

Addressing comorbidities in heart failure: When feeling better and living longer go in the same direction

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This article refers to 'Impact of comorbidities on health status measured using the Kansas City Cardiomyopathy Questionnaire in patients with heart failure with reduced and preserved ejection fraction' by M. Yang et al., published in this issue on pages 1606–1618.

Patients with heart failure (HF) are at high risk of disease progression resulting in clinical deterioration, repeated hospitalizations and death.^{1,2} In addition, they have a significantly lower health-related quality of life (HRQoL) compared with patients with other chronic conditions.^{3,4} HRQoL is uniquely sensed by each individual and refers to his subjective perception of the impact of both disease and treatment on his health status (symptoms, daily functioning, and subjective well-being).^{4–8} When measured using current scores, health status has multiple domains that evaluate the patient's experience of his/her symptoms, physical limitations and psychosocial limitations alongside with the burden of disease on the patient overall quality of life (Figure 1).^{4,5} HRQoL provides information into treatment effects from a patient's perspective and is often used to assess treatment effectiveness in addition to clinical endpoints, such as mortality and/or hospitalization, and is now recognized as an important modifiable patient-centred outcome.⁸

To assess HRQoL, disease-specific patient-reported outcome measures, such as the Kansas City Cardiomyopathy Questionnaire (KCCQ), are widely used to directly obtain patients' perspectives (Figure 1). KCCQ has been proven to be a valid, reliable, sensitive, and prognostically important measure of HRQoL for patients with HF.^{4–8} In chronic HF settings, a low KCCQ score is associated with adverse outcomes, mortality and hospitalization.^{9–12} Furthermore, the association between KCCQ scores and prognosis has been demonstrated also in patients with acute HF, at the time of discharge¹³ and 1 week after hospital discharge.¹⁴ This is clinically relevant, since improvement of long-term outcomes critically depends

on by optimizing pre- and post-discharge management of patients with acute HF.¹⁵ In all these studies, there was an independent association among KCCQ scores and death, HF hospitalization, even after adjusting for numerous other clinical characteristics. The independent association of KCCQ scores with clinical events is because the KCCQ captures an important domain that is not represented by any other clinical markers of disease severity, such as ejection fraction,⁷ New York Heart Association (NYHA) class,¹⁶ congestion¹⁷ or B-type natriuretic peptide.¹⁸

Patients with HF often have multiple comorbidities, both cardiovascular and non-cardiovascular, which accelerate disease progression, and worsen the response to treatment. In addition, a high burden of comorbidities has been consistently associated with higher rates of mortality and/or HF admissions in acute and chronic HF, both in clinical trials and in registries.^{19–22} Although it has been shown that comorbidities may significantly reduce HRQoL in patients with HF,²³ there are few data to describe the relationship between HRQoL and comorbidities, in terms of both their individual impact and global burden, in patients with HF subdivided based on their left ventricular ejection fraction (LVEF). Furthermore, the relative impact of comorbidities on specific domains of KCCQ is practically unknown.

In this issue of the Journal, Yang and colleagues²⁴ report the impact of comorbidities on HRQoL measured using the KCCQ in patients with HF from five large randomized clinical trials. This is the largest systematic assessment of the impact of comorbidities on KCCQ scores. A total of 20 159 patients with HF with reduced ejection fraction (HFrEF) and 6563 patients with HF with preserved ejection fraction (HFpEF) were included in the present analysis. The data derive from three HFrEF trials (ATMOSPHERE, PARADIGM-HF and DAPA-HF) and two HFpEF trials (TOPCAT and PARAGON-HF), collecting data on KCCQ.

Each comorbidity (except myocardial infarction) was more prevalent in HFpEF (Figure 2), and comorbidity burden in patients

The opinions expressed in this article are not necessarily those of the Editors of the *European Journal of Heart Failure* or of the European Society of Cardiology. doi: 10.1002/ejhf.2962.

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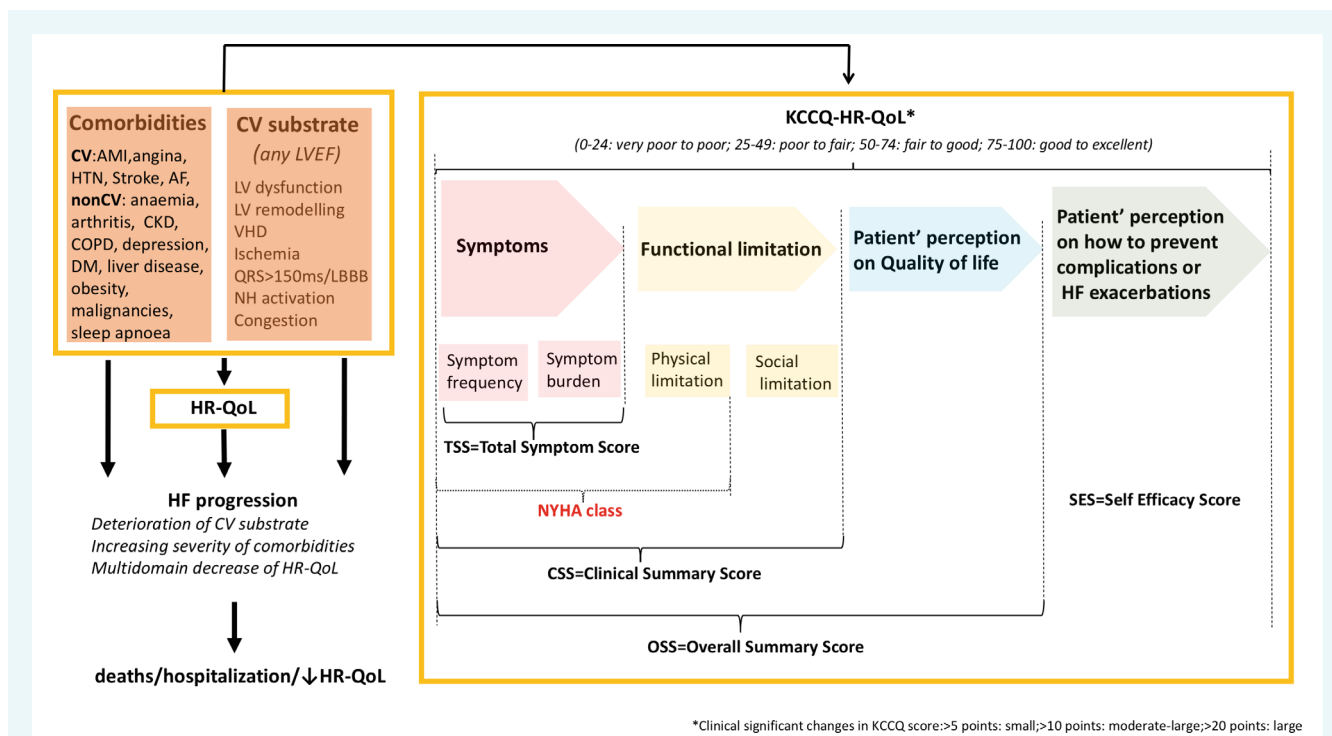


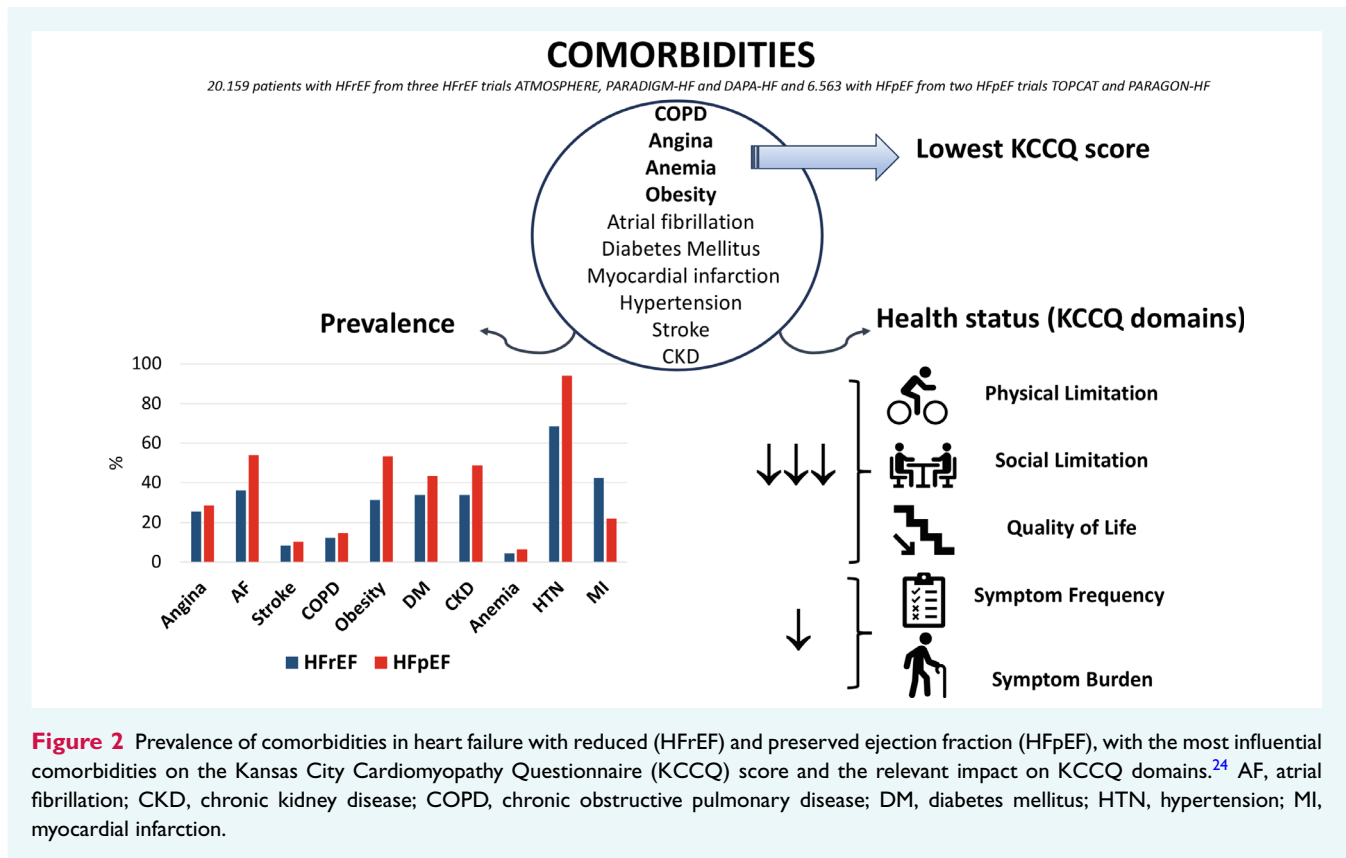
Figure 1 Determinants of health-related quality of life (HR-QoL) and their role in heart failure (HF) progression. The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a valid, reliable, responsive, and prognostically important measure of quality of life for patients with HF.^{4,5} KCCQ includes five domains with a score graded from 0 to 100 points. A change of more than 5 points in the KCCQ score is considered clinically significant. AF, atrial fibrillation; AMI, acute myocardial infarction; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; DM, diabetes mellitus; HTN, hypertension; LBBB, left bundle branch block; LV, left ventricular; LVEF, left ventricular ejection fraction; NH, neurohormonal activation; NYHA, New York Heart Association; VHD, valvular heart disease.

with HFpEF was also much higher than that in those with HFrEF (79.8% of patients with HFpEF had three or more comorbidities, compared to 59.7% of patients with HFrEF). Irrespective of LVEF, patients with higher comorbidity burden were older, more commonly with history of previous HF hospitalization, presenting with more clinical signs suggestive of congestion, and they had higher N-terminal pro-B-type natriuretic peptide levels and lower estimated glomerular filtration rate.

An increasing number of comorbidities was associated with decreasing scores and HFpEF patients had lower KCCQ domain scores and overall summary score (OSS) than HFrEF patients. The mean OSS was reduced to 71.3 and 67.8 in patients with HFrEF and HFpEF, respectively, and there was a stepwise reduction in domain scores and KCCQ-OSS with an increasing number of comorbidities. The physical and social limitation domains, as well as the quality of life domain, were reduced more with multiple comorbidities than the symptom frequency and symptom burden domains, irrespective of LVEF. In both HFrEF and HFpEF, chronic obstructive pulmonary disease, angina, anaemia, and obesity were associated with the lowest scores (Figure 2). Obesity was associated with the greatest reduction in scores and the impact of obesity was greater in HFpEF than in HFrEF. Anaemia was also associated with moderate reductions in scores in HFrEF, but the reductions in scores were much larger in HFpEF.

The results of the current study²⁴ demonstrate that both cardiovascular and non-cardiovascular comorbidities contribute to reduced quality of life. This is in agreement with other studies showing that more than one-half of the patient population did not rate HF as the primary limitation to their quality of life.²⁵ The finding that patients may be more limited in their HRQoL due to associated comorbidities, rather than HF *per se*, underlines the potential futility of focusing on HF-specific therapies alone to improve HRQoL in all patients with HF. It may also explain why it may be difficult to improve quality of life using HF-targeted therapies alone, particularly in patients with HFpEF who have a higher burden of comorbidities.²⁶ Notably, the comorbidities associated with the highest impact on KCCQ scores, anaemia, angina, chronic obstructive pulmonary disease and obesity, in both HFrEF and HFpEF, are 'treatable' comorbidities,²⁷ demonstrating the potential of their treatment to improve health status in patients with HF.

Another important finding of the present study was that, generally, the largest reductions in domain scores were for quality of life, social limitations, and physical limitations rather than symptom burden or symptom frequency.²⁴ This is clinically important because physician assessment, based on NYHA class, focus on symptoms and functional limitations and, therefore, underestimate the impact of HF on patient well-being. NYHA class is typically rated from the



clinician's perspective rather than from the patients. A comparison between physician- and patient-reported NYHA class demonstrated agreement in only half of the cases.²⁸ The superiority of KCCQ may be due both to the subjectivity of clinician's assessment based on NYHA class and to the inclusion of additional areas, such as the social limitation and self-efficacy domains (Figure 1).

In the current study, due to the entry selection in randomized controlled trials, the investigators used a binary classification of HF and this is a possible limitation as current guidelines recommend classification of HF in three LVEF categories² and several studies have demonstrated different patterns of association between number/type of comorbidity and outcomes in each of the three ejection fraction categories.^{21,29} Furthermore, in one study, the influence of comorbidities on HRQoL and mortality was greater in patients with HF with mildly reduced ejection fraction than in patients with HFrEF or HFpEF.²⁹ Comorbidities in this study were collected in clinical trial settings with strict exclusion criteria, that may differ by number and severity as compared with a 'real-world' population. Thus, we may expect that a higher comorbidity burden or more severe comorbidities will be more detrimental on HRQoL of HF patients in real life.

The results of this study²⁴ are of significant relevance, providing the basis for future research to guide clinical practice, since they highlight the importance of considering and treating comorbidities in the overall management of patients with HF in order to improve their HRQoL. Targeting comorbidities is confirmed as a major component in the comprehensive management of HF

patients.^{2,27} We suggest the need for a critical reappraisal of treatment strategies in HF in which clinicians target comorbidities, in addition to targeting the underlying cardiac dysfunction. The association between each individual comorbidity and the KCCQ score varied substantially in patients with HFrEF and HFpEF,²⁴ suggesting that an 'ejection fraction-specific' multidisciplinary approach with distinct comorbidity management programmes should be applied. This approach may be particularly relevant for HFpEF patients, for whom, except for sodium–glucose cotransporter 2 inhibitors, no therapies are available to improve HRQoL and to reduce morbidity and mortality. In addition, on the basis of the current research, improved management of specific comorbidities in patients with HFpEF may have an even greater impact than in HFrEF.

The structured assessment of HRQoL via the KCCQ score puts the patient's perspective at the forefront and can identify areas of specific need. This helps to facilitate shared decision-making and ensure that patient preferences are used to guide management. However, despite long-term history of use in clinical trials, validated HRQoL tools are not used routinely in clinical practice yet, and Yang *et al.*²⁴ must be congratulated for their further contribution to have HRQoL at the forefront of HF research and treatment.

Conflict of interest: none declared.

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