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This editorial refers to the article by Butler J. *et al.* entitled “Minimally Clinically Important Difference in Quality of Life Scores for Patients with Heart Failure and Reduced Ejection Fraction” published in the *European Journal of Heart Failure*.

Health-related quality of life scores: ending the minimum 5-point difference as the clinically meaningful threshold

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Heart failure (HF) patients experience diminished health status, including reductions in physical activity and health-related quality of life (HRQoL). HRQoL scores have been used as endpoints and intermediate prognostic markers in HF trials¹. In heart failure with reduced ejection fraction (HFrEF), an improvement in HRQoL points towards a beneficial treatment effect¹. The impact of HRQoL improvements in heart failure with preserved ejection fraction (HFpEF) have been harder to assess due to the lack of trials with a convincingly positive result. In the case of the Kansas City Cardiomyopathy Questionnaire (KCCQ, on which the overall score ranges from 0 to 100, with a higher score indicating a better quality of life) a 5-point change in the overall score has been considered to be a clinically meaningful difference in the health status of the patient².

In the FAIR-HF trial³, 459 symptomatic HFrEF patients with iron deficiency were randomly assigned to receive intravenous iron (ferric carboxymaltose) or saline (placebo). The primary endpoints were the self-reported Patient Global Assessment (PGA) and NYHA functional class at 24 weeks; HRQoL assessed by the KCCQ was a secondary end-point. Intravenous ferric carboxymaltose improved symptoms, functional capacity, and HRQoL. In the PGA, a general HRQoL tool based on a Likert scale (on which patients can classify their status as much improved, moderately improved, a little improved, unchanged, a little worse, moderately worse, or much worse/dead), 50% of patients in the ferric carboxymaltose group reported that they felt much or moderately improved, as compared with 28% of patients in the placebo group (odds ratio for being in a better rank, 2.51; 95% CI, 1.75 to 3.61; $p < 0.001$). The KCCQ score started around 53 points in both treatment groups and improved by 14 points in the ferric carboxymaltose group and by 6 points in the placebo group, which gave a treatment effect difference of +7 points in favor of ferric carboxymaltose ($p < 0.001$).

In this issue of the *European Journal of Heart Failure*, Butler J. *et al.* asked an interesting research question which is what are the magnitudes of change in KCCQ that are clinically important to patients (as assessed by the PGA) to determine the minimal clinically importance differences (MCID) as a patient-centered measure. The correlations between the PGA and the KCCQ were fair and most KCCQ domain scores had a less than 5-point MCID for “little improvement”, suggesting that KCCQ changes of smaller magnitude than the traditional 5-point threshold may be clinically meaningful, which may be relevant for the interpretation of patient reported outcomes and for the endpoint selection in future HF trials.

Looking into other recent HF drug trials, a similar pattern is observed. For example, in the PARADIGM-HF trial, sacubitril/valsartan (vs. enalapril) improved KCCQ by (“only”) +1.3 points⁴; still, treatment with sacubitril/valsartan resulted in a 20% relative reduction of HF hospitalization or cardiovascular death⁵. In the DAPA-HF trial, dapagliflozin (vs. placebo) improved KCCQ by +2.8 points and reduced HF hospitalizations or cardiovascular death by 26%⁶. Improvements of ± 1 point in KCCQ were also observed in TOPCAT and PARAGON-HF, which were HFpEF trials with marginal treatment effects in favor of spironolactone and sacubitril/valsartan (vs. placebo and valsartan), respectively; with marked internal heterogeneity, as elsewhere discussed⁷⁻⁹. The association between

the KCCQ score changes and subsequent clinical outcomes were studied in the HF-ACTION trial, where a nonlinear relationship between change in KCCQ and outcomes was found with any increment up to 8 points and any decrease being associated with better and worse outcomes, respectively¹⁰. Findings that support the notion that improvements below 5 points are clinically relevant. In HF patients, physical limitation, daily activities, obesity, non-cardiac co-morbid conditions, social and psychological factors may have major impact in HRQoL and not necessarily be improved by a cardiovascular treatment¹¹. Moreover, HF is a chronic disease that inexorably will deteriorate with aging. Hence, if a given HF drug is capable of, at least, stabilize or provide little improvement (vs. a placebo or active control) to a patient's quality of life that's already a lot to ask for a pill. Therefore, a threshold lower than 5 points in HRQoL should be considered as clinically meaningful. In a trial, this can be assessed with a binary outcome with "1" indicating a "event" when any HRQoL deterioration is observed. When assessing HRQoL the totality of events should also be incorporated i.e., patients that were hospitalized or died before the HRQoL evaluation should be considered in the analysis; this can be achieved by using statistical techniques such as the "win-ratio"¹². **Table 1.**

In conclusion, small changes in HRQoL should be considered as clinically meaningful, providing that patients who were hospitalized or died before the HRQoL assessment are considered for the analysis.

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Table 1. Recent drug heart failure trials, treatment effect on health-related quality of life as assessed by the KCCQ, and morbidity-mortality

Trial	KCCQ score baseline	KCCQ score change (6-12mo)	HFH or CV death
HFrEF			
FAIR-HF (n =459) (ferric carboxymaltose vs. placebo)	53±1	Active: +14 Placebo: +6 <u>Difference: +7±2</u>	↓ §
SHIFT (n =1944) (ivabradine vs. placebo)	65±20	Active: +6.7 Placebo: +4.3 <u>Difference: +2.4 (0.91–3.85)</u>	↓ HR =0.82 (0.75–0.90)
PARADIGM-HF (n =7623) (sacubitril/valsartan vs. enalapril)	73±19	Active: +1.1 Control: -0.1 <u>Difference: +1.3 (0.6–2.0)</u>	↓ HR =0.80 (0.73-0.87)
DAPA-HF (n =4443) (dapagliflozin vs. placebo)	±68 ¥	Active: +6.1 Placebo: +3.3 <u>Difference: +2.8 ¥</u>	↓ HR =0.74 (0.65-0.85)
HFpEF			
TOPCAT (n =3400) (spironolactone vs. placebo)	55±20	Active: +8 ¥ Placebo: +7 ¥ <u>Difference: +1.3±0.4</u>	-- HR =0.89 (0.77-1.04)
PARAGON-HF (n =4822) (sacubitril/valsartan vs. valsartan)	71±19	Active: -1.6 Placebo: -2.6 <u>Difference: +1.0 (0.0-2.1) €</u>	-- RR =0.87 (0.75-1.01)
Interpretation			
<ul style="list-style-type: none"> • HRQoL commonly improves in both the placebo and active groups during the trial; • HRQoL (active – placebo arm) difference is usually small (<5 points) in major outcome trials; • Early (6-12mo) “small” improvements or even stability in HRQoL (i.e., score ≥0) suggest a subsequent morbidity-mortality treatment benefit; • Minimal clinically importance differences in KCCQ were lower than the traditional 5 points, suggesting that even changes <5 points may be clinically meaningful; <p>✓ Overall, these findings suggest a treatment providing any improvement in HRQoL beyond the placebo effect is clinically meaningful and suggests a treatment benefit.</p>			
Clinical and research implications			
<ul style="list-style-type: none"> • A threshold lower than 5 points in HRQoL should be considered as clinical meaningful; • HRQoL improvement could be assessed as a dichotomous (“binary”) variable with an event indicator if deterioration occurs i.e., an event is considered if the patient HRQoL gets worse; • A sensible time-point to assess HRQoL should be used i.e., when most patients are still in the trial and an effect of treatment is expected (usually 6-12 months after randomization seems appropriate); • The totality of events should be considered i.e., non-fatal (e.g., HF hospitalizations) and fatal events occurring prior to the HRQoL determination should not be ignored (“censored”); <p>✓ The “win-ratio” provides such a statistical solution by considering all patient-pairs and the totality of events by their hierarchical importance (e.g., fatal, non-fatal, HRQoL) to determine the “winner” (active or placebo/control).</p>			

Legend: HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; KCCQ, Kansas City Cardiomyopathy Questionnaire; HRQoL, health-related quality of life as measures by the KCCQ; §, no hazard ratio reported because FAIR-HF was underpowered for morbidity-mortality outcomes; £, overall summary (OS) of KCCQ; ¥, data/point estimated retrieved from a figure without confidence intervals; €, results for the KCCQ clinical summary score; HR, time-to-first event hazard ratio; RR, total event risk ratio.

↓, event rate decreases with treatment; --, neutral results (“borderline neutral” in PARAGON-HF and TOPCAT, the latter with marked geographical differences, as previously described).