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VIEWPOINT

Current challenges for using the Kansas City Cardiomyopathy Questionnaire to obtain a standardized patient-reported health status outcome

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In April 2020, the U.S. Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) approved the use of the Kansas City Cardiomyopathy Questionnaire (KCCQ) as a primary endpoint in drug trials for patients with heart failure (HF).[1] Noted in the FDA approval is a recommendation to establish thresholds for clinically meaningful within-patient change on KCCQ subscales.[1] This approval represents an important step forward for using a patient-reported outcome measure to evaluate clinical services. Given the importance of this development, it is essential to discuss three critical challenges that are evident from recent HF trials (*Table 1*),[2–8] and that need to be resolved as clinicians or patients attempt to use the KCCQ to obtain a standardized evaluation of clinically meaningful change in patient health status.

The patient's Kansas City Cardiomyopathy Questionnaire starting point

Guidelines for categorizing qualitative differences in a patient's KCCQ score have yet to be established. Recommended threshold scores have been reported for poor, fair, good, and excellent levels of functioning on the KCCQ overall summary score (OSS): ≤25, >25 to 50, >50 to 75, and >75 to 100, respectively.[9] These quartile ranges were used successfully in drug trials such as EPHESUS[2] to predict clinical outcomes at 2 years. However, a considerable range of alternative threshold scores for the KCCQ have been used to detect clinically meaningful differences in reported health status. In PARAGON-HF,[3] KCCQ-OSS quartiles associated with the clinical severity of HF signs and symptoms were based on threshold scores of 59.1, 74.2, 86.5, and >86.5. In the DAPA-HF trial,[5] qualitative differences in HF clinical outcomes were based upon tertile scores on KCCQ subscales with thresholds of ≤65.6, 65.7 to 87.5, and >87.5 points. These trials indicate that the empirical guideline is quite variable for designating KCCQ quantile values that differentiate between poor, fair, good, and excellent health status. There is a current need to resolve this issue.

Clinically meaningful KCCQ cut-off points may differ for populations with different disease states or comorbidities. However, putting the application of set cut-off points into practice will be a challenge as disease-specific thresholds are not presently available. In the CASA trial, Flint *et al.*[4] used KCCQ-OSS quartiles based on cut-off values of 25, 50, 60, and 75 to identify HF patients who presented with deficits in quality of life domains for physical symptom burden, depression, anxiety, and spiritual well-being. Statistical sensitivity to identify deficits in at least one quality of life domain was optimized using a KCCQ score ≤60. Taken together, the above findings suggest that different KCCQ threshold scores are required to identify clinical deficits in health status for HF patients with different comorbid conditions.

Clinically meaningful change

The second challenge that clinicians and patients face is in defining clinically meaningful KCCQ change. How much is necessary and

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Table 1 Summary of key clinical trials reporting Kansas City Cardiomyopathy Questionnaire outcomes

Author	Trial Name	Intervention	Metric	Clinical cut-off points
Kosiborod *et al.*[2]	EPHESUS	Drug: eplerenone	Quartiles (OSS)	Thresholds: ≤25, >25 to 50, >50 to 75, and >75 to 100 Improvement: >10 point change Stable/no change: > −10 to <10 points change Decline: ≤ −10 point change
Chandra *et al.*[3]	PARAGON-HF	Drug: sacubitril/valsartan or valsartan	Quartiles (OSS)	Thresholds: 59.1, 74.2, 86.5, and >86.5
Flint *et al.*[4]	CASA	Telemonitoring	Quartiles (OSS)	Thresholds: 25, 50, 60, and 75
Kosiborod *et al.*[5]	DAPA-HF	Drug: dapagliflozin	Tertiles (subscales)	Thresholds: ≤ 65.6, 65.7 to 87.5, and >87.5 Small change: ≥5 point change Moderate change: ≥10 point change Large change: ≥15 point change
Teerlink *et al.*[6]	GALACTIC-HF	Drug: omecamtiv mecarbil	Comparing mean differences (TSS)	Cut-off points not reported Higher scores indicate lower frequency and severity of symptoms
Lewis *et al.*[7]	PARADIGM-HF	Drugs: sacubitril/valsartan vs. enalapril	Repeated measures analysis (CSS and OSS)	Improvement: ≥5 point increase Stable/no change: −5 to 5 point change Decline: ≥5 point decrease
Luo *et al.*[8]	HF-ACTION	Aerobic exercise training	Cox proportional hazards models (OSS)	Improvement: ≥5 point increase Stable/no change: <5 point change Decline: ≥5 point decrease

CSS, clinical summary score; OSS, overall summary score; TSS, total symptom score.

sufficient to detect deterioration or improvement in health status? A current guideline indicates that KCCQ changes of 5, 10, and 22-point increases represent small, moderate, and large clinical improvements, respectively; while 5, 17, and 25-point decreases represent a small, moderate, and large deterioration in functioning, respectively.[10] In EPHESUS,[2] an alternative model was used where a change score of less than −10, between −10 and 10, and >10 was significantly associated with deterioration, no change, and improvement in clinical outcome, respectively. An additional model of clinically significant deterioration or improvement in the KCCQ was used in the DAPA-HF trial,[4] using 5-point increments, with the criteria for small change at ≥5 points, moderate at ≥10 points, and large at ≥15 points. More recently, the criterion for defining a clinically important difference on the KCCQ was examined in the FAIR-HF trial.[11] Improved clinical outcomes were associated with changes that were numerically less than the conventional 5-point threshold.[11] The diversity of the above-noted models for interpreting clinically meaningful change in the KCCQ is problematic because it undermines efforts to compare outcomes or generalize findings across clinical trials.

Understanding how changes in the KCCQ predict the patient's clinical outcome and overall functional status is essential for the clinical use of this instrument. In EPHESUS,[2] change in KCCQ-OSS was linearly associated with both all-cause mortality, and the combined outcome of cardiovascular death or hospitalization. The GALACTIC-HF trial[6] indicated that the incidence for a composite outcome of cardiovascular death, hospitalization, or emergency department visit due to HF was reduced for patients randomized to omecamtiv mecarbil vs. placebo. Importantly, however, these groups did not differ significantly in a pre-specified analysis of change in the KCCQ total symptom score. This finding reminds us that there may not be a direct relationship between patient-reported improvement on the KCCQ and clinical outcomes. This challenges investigators to specify key variables that moderate the KCCQ profile of perceived health status, as well as factors that mediate its association with clinical outcomes.

Change relative to baseline

The third issue for interpreting KCCQ scores arises from the interplay between reported KCCQ change and initial perceived health status. The law of initial values indicates that the potential increase in a physiologic or psychological response (e.g. KCCQ score) following a stimulus (e.g. treatment) is diminished according to the magnitude of the baseline value (ceiling effect), while the inverse (floor effect) is also true. As illustrated in the PARADIGM-HF trial,[4] change was classified as having improved or deteriorated if the KCCQ increased or decreased by ≥5 points from baseline, respectively, and a stable score was defined as being between −5 and 5 points. In the DAPA-HF trial,[5] patients were considered to have improved their health status if the KCCQ score increased by 5 points, or if it remained ≥95 points at both baseline and the 8-month outcome, due to the arithmetic limit of being able to demonstrate a meaningful increase. The DAPA-HF trial exemplifies how it is essential to consider the baseline KCCQ value when evaluating therapeutic outcomes from a treatment, but it also raises the question of how we define therapeutic outcome when the patient's initial health status is within a poor, fair, good, or excellent level. For

example, it is plausible that a KCCQ decrease of 5 points would be interpreted quite differently if the patient's baseline score was in an excellent health status category of >75 to 100 as defined by Spertus *et al.*,[10] or >87.5 as defined by Kosiborod *et al.*,[5] vs. a poor or good category.

It is notable that the developer of the KCCQ and colleagues recently published a framework for interpreting the KCCQ as a trial endpoint. Their state-of-the-art review[12] advocates using the original KCCQ guidelines where small, moderate-to-large, and large-to-very large clinical changes are defined by changes of 5, 10, and 20 points, respectively. Before this proposed framework can be used with confidence by clinicians and patients, it may be necessary to address how change scores from numerous trials (as noted above) should be clinically interpreted where different quantiles of KCCQ change were required to demonstrate a prognostic association with clinical outcomes. In addition, the linear nature of KCCQ improvement was recently questioned by findings from the HF-ACTION trial.[8] Luo *et al.*[8] reported that risk reduction for all-cause mortality and hospitalization among HF patients in a home-based cardiac rehabilitation programme was evident up to an 8-point increase on the KCCQ-OSS, but not beyond that magnitude of change.

Conclusions

The clinical trials cited in this viewpoint illustrate the need for an evidence-based framework to standardize the methods of analysis and interpretation of the KCCQ, in order to guide teams of clinicians and researchers in defining a clinically meaningful outcome. The use of the KCCQ in evaluating clinical outcomes has differed across trials according to (i) pre-defined cut-off values for categories of perceived health status,[2–5] (ii) pre-defined magnitudes of change in which either a single change score (e.g. >10 points),[2,7,8] or multiple change scores (e.g. ≥5, 10, or 15 points)[5] represent clinically meaningful increments of small, moderate or large improvement or deterioration, and (iii) a change score that is evaluated relative to the patient's starting point (e.g. a KCCQ score ≥95 which is within an excellent category of functioning).[5] Regarding the interpretation of change, it is important to determine whether it is *change* in the KCCQ score, or *position* in the top or bottom category of a KCCQ quantile, or a combination of both that is necessary and sufficient to account independently for clinical outcomes in HF. An evidence-based guideline for the analysis of the KCCQ is a priority for clinical research in order to facilitate a standardized interpretation of outcomes across trials.

In sum, we remain enthusiastic about using validated instruments such as the KCCQ to assess patient-reported health status in clinical medicine. Research on the KCCQ has provided foundational evidence in support of the use of patient-reported outcome measures to evaluate established interventions in HF. That being said, findings from recent trials underscore the need to provide patients and clinicians with an evidence-based guideline on how to best use the KCCQ to evaluate the efficacy of treatments for HF.

Conflict of interest: none declared.

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