	KCCQ at baseline and 3 months	KCCQ improved: 69 vs. 62 ($p = 0.007$)
	Exercise and caloric restriction[94]	100 obese	67 ± 5 years, BMI 39 ± 5, 60% LVEF	KCCQ at 20 weeks	Diet (−7 points, $p < 0.001$) but not exercise (−2 points) improved KCCQ
Holistic approach					
Patient's education and self-management	Education on drug adherence[97]	82	57% male, 60 ± 5 years	MLHFQ at 12 months	No benefit on QoL
	Systematic IPD meta-analysis[98]	5624 (20 studies)	56% male, 69 years	KCCQ and MLHFQ at 6 and 12 months	No benefit on QoL
	Systematic review[99]	7 studies	1178	MLHFQ at 12 months	Only one study documented improvement in QoL
Motivational interviewing (MI)	Systematic review and meta-analysis[100]	1214 (9 studies)	65% males, 58–78 years	1–16 months of follow-up	MI improved self-care confidence and self-care management and self-care maintenance
Psychological interventions	Systematic review[20]	757 (9 studies)	40–68 years	KCCQ and MLHFQ with 3–12 months of follow-up	Four studies reported improvement in QoL
Supportive care	Systematic review and meta-analysis[101]	867 (10 studies)	33–79 years	MLHFQ with 12 weeks to 12 months of follow-up	No benefit on QoL

CBT, cognitive behavioural therapy; CRT-P/CRT-D, cardiac resynchronization therapy with pacing/defibrillator; HFpEF, heart failure with preserved ejection fraction; IPD, individual patient data. For remaining abbreviations, refer to *Tables 1–4*.

Motivational Interviewing is a widely adopted counselling intervention which elicits and strengthens motivation to change and has been used as an effective strategy for improving HF self-care behaviours (i.e. self-care maintenance, management, physical activity, and knowledge). A systemic review showed that this strategy reduces the burden of HF physical symptoms, especially when the intervention is performed on both patients and caregivers as a dyad.[100,102]

Psychological intervention for patient's empowerment refers to a process that enables people to have greater influence over their own health by gaining greater control of what they themselves define as important. It refers to well-informed patients taking responsibility for their own health, to as great an extent as possible, and the expected benefits of improved QoL. In a systemic review of nine studies, four have found to improve outcomes including QoL, mental health (depression, anxiety) and adherence.[103]

Supportive care is a multidisciplinary holistic care provided in the patient and his family, from the time of diagnosis along with treatment aiming to prolong life expectancy and improve QoL and into end-of-life care. It is composed of four components: communication and decision making, education, symptom management, and psychological and spiritual issues, initially provided to patients with cancer. In the meta- synthesis of Kyriakou *et al.*[101,104] supportive care showed a not significant effect on QoL but a positive effect of the interventions on the physical and emotional dimensions.

Mobile health

Mobile health (mHealth), broadly defined as the use of mobile computing and wireless communication technologies in health care, offers scalable and affordable opportunities for expanding delivery of care services outside of hospital settings to assist patients with self- monitoring and management of HF symptoms.[105]

In a systematic review on 18 studies on mHealth, QoL was investigated in 11: in only 4 that contained telemonitoring combined with telephone support, QoL improved.[106]

There was insufficient data on the cost-effectiveness of mHealth interventions to do meaningful analysis.

Gaps in knowledge and conclusions

A QoL instrument may be useful for many different purposes, for example, for long-term follow-up of individual patients or in the evaluation of treatments designed to improve QoL. But we can identify at least two gaps in knowledge.

What is the minimal clinical important difference for quality of life in heart failure?

It is critical to ascertain the magnitude of within-patient change that is meaningful to patients.[107]

As a tool (such as QoL questionnaire) becomes more common to assess treatment efficacy it is critical to leverage clinically important thresholds of change and to analyse the results to provide more clinically relevant ways of understanding the benefits of treatment. In this aspect, the definition of minimal clinical important difference, i.e. the level that is meaningful to patients, is crucial. Both KCCQ and MLHFQ were designed and validated as HF-specific tools to evaluate health status. While population-level mean differences between the active and control groups can be compared in a research setting, understanding how these differences impact individual patient QoL is more complicated.

To do this, is it necessary to identify groups of patients who experience small, moderate, or large improvements or deteriorations. Efforts to understand the within-patient change have created estimates close to the original thresholds of 5, 10, and 15–20 points that indicate small to moderate (but clinically important), moderate to large, and large to very large clinical changes, respectively.

Trials can not only report the mean differences in scores between groups but also the proportion of participants in each arm who have changes of different levels. This is achieved by responder analysis and reporting the proportions of patients who achieve benefits of various levels, e.g. 5-, 10-, and 15-point improvement in KCCQ score. These numbers can be converted to the total number-needed-to-treat (NNT) for one patient to experience an important change in health status, e.g. patients treated with dapagliflozin had more patients than placebo who experienced 5- (58.3% vs. 50.9%), 10- (54.5% vs. 47.6%) and 15-point (54.0% vs. 48.2%) improvement in KCCQ-TSS, corresponding to NNTs of 14, 15, and 18, respectively.[40]

Such information may be valuable for clinicians and patients to understand the treatment benefits. These are potential ways to leverage health status outcomes to provide intuitive ways to quantify and understand the benefits of treatments.

Do we need a new quality of life measurement tool in heart failure?

Quality of life has many characteristics, including physical exercise ability, congested symptoms, psychological effects of disease, social functioning, cognitive impairment, sleep quality, and anxiety.

However, most treatments are highly specific in improving a specific function, such as haemodynamic or muscular, and hence having effects largely focused on one particular sign or symptom.

Perhaps current scoring systems for general QoL are too wide to detect changes caused by treatment interventions.

Thus, instead of searching for the holy grail of a single QoL tool, we may be better off breaking it down into pieces and developing tools, more sensitive to specific disease components impacting on QoL.

A second consideration is whether a QoL instrument should be more personalized and considering differences in QoL between young persons with minor sickness vs. extremely elderly people with various comorbidities and restricted exercise capacity.

An alternate strategy, which has not been created, is to build a QoL score that crosses severe disease to small disease within an individual patient's expectations, so that scores are benchmarked (e.g. on a 0–100 score) relevant to their expectations.

It is for these reasons that the Heart Failure Association is developing a new score for QoL in HF, sensitive to mechanism-specific interventions and tailored to be sensitive to changes within individual patients.

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