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

Nicolette Stogios¹,²†, Gabriel Fezza¹,³†, Julia V. Wong¹, Heather J. Ross²,⁴,⁵, Michael E. Farkouh²,⁴,⁵, and Robert P. Nolan¹,²,⁵*

¹Behavioural Cardiology Research Unit, University Health Network (UHN), Toronto, ON, Canada; ²Faculty of Medicine, University of Toronto, Toronto, ON, Canada; ³Faculty of Health, York University, Toronto, ON, Canada; ⁴Ted Rogers Centre for Heart Research, University Health Network, Toronto, ON, Canada; and ⁵Peter Munk Cardiac Centre, University Health Network, Toronto, ON, Canada

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.³ These quartile ranges were used successfully in drug trials such as EPHESUS¹ 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,⁴ 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...
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. In EPESUS, 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, 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 GALACTIC-HF trial. Improved clinical outcomes were associated with changes that were numerically less than the conventional 5-point threshold. 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 EPESUS, 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 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, 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, 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., or >87.5 as defined by Kosiborod et al., 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 recently published a framework for interpreting the KCCQ as 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)3 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).3

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.

References

1. U.S. Food and Drug Administration. DDT COA #000084: Kansas City Cardiomyopathy Questionnaire (KCCQ). https://www.fda.gov/drugs/ddt-coa-000084-kansas-city-cardiomyopathy-questionnaire-kccq (24 February 2021).
2. Kosiborod M, Soto GE, Jones PG, Krumholz HM, Weintraub WS, Deedwania P, Spertus JA. Identifying heart failure patients at high risk for near-term cardiovascular events with serial health status assessments. Circulation 2007;115:1972–1981.
3. Chandra A, Vaduganathan M, Lewis EF, Claggett BL, Rizkala AR, Wang W, Lefkowitz MP, Shi VC, Anand IS, Gej J, Lam CM, Maggioni AP, Martinez F, Packner M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, Van Veldhuisen DJ, Zannad F, Zile MR, McMurray JJ. Solomon SD; PARAGON-HF Investigators. Health-related quality of life in heart failure with preserved ejection fraction: the PARAGON-HF trial. JACC Heart Fail 2019;7:862–874.
4. Flint KM, Fairclough DL, Spertus JA, Borkoam DB. Does heart failure-specific health status identify patients with bothersome symptoms, depression, anxiety, and/or poorer spiritual well-being? Eur Heart J Qual Care Clin Outcomes 2019;5:233–241.
5. Kosiborod MN, Jhund PS, Docherty KF, Diez M, Petrie MC, Verma S, Nicolau JC, Merkely B, Kitakaze M, DeMets DL, Inzucchi SE, Kaber L, Martinez FA, Ponikowski P, Sabatine MS, Solomon SD, Bengtsson O, Lindholm D, Niklasson A, Sjöstrand M, Langkilde AM, McMurray JJ. Effects of dapagliflozin on function, and quality of life in patients with heart failure and reduced ejection fraction: results from the DAPA-HF trial. Circulation 2020;141:90–99.
6. Teerlink JR, Diaz R, Felker GM, McMurray JJ, Metra M, Solomon SD, Adams KF, Anand I, Arias-Mendoza A, Biering-Sørensen T, Bohn M, Bonderman D, Cleland JG, Corbalan R, Crespo-Leiro MG, Dahlström U, Echeverria LE, Fang JC, Filippatos G, Fonseca C, Goncalvesova E, Goudev AR, Howlest JG, Lameur DE, Li J, Lund M, Macdonald P, Maree V, Momomura SI, O’Meara E, Parkhomenko A, Pankowski P, Ramires FJ, Serpytis P, Silva K, Spinjar N, Suter TM, Tomcsanyi J, Vandekerckhove H, Yinekas P, Zaiss FA, Yilmaz MB, Zannad F, Sharpsen L, Legg J, Varin C, Hornarper N, Abbasai S, Malik F, Kurze CE; GALACTIC-HF Investigators. Cardiac myosin activation with omecamtiv mecarbil in systolic heart failure. N Engl J Med 2021;384:105–116.
7. Lewis EF, Cloggett BL, McMurray JJ, Packner M, Lefkowitz MP, Rouleau JL, Liu J, Shi VC, Zile MR, Desai AS, Solomon SD, Swedberg K. Health-related quality of life outcomes in PARADIGM-HF. Circ Heart Fail 2017;10:e003430.
8. Luo N, O’Connor CM, Cooper LB, Sun JL, Coles A, Reed SD, Whellan DJ, Phu LL, Kraus WE, Mentz RJ. Relationship between changing patient-reported outcomes and subsequent clinical events in patients with chronic heart failure: insights from HF-ACTION. Eur J Heart Fail 2019;21:63–70.
9. Spertus JA, Jones PG. Development and validation of a short version of the Kansas City Cardiomyopathy Questionnaire. Circ Cardiovasc Qual Outcomes 2015;8:469–476.
10. Spertus J, Peterson E, Conrad MW, Heidenreich PA, Krumholz HM, Jones P, McCullough P, Pina I, Tooey J, Weintraub WS, Rumsfeld JS. Cardiovascular Outcomes Research Consortium. Monitoring clinical changes in patients with heart failure: a comparison of methods. Am Heart J 2005;150:707–715.
11. Butler J, Khan MS, Mori C, Filippatos GS, Ponikowski P, Comin-Colet J, Roubert B, Spertus JA, Anker SD. Minimal clinically important difference in quality of life scores for patients with heart failure and reduced ejection fraction. Eur J Heart Fail 2020;22:1009–1005.
12. Spertus JA, Jones PG, Sandhu AT, Arnold SV. Interpreting the Kansas City Cardiomyopathy Questionnaire in clinical trials and clinical care: JACC state-of-the-art review. J Am Coll Cardiol 2020;76:2379–2390.