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Health-Related Quality of Life in Comorbid Heart Failure With Reduced Ejection Fraction and Diabetes Mellitus

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Patients with heart failure with reduced ejection fraction (HFrEF) face high risks of deterioration in health status, hospitalization, or death. Diabetes mellitus (DM) is a frequent comorbidity which adds therapeutic complexity and further contributes to adverse health outlook. The Food and Drug Administration recently reinforced that therapies safely improving patient-reported outcomes, such as HRQOL, may meet standards for regulatory approval in HF(1). Despite its broad recognition as an important, patient-centered outcome, few real-world data are available tracking the expected history of HRQOL over time. We explore longitudinal changes in HRQOL among ambulatory patients with comorbid DM and HFrEF in a contemporary US registry.

From December 2015 to October 2017, across 152 US sites, CHAMP-HF enrolled 4,983 adults with chronic HFrEF(40%) receiving 1 oral HF therapy. Key exclusion criteria included enrollment in an interventional study, planned or history of heart transplantation,

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left ventricular assist system, or dialysis, hospice care, or life expectancy < 1-year. We further excluded patients who were missing all demographic data (n=13). Follow-up was available through October 2018.

The 12-item Kansas City Cardiomyopathy Questionnaire Short Form (KCCQ) is a validated multi-domain HF-specific tool with scores ranging from 0 (worst) to 100 (best). The EuroQol-5 Dimension (EQ-5D) is a standardized generic instrument that is summarized as a single index (0 [dead] to 1 [best health]) across 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

Among patients alive with paired baseline and 12-month KCCQ and/or EQ5D scores (n=3,093), we assessed the association between DM and HRQOL using linear regression models, adjusted for baseline HRQOL and 11 pre-specified covariates (age, sex, current smoking, chronic obstructive pulmonary disease, EF, systolic blood pressure, body mass index, serum creatinine, first diagnosis of HF < 18 months, β -blocker, and angiotensin-converting enzyme inhibitor or angiotensin receptor blocker). Participation required written informed consent. The study was approved by site institutional review boards or ethics committees.

Of 4,970 CHAMP-HF participants analyzed, 2,085 (42%) had a history of DM. Patients with DM were older (68 [60–75] vs. 67 [57–76] years), less likely to be white (70.4% vs. 75.8%) or have private insurance (23.6% vs. 27.4%), and more frequently had cardiovascular comorbidities and histories of HF hospitalization within 12 months (40.6% vs. 36%); all $P < 0.02$.

Compared with those without DM, patients with DM had lower baseline KCCQ-OS (61.7 ± 24.1 vs. 66.4 ± 23.2; $P < 0.001$) and EQ-5D scores (0.78 ± 0.16 vs. 0.82 ± 0.15; $P < 0.001$). Absolute differences across KCCQ domains ranged from ~3 to 6 (quality of life 3.2; social limitations 4.4; symptom frequency 5.1; physical limitations 6.2); $P < 0.001$ for all. After accounting for covariates, patients with DM had 2.8 (95% CI 1.2–4.4, $P < 0.001$) lower adjusted KCCQ-OS scores.

Over 12-months, patients with DM (62.9 ± 23.4 to 69.0 ± 22.4; difference +6.1 ± 21.0) and without DM (67.7 ± 22.6 to 73.3 ± 21.8; difference +5.7 ± 19.7) experienced longitudinal improvements KCCQ-OS scores; most increases were observed within 3-months (Figure). Similarly, EQ5D scores increased in patients with DM (0.79 ± 0.16 to 0.80 ± 0.16; difference 0.01 ± 0.16) and without DM (0.82 ± 0.14 to 0.83 ± 0.16; difference 0.01 ± 0.14). Irrespective of DM status, 49%, 37%, and 20% experienced longitudinal increases in KCCQ-OS by 5, 10, and 20 points, respectively. At 12-months, differences in adjusted KCCQ-OS scores persisted between patients with and without DM: difference 2.4 (95% CI 0.9–3.9, $P = 0.001$).

Patients with comorbid DM have worse HRQOL throughout their longitudinal experience as ascertained across key domains of 2 validated questionnaires. Regardless of DM status, half of patients experience clinically meaningful 5-point improvements in KCCQ-OS by 1-year, despite CHAMP-HF being a non-interventional study with limited changes to dosing of guideline-directed medical therapies (2). This finding may reflect favorable perceptions of health under study observation (Hawthorne effect), selective retention of a healthier cohort

(as patients with worse HRQOL may be more likely to die), and/or regression to the mean (due to a tendency of worse health status at study enrollment). These short-term improvements, coupled with wide confidence intervals and variation in trajectories of patient-reported outcomes, may explain seemingly modest *average* between-arm treatment effects on KCCQ with effective recent HF_rEF therapies: dapagliflozin (+2.8 in KCCQ total symptoms score over 8-months)(3) and sacubitril/valsartan (+1.3 in KCCQ-OS over 8-months)(4). In the evaluation of HRQOL changes in a HF trial, statistical approaches such as the win-ratio should be used to account for competing risks of death. These CHAMP-HF data corroborate the broad health consequences of DM adversely impacting patient experience and inform designs of studies employing HRQOL as an endpoint.

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DISCLOSURES

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ABBREVIATIONS

DM	Diabetes mellitus
EQ-5D	European Quality of Life Five Dimension
HF_rEF	Heart failure with reduced ejection fraction
HRQOL	Health-related quality of life
KCCQ	Kansas City Cardiomyopathy Questionnaire

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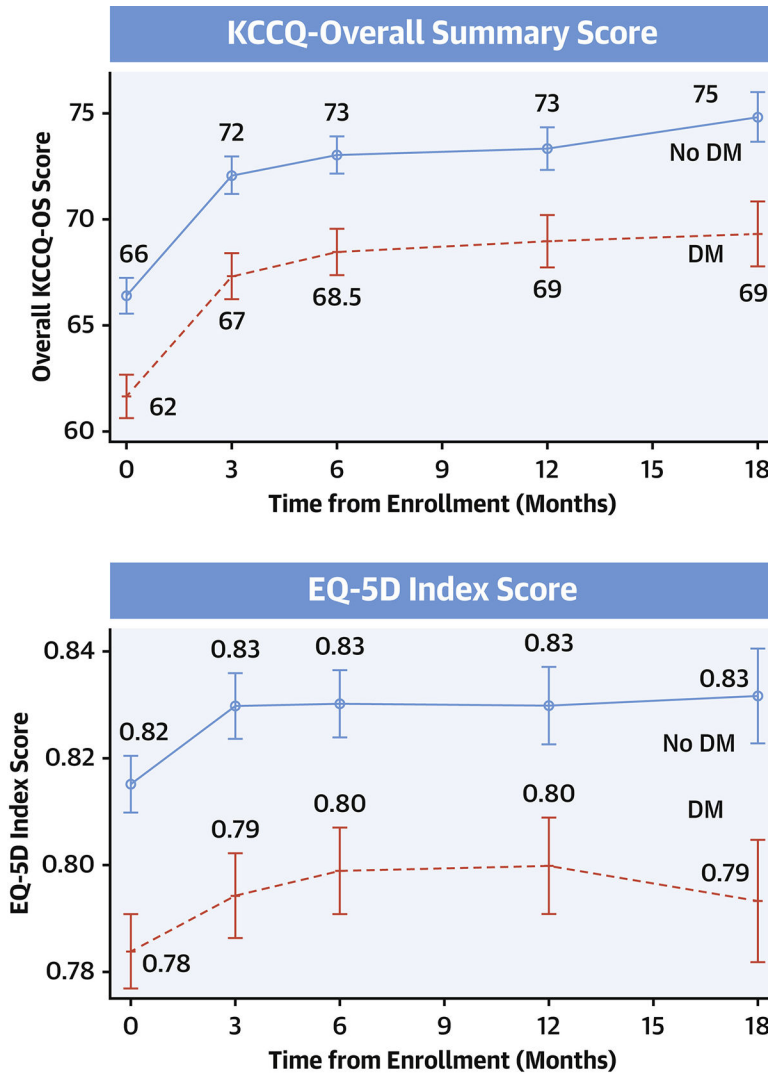


Figure 1. Measures of Health-Related Quality of Life at Baseline and Through 18 Months in Chronic Heart Failure with Reduced Ejection Fraction by Diabetes Mellitus (DM) Status
 The Kansas City Cardiomyopathy Questionnaire (KCCQ) interrogates heart failure symptoms, physical and social limitations, and quality of life, which is summarized as the KCCQ overall summary score (KCCQ-OS). KCCQ scores range from 0 (worst) to 100 (best) health status with a difference of 5-points considered clinically meaningful. EuroQol-5 Dimension (EQ-5D) is summarized as a single index (0 [dead] to 1 [best health]) across 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Patients with comorbid DM have worse health-related quality of life, determined by these 2 validated questionnaires, at baseline and through 18 months follow-up.