ESC European Society of Cardiology

European Journal of Heart Failure (2024)
doi:10.1002/ejhf.3263

RESEARCH ARTICLE

Dapagliflozin and quality of life measured using the EuroQol 5-dimension questionnaire in patients with heart failure with reduced and mildly reduced/preserved ejection fraction

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Received 29 January 2024; revised 13 March 2024; accepted 13 April 2024

Aims

Although much is known about the usefulness of heart failure (HF)-specific instruments for assessing patient well-being, less is known about the value of generic instruments for the measurement of health-related quality of life (HRQL) in HF. The aim of this study was to assess the relationship between the EuroQol 5-dimension 5-level (EQ-5D-5L) visual analogue scale (VAS) and index scores, clinical characteristics, and outcomes in patients with HF and the effect of dapagliflozin on these scores.

Methods and results

We performed a patient-level pooled analysis of the DAPA-HF and DELIVER trials, which investigated the effectiveness and safety of dapagliflozin in patients with HF and reduced ejection fraction (HFrEF) and mildly reduced/preserved ejection fraction (HFmrEF/HFpEF), respectively. Patients reporting higher (better) EQ-5D-5L VAS and index scores had a lower prevalence of comorbidities, including atrial fibrillation and hypertension, than patients with a worse score. They were also more likely to have better investigator-reported (New York Heart Association class) and patient-self-reported (Kansas City Cardiomyopathy Questionnaire) health status and lower median N-terminal pro-B-type natriuretic peptide levels. Compared to patients with the lowest scores (Q1), those with higher EQ-5D-5L VAS scores had better outcomes: the hazard ratio for the composite of cardiovascular death or worsening HF was 0.81 (95% confidence interval 0.72–0.91) in Q2, 0.74 (0.65–0.84) in Q3, and 0.62 (0.54–0.72) in Q4. The risk of each component of the composite outcome, and all-cause death, was also lower in patients with better scores. Similar findings were observed for the index score. Treatment with dapagliflozin improved both EQ-5D-5L VAS and index scores across the range of ejection fraction.

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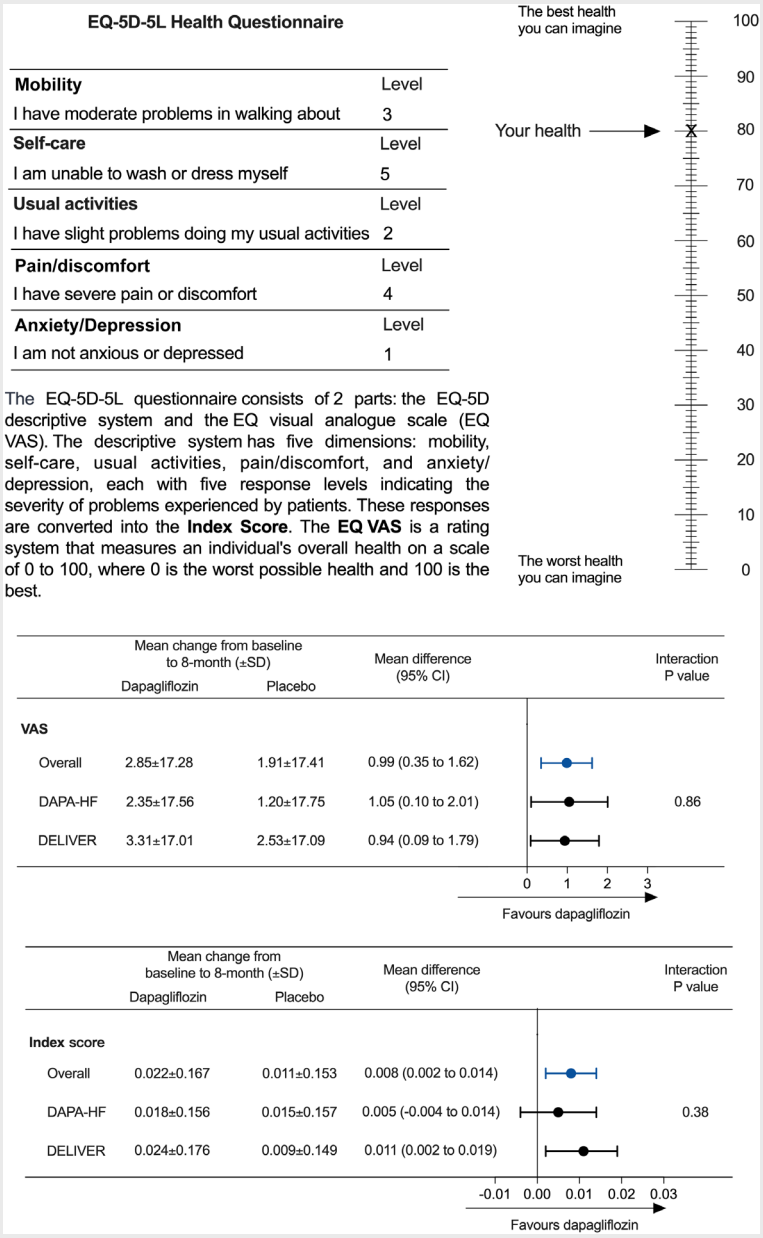
Conclusions Both higher (better) EQ-5D-5L VAS and index scores were associated with better outcomes. Dapagliflozin treatment improved EQ-5D-5L VAS and index scores, irrespective of ejection fraction.

Graphical Abstract



Heath status measured using the EuroQol 5-dimension 5-level (EQ-5D-5L) questionnaire in patients with heart failure with reduced and mildly reduced/preserved ejection fraction. An analysis of covariance (ANCOVA) adjusted for baseline value was performed to test for the treatment effect. CI, confidence interval; SD, standard deviation; VAS, visual analogue scale.

Keywords Quality of life • EQ-5D index • Visual analogue scale • Dapagliflozin • Heart failure • Symptoms

Introduction

The instrument most used to assess the impact of heart failure (HF) on patient well-being in contemporary studies is the Kansas City Cardiomyopathy Questionnaire (KCCQ), both versions of which focus on disease-specific symptoms (e.g. shortness of breath, fatigue, or ankle swelling) and the impact of these on everyday activities.[1–7] Although a couple of questions address psychological well-being, these are also focused on HF (e.g. 'Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of your heart failure?').[1] However, patients with HF, especially those with preserved ejection fraction (HFpEF), often have comorbidities that may also affect their health status, and a more generic health-related quality of life (HRQL) instrument may provide additional information on overall patient well-being than obtained using the disease-specific KCCQ.[8–11] A more generic instrument may also integrate any benefits accruing from the ancillary effects of HF therapies on associated comorbidities such as anaemia and iron deficiency, diabetes (and requirement for glucose-lowering therapies), kidney dysfunction, and obesity.[2–5,12,13] Generic HRQL instruments also allow comparison of the impact of different diseases on patients and even allow comparison of the effect of a specific treatment across disease states, e.g. a sodium–glucose cotransporter 2 inhibitor (SGLT2i) in HF and chronic kidney disease.

The EuroQol 5-dimension (EQ-5D) questionnaire is the most widely utilized generic HRQL instrument.[14–16] There are two versions of the EQ-5D, the 3-level EQ-5D (EQ-5D-3L) and the 5-level EQ-5D (EQ-5D-5L).[17] The EQ-5D-5L was introduced in 2009 to improve the performance of the EQ-5D-3L, addressing issues such as ceiling and floor effects, and increasing instrument sensitivity.[17–22] The EQ-5D-5L instrument consists of the EQ visual analogue scale (EQ VAS) and the EQ-5D descriptive system. The EQ VAS is a rating system ('thermometer') that provides a single score representing an individual's self-perceived health status on a scale of 0 to 100, where 0 is the worst possible health and 100 is the best. The descriptive system addresses multiple dimensions such as mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, providing a comprehensive evaluation of the impact of medical conditions.[23] These five dimensions are incorporated into the EQ-5D index score, a single numerical value.[24–26]

In the US CHAMP-HF registry of patients diagnosed with HF with reduced ejection fraction (HFrEF), the median VAS score was 62 (50–80), while the median index score was 0.82 (0.73–0.88).[14] In the Swedish HF Registry, which included 3495 patients spanning the full spectrum of left ventricular ejection fraction (LVEF), the median index score was 0.88 (0.34–0.97).[27] In the Alberta Heart Study conducted in Canada, the median VAS score among patients with HFrEF was 70 (50–80), with a comparable median VAS score of 70 (55–80) observed in patients with HFpEF.[28] A moderate-to-strong correlation has been demonstrated between EQ-5D scores and disease-specific measures such as the Minnesota Living with Heart Failure Questionnaire (MLHFQ) and the KCCQ in individuals with HF.[14,29] Previous studies have shown that SGLT2i improve New York Heart Association (NYHA) functional class and KCCQ in patients with HF but their effects on general HRQL have not been reported.[2–5] Therefore, in the present analysis, we aimed to evaluate the effect of dapagliflozin on these scores, along with the value of the VAS and index scores in predicting outcomes in patients with HF, across the range of LVEF. The analysis of the effect of dapagliflozin on the EQ-5D-5L was an exploratory endpoint in both DAPA-HF and DELIVER.

Methods

Trials and patients

For the present analyses, we pooled individual patient-level data from DAPA-HF (NCT03036124) and DELIVER (NCT03619213). The design, baseline characteristics, and outcomes of these trials have been reported previously.[2,3,30–33] Briefly, in DAPA-HF 4744 patients with HF in NYHA functional class II–IV, with LVEF ≤40% (HFrEF) and elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) were randomized to receive the SGLT2i dapagliflozin or placebo. Participants were required to receive guideline-recommended treatments. DELIVER compared dapagliflozin with placebo in 6263 ambulatory and hospitalized patients in NYHA functional class II–IV, with LVEF >40% (HF with mildly reduced ejection fraction [HFmrEF]/HFpEF) and elevated NT-proBNP. Participants were required to have evidence of structural heart disease (i.e. left ventricular hypertrophy or left atrial enlargement). The two trials shared the most key exclusion criteria including a history of type 1 diabetes, symptomatic hypotension or a systolic blood pressure (SBP) <95 mmHg. However, the threshold for estimated glomerular filtration rate was lower in DELIVER (25 ml/min/1.73 m^2 vs. 30 ml/min/1.73 m^2 in DAPA-HF). Both trials were approved by institutional review boards or ethics committees at individual study sites and written informed consent was provided by all patients.

EuroQol 5-dimension questionnaire

In both of the trials, EQ-5D was used to measure the general quality of life in patients with HFrEF and HFmrEF/HFpEF. This questionnaire has two sections: a 5-level 5-dimensional (EQ-5D-5L) descriptive section defining health status, and a VAS index value section capturing a self-rating of health status (*Graphical Abstract*). The 5 dimensions of the descriptive section consist of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension can then be further divided into 5 levels (1–5), i.e. no problem, slight problem, moderate problem, severe problem, and extreme problem. Based on their self-reported answers, a health state can be defined by a 5-digit number that combines the severity levels from each of the 5 dimensions, where '11111' represents no problems in any dimension and '55555' means extreme problems in all dimensions. An example of an EQ-5D-5L health state is shown in the *Graphical Abstract*. There are a total of $5^5 = 3125$ possible health states in EQ-5D-5L, and each state can be converted into a single summary index (the EQ-5D index score) by applying scores from a national valuation set generated from a population-based preference survey that represents its relative societal preference. The EQ-5D index score is a quantifiable metric ranging between 0 and 1, with 1 denoting optimal health and 0 signifying a health state comparable to death. Additionally, negative values may be assigned to health states deemed more undesirable than being deceased.[24] Given there is no published value set yet for some countries, we used the directly measured Uruguay EQ-5D-5L value set for Argentina and Brazil; the Polish value set for Bulgaria, Czech

Republic and Slovakia; and the UK value set for Saudi Arabia to estimate EQ-5D-5L index values. The EQ-5D-5L index of Russia was estimated using a newly developed Russian EQ-5D-3L value set together with the EuroQol Group cross-over methodology.[24,34]

The EQ-VAS component of the EQ-5D-5L is a quantitative measure ranging from 0 to 100, with 0 being the worst imaginable health state and 100 being the best. All questionnaires were self-administered under the supervision of the clinician at baseline, as well as after 8 months of follow-up. In this analysis, we analysed the effects of dapagliflozin versus placebo on the change in EQ-5D-5L VAS and index scores from baseline to 8 months.

The study incorporated all available data collected at the baseline and 8-month time points without performing any imputation for missing values.

Clinical outcomes

The primary outcome for both trials was the composite of worsening HF or cardiovascular (CV) death, examined as a time-to-first event. In the present study, we analysed this composite as well as its components. We also analysed the occurrence of death from any cause. All the outcomes were adjudicated by endpoint committees as indicated in the original trial reports.

Statistical analysis

In this analysis, baseline characteristics are reported for each EQ VAS category, and index score category, as means ± standard deviation (SD), median with interquartile range (IQR) and frequencies with proportions, as appropriate. The Jonckheere–Terpstra test was used to test for trends across groups for continuous variables, the Cochran–Armitage test for binary variables, and the Cochran–Mantel–Haenszel test for categorical variables, respectively. Baseline VAS and index scores between HFrEF and HFmrEF/HFpEF were compared by two-sample Student's *t*-test or Mann–Whitney U test.

The incidence of each outcome is reported as a rate per 100 patient-years of follow-up. The time-to-first occurrence of each endpoint was evaluated using Kaplan–Meier estimates and Cox proportional-hazards models, stratified according to diabetes mellitus status and trial and adjusted for treatment assignment and history of HF hospitalization (except in the analysis of all-cause death), and hazard ratios (HRs) with 95% confidence intervals (CIs) were reported. In addition, we also report the HR from models with further adjustment for geographical region, age, sex, heart rate, SBP, body mass index (BMI), NYHA functional class, LVEF, estimated glomerular filtration rate, log-transformed NT-proBNP, atrial fibrillation, history of myocardial infarction, and stroke.

The associations between the VAS score, as a continuous variable, adjusted for treatment and history of HF hospitalization (apart from all-cause death) with stratification by diabetes status and trial, and the risk of each major clinical outcome was modelled using restricted cubic splines with median population VAS as reference. The five knots were placed at default positions according to percentiles of the VAS score (5, 27.5, 50, 72.5, and 95 centiles). This was repeated with the additional adjustments with the variables listed above. The incidence rates of individual and composite time-to-first outcomes across the spectrum of VAS scores were examined utilizing a Poisson regression model with restricted cubic splines also employing five knots. The effect of randomized treatment compared with placebo on each of the time to first event endpoints across baseline VAS score as a continuous variable was modelled flexibly using restricted cubic splines with three knots (at 10th, 50th, and 90th percentile). A model with five knots was unstable and a model with three knots was stable with the lowest Akaike information criterion value. We also adjusted for baseline VAS score, history of HF hospitalization (apart from all-cause death) and diabetes status. These analyses were also conducted for the index score.

All analyses were conducted using Stata/SE version 17.0 (Stata Corp, College Station, TX, USA) and SAS version 9.4 (SAS Institute, Cary, NC, USA). A significance level of 0.05 was considered to be statistically significant. Utility index score was calculated using the eq5d package of R version 4.1.3.

Results

Of the 11 007 patients randomized in DAPA-HF and DELIVER, 9947 (90.4%) had a baseline VAS score and 10 135 (92.1%) a baseline index score. The corresponding numbers at 8 months

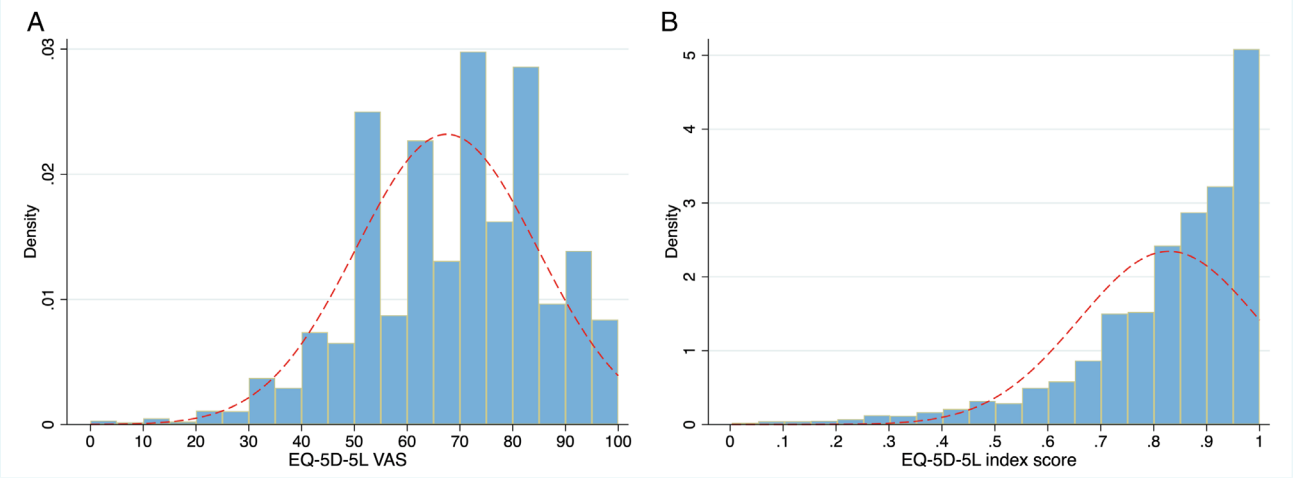


Figure 1 Distribution of the EuroQol 5-dimension 5-level visual analogue scale (EQ-5D-5L VAS) (*A*) and index score (*B*).

Table 1 Baseline characteristics according to quartile of EuroQol 5-dimension 5-level visual analogue scale score at baseline

Patient characteristics at baseline	Quartile 1 (very low: 0–55)	Quartile 2 (low: 56–70)	Quartile 3 (moderate: 71–80)	Quartile 4 (high: 81–100)	*p*-value
n (%)	2536 (25.5)	3069 (30.9)	2324 (23.4)	2018 (20.3)	
Demographic characteristics					
Age, years	69.5 ± 10.0	69.1 ± 10.5	69.4 ± 10.2	68.8 ± 10.7	0.277
Sex					<0.001
Female	973 (38.4)	1026 (33.4)	728 (31.3)	587 (29.1)	
Male	1563 (61.6)	2043 (66.6)	1596 (68.7)	1431 (70.9)	
Region					<0.001
North America	320 (12.6)	352 (11.5)	346 (14.9)	415 (20.6)	
Latin America	425 (16.8)	593 (19.3)	461 (19.8)	357 (17.7)	
Western Europe	234 (9.2)	305 (9.9)	257 (11.1)	181 (9.0)	
Eastern Europe[a]	1248 (49.2)	1206 (39.3)	674 (29.0)	474 (23.5)	
Asia/Pacific and other	309 (12.2)	613 (20.0)	586 (25.2)	591 (29.3)	
Race					<0.001
White	2060 (81.2)	2255 (73.5)	1553 (66.8)	1247 (61.8)	
Black	91 (3.6)	88 (2.9)	81 (3.5)	88 (4.4)	
Asian	308 (12.1)	596 (19.4)	581 (25.0)	595 (29.5)	
Other	77 (3.0)	130 (4.2)	109 (4.7)	88 (4.4)	
SBP, mmHg	125.6 ± 15.8	125.5 ± 15.9	125.7 ± 16.1	124.4 ± 16.2	0.008
SBP category					0.001
<110	418 (16.5)	546 (17.8)	396 (17.0)	394 (19.5)	
110–119	464 (18.3)	520 (16.9)	468 (20.1)	413 (20.5)	
120–129	642 (25.3)	768 (25.0)	553 (23.8)	487 (24.1)	
130–139	556 (21.9)	695 (22.6)	465 (20.0)	374 (18.5)	
≥140	456 (18.0)	540 (17.6)	442 (19.0)	350 (17.3)	
DBP, mmHg	74.3 ± 10.1	74.1 ± 10.2	73.6 ± 10.6	73.4 ± 10.7	<0.001
PP, mmHg	51.3 ± 13.3	51.5 ± 13.4	52.1 ± 13.7	51.1 ± 13.8	0.715
MAP, mmHg	91.4 ± 10.6	91.2 ± 10.6	90.9 ± 10.9	90.4 ± 11.0	<0.001
HR, bpm	72.3 ± 11.7	71.4 ± 11.3	70.9 ± 12.0	70.7 ± 11.5	<0.001
BMI, kg/m^2	29.4 (25.1–33.8)	28.4 (25.0–32.8)	28.0 (24.9–32.0)	27.9 (24.0–32.0)	<0.001
BMI category					<0.001
<18.5	28 (1.1)	39 (1.3)	19 (0.8)	21 (1.0)	
18.5–25.0	510 (20.1)	686 (22.4)	568 (24.5)	549 (27.2)	
25.0–30	798 (31.5)	1084 (35.3)	861 (37.1)	710 (35.2)	
≥30.0	1197 (47.3)	1260 (41.1)	875 (37.7)	736 (36.5)	
Comorbidities and smoking					
Atrial fibrillation (history)	1311 (51.7)	1487 (48.5)	1086 (46.7)	909 (45.0)	<0.001
Hypertension	2198 (86.7)	2544 (82.9)	1885 (81.1)	1593 (78.9)	<0.001
CHD[b]	1512 (59.6)	1795 (58.5)	1321 (56.8)	1090 (54.0)	<0.001
Angina pectoris[c]	736 (29.0)	780 (25.4)	493 (21.2)	389 (19.3)	<0.001
MI	926 (36.5)	1054 (34.3)	778 (33.5)	654 (32.4)	0.003
Prior PCI/CABG	971 (38.3)	1170 (38.1)	912 (39.2)	765 (37.9)	0.951
PCI	805 (31.7)	924 (30.1)	725 (31.2)	601 (29.8)	0.288
CABG	362 (14.3)	454 (14.8)	316 (13.6)	297 (14.7)	0.971
Cerebrovascular disease					
Stroke	287 (11.3)	297 (9.7)	187 (8.0)	175 (8.7)	<0.001
Prior TIA	84 (3.3)	107 (3.5)	63 (2.7)	65 (3.2)	0.470
Non-cardiovascular systems					
COPD/asthma	482 (19.0)	475 (15.5)	293 (12.6)	281 (13.9)	<0.001
Diabetes mellitus	1185 (46.7)	1337 (43.6)	933 (40.1)	823 (40.8)	<0.001
Anaemia[c,d]	310 (29.2)	371 (26.1)	251 (26.3)	252 (27.4)	0.416
Current smoker	285 (11.2)	351 (11.4)	224 (9.6)	244 (12.1)	0.939

Table 1 (Continued)

Patient characteristics at baseline	Quartile 1 (very low: 0–55)	Quartile 2 (low: 56–70)	Quartile 3 (moderate: 71–80)	Quartile 4 (high: 81–100)	*p*-value
HF characteristics and investigations					
Ischaemic aetiology[e]	1426 (56.2)	1665 (54.3)	1243 (53.5)	1011 (50.1)	<0.001
Time since HF diagnosis					0.004
≤1 year	651 (25.7)	844 (27.5)	714 (30.7)	580 (28.8)	
>1–5 years	1004 (39.6)	1211 (39.5)	899 (38.7)	798 (39.6)	
>5 years	881 (34.7)	1013 (33.0)	711 (30.6)	636 (31.6)	
Previous hospitalization for HF	1212 (47.8)	1330 (43.3)	1012 (43.5)	847 (42.0)	<0.001
NYHA class III/IV	1080 (42.6)	915 (29.8)	485 (20.9)	320 (15.9)	<0.001
KCCQ clinical summary score	56.2 (41.7–70.8)	69.0 (54.9–81.9)	79.2 (64.6–90.3)	86.8 (75.0–95.8)	<0.001
KCCQ total symptom score	53.3 (39.6–66.9)	66.2 (52.9–78.8)	76.2 (62.5–87.5)	85.0 (74.0–93.3)	<0.001
KCCQ overall summary score	58.3 (41.7–75.0)	70.8 (56.2–85.4)	81.2 (66.7–93.8)	89.6 (77.1–100.0)	<0.001
EQ-5D-5L: mobility					<0.001
No problem	427 (16.8)	924 (30.1)	1108 (47.7)	1223 (60.6)	
Slight problem	639 (25.2)	1104 (36.0)	727 (31.3)	530 (26.3)	
Moderate problem	976 (38.5)	824 (26.8)	398 (17.1)	218 (10.8)	
Severe problem	473 (18.7)	203 (6.6)	81 (3.5)	42 (2.1)	
Unable to do	21 (0.8)	14 (0.5)	10 (0.4)	5 (0.2)	
EQ-5D-5L: self-care					<0.001
No problem	1179 (46.5)	1958 (63.8)	1780 (76.6)	1780 (88.2)	
Slight problem	700 (27.6)	743 (24.2)	402 (17.3)	173 (8.6)	
Moderate problem	515 (20.3)	318 (10.4)	116 (5.0)	50 (2.5)	
Severe problem	121 (4.8)	40 (1.3)	19 (0.8)	10 (0.5)	
Unable to do	21 (0.8)	10 (0.3)	7 (0.3)	5 (0.2)	
EQ-5D-5L: usual activities					<0.001
No problem	482 (19.0)	984 (32.1)	1136 (48.9)	1362 (67.5)	
Slight problem	740 (29.2)	1202 (39.2)	847 (36.4)	492 (24.4)	
Moderate problem	922 (36.4)	726 (23.7)	281 (12.1)	131 (6.5)	
Severe problem	336 (13.2)	135 (4.4)	48 (2.1)	23 (1.1)	
Unable to do	56 (2.2)	22 (0.7)	12 (0.5)	10 (0.5)	
EQ-5D-5L: pain/discomfort					<0.001
No	642 (25.3)	1233 (40.2)	1291 (55.6)	1368 (67.8)	
Slight	840 (33.1)	1155 (37.6)	728 (31.3)	488 (24.2)	
Moderate	813 (32.1)	570 (18.6)	262 (11.3)	133 (6.6)	
Severe	213 (8.4)	98 (3.2)	40 (1.7)	24 (1.2)	
Extreme	28 (1.1)	13 (0.4)	3 (0.1)	5 (0.2)	
EQ-5D-5L: anxiety/depression					<0.001
No	897 (35.4)	1675 (54.6)	1558 (67.0)	1571 (77.8)	
Slight	833 (32.8)	933 (30.4)	566 (24.4)	334 (16.6)	
Moderate	603 (23.8)	398 (13.0)	170 (7.3)	92 (4.6)	
Severe	166 (6.5)	49 (1.6)	25 (1.1)	19 (0.9)	
Extreme	37 (1.5)	14 (0.5)	5 (0.2)	2 (0.1)	
ECG findings and NT-proBNP					
Atrial fibrillation/flutter	943 (37.2)	1072 (35.0)	770 (33.1)	624 (31.0)	<0.001
Paced rhythm	245 (9.7)	282 (9.2)	213 (9.2)	182 (9.0)	0.472
NT-proBNP, pg/ml	1318.0 (761.0–2605.2)	1197.5 (719.0–2128.0)	1137.7 (671.4–1956.5)	1084.0 (686.5–1851.8)	<0.001
Atrial fibrillation/flutter[f]	1669 (1073–2921)	1559 (1014–2517)	1460 (1014–2309)	1448 (1028–2262)	<0.001
No atrial fibrillation/flutter[f]	1074 (606–2309)	992 (582–1855)	931 (536–1713)	908 (563–1554)	<0.001
LVEF and other laboratory investigations					
LVEF, %	43.9 ± 13.4	43.6 ± 13.9	44.7 ± 14.2	43.6 ± 14.1	0.791
Haemoglobin, g/L[d]	135.0 (124.0–145.0)	137.0 (126.0–148.0)	137.0 (126.0–147.0)	137.0 (126.0–146.0)	0.204
Creatinine, μmol/L	100.0 (83.0–122.0)	97.2 (82.0–119.0)	97.2 (81.3–117.6)	97.2 (81.3–118.0)	0.001
eGFR, ml/min/1.73 m^2	60.0 (46.0–75.0)	63.0 (48.0–77.0)	63.0 (49.0–78.0)	63.0 (50.0–79.0)	<0.001
eGFR <60 ml/min/1.73 m^2	1253 (49.4)	1373 (44.7)	1016 (43.7)	853 (42.3)	<0.001

Table 1 (Continued)

Patient characteristics at baseline	Quartile 1 (very low: 0–55)	Quartile 2 (low: 56–70)	Quartile 3 (moderate: 71–80)	Quartile 4 (high: 81–100)	*p*-value
Medication and other interventions					
Diuretics	2466 (97.2)	2955 (96.3)	2225 (95.7)	1909 (94.6)	<0.001
Loop	2072 (81.7)	2455 (80.0)	1780 (76.6)	1503 (74.5)	<0.001
Thiazides	283 (11.2)	333 (10.9)	249 (10.7)	196 (9.7)	0.131
Digitalis	248 (9.8)	353 (11.5)	256 (11.0)	217 (10.8)	0.160
Beta-blocker	2288 (90.2)	2728 (88.9)	2076 (89.3)	1751 (86.8)	0.001
MRA	1445 (57.0)	1718 (56.0)	1247 (53.7)	1074 (53.2)	0.003
ACEI/ARB/ARNI	2158 (85.1)	2615 (85.2)	1970 (84.8)	1663 (82.4)	0.016
CCB	571 (22.5)	619 (20.2)	524 (22.5)	431 (21.4)	0.827
Nitrates	335 (13.2)	409 (13.3)	293 (12.6)	293 (14.5)	0.370
Statins	1666 (65.7)	1981 (64.5)	1551 (66.7)	1331 (66.0)	0.467
Antiarrhythmics	280 (11.0)	342 (11.1)	254 (10.9)	212 (10.5)	0.544
Antiplatelet	1179 (46.5)	1437 (46.8)	1122 (48.3)	988 (49.0)	0.056
Anticoagulant	1293 (51.0)	1500 (48.9)	1141 (49.1)	958 (47.5)	0.029
Insulin in patients with diabetes	383 (32.3)	369 (27.6)	270 (28.9)	203 (24.7)	<0.001
Pacemaker	332 (13.1)	360 (11.7)	279 (12.0)	262 (13.0)	0.932
ICD[g]	330 (13.0)	395 (12.9)	302 (13.0)	309 (15.3)	0.036
CRT-P or CRT-D	107 (4.2)	133 (4.3)	102 (4.4)	86 (4.3)	0.909

Data are presented as mean ± standard deviation, median (interquartile range) for continuous measures, and *n* (%) for categorical measures.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; CABG, coronary artery bypass grafting; CCB, calcium-channel blocker; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P, cardiac resynchronization therapy with pacemaker; DBP, diastolic blood pressure; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; EQ-5D-5L, EuroQol 5-dimension 5-level questionnaire; HF, heart failure; HR, heart rate; ICD, implantable cardioverter defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; PCI, percutaneous coronary intervention; PP, pulse pressure; TIA, transient ischaemic attack.
[a]Including Central Europe and Russia.
[b]CHD: angina, MI, PCI, CABG, ischaemic aetiology.
[c]Haemoglobin <130 g/L for males and 120 g/L for females.
[d]Only DAPA-HF.
[e]In DELIVER, ischaemic aetiology: any of angina, coronary artery stenosis, MI, PCI, CABG.
[f]Based on ECG.
[g]Including CRT-D.

were 8468 (76.9%) and 8468 (76.9%), respectively (online supplementary *Table S1*), and the distribution of these two scores is shown in *Figure 1* (and by HF phenotype in online supplementary *Tables S2* and *S3*). The VAS was broadly similar between men and women across the health states (online supplementary *Tables S2* and *S3*).

The median baseline VAS and index scores for patients with HFrEF and HFmrEF/HFpEF were 70 (57–80) and 70 (54–80) ($p = 0.014$), and 0.88 (0.77–0.95) and 0.87 (0.74–0.95) ($p < 0.001$), respectively (mean baseline VAS score and index scores for HFrEF and HFmrEF/HFpEF were 68.1 ± 17.4 and 67.1 ± 17.1, $p = 0.005$, and 0.84 ± 0.17 and 0.81 ± 0.19, $p < 0.001$, respectively).

Patient characteristics

Patient characteristics according to the visual analogue scale score

Demographic characteristics, physiological measurements, and comorbidities

Baseline characteristics according to the VAS score, divided by quartile, are presented in *Table 1*. Compared with patients with lower (worse) VAS scores, those with higher (better) scores were more often male, less likely to be White, had less chronic kidney disease, and had a lower BMI and a slower heart rate. Those with higher scores were also less likely to have a history of atrial fibrillation, hypertension, and coronary heart disease. Age did not differ significantly by VAS score.

Heart failure characteristics and treatments

Patients with higher (better) VAS scores were less likely to have an ischaemic aetiology, had shorter-duration HF, a lower rate of prior HF hospitalization, and lower NT-proBNP levels. Both physician (NYHA functional class) and patient-reported (KCCQ summary scores) assessments of HF were better in those with higher VAS scores. LVEF did not differ significantly by VAS score.

Patient characteristics according to the EuroQol 5-dimension index score

Demographic characteristics, physiological measurements, and comorbidities

Baseline characteristics according to the EQ-5D index score, divided by quartile, are presented in online supplementary *Table S4*.

Table 2 Clinical outcomes according to quartile of EuroQol 5-dimension 5-level visual analogue scale score at baseline

Clinical outcomes	Quartile 1 (very low: 0–55)	Quartile 2 (low: 56–70)	Quartile 3 (moderate: 71–80)	Quartile 4 (high: 81–100)
n (%)	2536 (25.5)	3069 (30.9)	2324 (23.4)	2018 (20.3)
CV death or worsening HF				
n (%)	576 (22.7)	556 (18.1)	381 (16.4)	278 (13.8)
Rate per 100 patient-years (95% CI)	13.06 (12.04–14.18)	10.42 (9.59–11.33)	9.28 (8.39–10.26)	7.89 (7.02–8.88)
Unadjusted HR (95% CI)[a]	Ref.	0.81 (0.72–0.91)	0.74 (0.65–0.84)	0.62 (0.54–0.72)
Additional adjusted HR (95% CI)[b]	Ref.	0.92 (0.82–1.04)	0.87 (0.76–1.00)	0.77 (0.66–0.89)
Worsening HF event				
n (%)	388 (15.3)	374 (12.2)	270 (11.6)	192 (9.5)
Rate per 100 patient-years (95% CI)	8.80 (7.97–9.72)	7.01 (6.34–7.56)	6.58 (5.84–7.41)	5.45 (4.73–6.28)
Unadjusted HR (95% CI)[a]	Ref.	0.81 (0.71–0.94)	0.78 (0.67–0.91)	0.65 (0.54–0.77)
Additional adjusted HR (95% CI)[b]	Ref.	0.92 (0.79–1.06)	0.89 (0.76–1.04)	0.76 (0.64–0.92)
CV death				
n (%)	300 (11.8)	287 (9.4)	176 (7.6)	129 (6.4)
Rate per 100 patient-years (95% CI)	6.23 (5.56–6.97)	5.05 (4.50–5.67)	4.04 (3.49–4.68)	3.49 (2.94–4.15)
Unadjusted HR (95% CI)[a]	Ref.	0.80 (0.68–0.95)	0.67 (0.56–0.81)	0.57 (0.46–0.70)
Additional adjusted HR (95% CI)[b]	Ref.	0.96 (0.82–1.14)	0.88 (0.73–1.07)	0.80 (0.64–0.99)
All-cause death				
n (%)	474 (18.7)	467 (15.2)	282 (12.1)	220 (10.9)
Rate per 100 patient-years (95% CI)	9.83 (8.98–10.75)	8.20 (7.49–8.98)	6.47 (5.76–7.27)	5.95 (5.21–6.79)
Unadjusted HR (95% CI)[a]	Ref.	0.84 (0.73–0.95)	0.67 (0.58–0.78)	0.61 (0.52–0.72)
Additional adjusted HR (95% CI)[b]	Ref.	0.97 (0.85–1.11)	0.83 (0.71–0.97)	0.81 (0.68–0.95)

BMI, body mass index; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure.
[a]Baseline model stratified by diabetes status and trial and adjusted for treatment assignment and history of HF hospitalization (except all-cause death).
[b]Further adjusted for region, age, sex, heart rate, SBP, BMI, NYHA functional class III/IV, LVEF, eGFR, NT-proBNP (log-transformed), atrial fibrillation, myocardial infarction, and stroke.

Patients with higher (better) index scores were younger, more often male, and less often Black. SBP and heart rate were slightly higher in patients with higher index scores. Patients with higher index scores were less likely to have a history of atrial fibrillation, hypertension, stroke, chronic obstructive pulmonary disease/asthma, diabetes, and anaemia. Patients with higher index scores also had a lower BMI and better kidney function.

Heart failure characteristics and treatments

Patients with higher index scores generally had better KCCQ scores and NYHA functional class, and lower NT-proBNP levels. Compared to those with lower (worse) index scores, patients with higher scores had had shorter-duration HF.

A comparison of patients who completed and did not complete the questionnaire is shown in online supplementary *Table S5*.

Clinical outcomes

Clinical outcomes according to the visual analogue scale score

Patients with higher VAS scores had a lower risk of all outcomes examined (*Table 2* and *Figure 2*). The HR for the primary composite endpoint of CV death or worsening HF, using the lowest (worst) score quartile (quartile 1) as reference were 0.81 (0.72–0.91), 0.74 (0.65–0.84), and 0.62 (0.54–0.72) in quartiles 2, 3, and 4, respectively. Although individual HR were attenuated by adjustment for recognized prognostic variables including NT-proBNP, the adjusted HR for quartiles 2–4 remained significantly lower, compared to quartile 1, for all clinical outcomes. *Figure 3* shows HR for each clinical outcome according to the baseline VAS score, analysed as a continuous variable, using the median value as the reference. There was a linear increase in each outcome with decreasing VAS score. Analysis of incidence rates of each outcome according to baseline VAS score showed a similar pattern.

Clinical outcomes according to the index score

Analyses of index scores using the same approach gave similar results (*Table 3*, online supplementary *Figures S1–S3*).

Results reported by HFpEF (LVEF ≥50%) and HFrEF separately are shown in online supplementary *Tables S6–S9*.

Effect of dapagliflozin on visual analogue scale and index scores

Effect of dapagliflozin on the visual analogue scale score

The VAS score increased from baseline to 8 months by a mean of 2.85 points in the dapagliflozin group and 1.91 points in the placebo group, resulting in a difference of 0.99 (95% CI 0.35–1.62) points (*Graphical Abstract*). *Figure 4A* shows the difference between dapagliflozin and placebo for the change in the VAS score from baseline to 8 months, across the spectrum of LVEF, examined as a

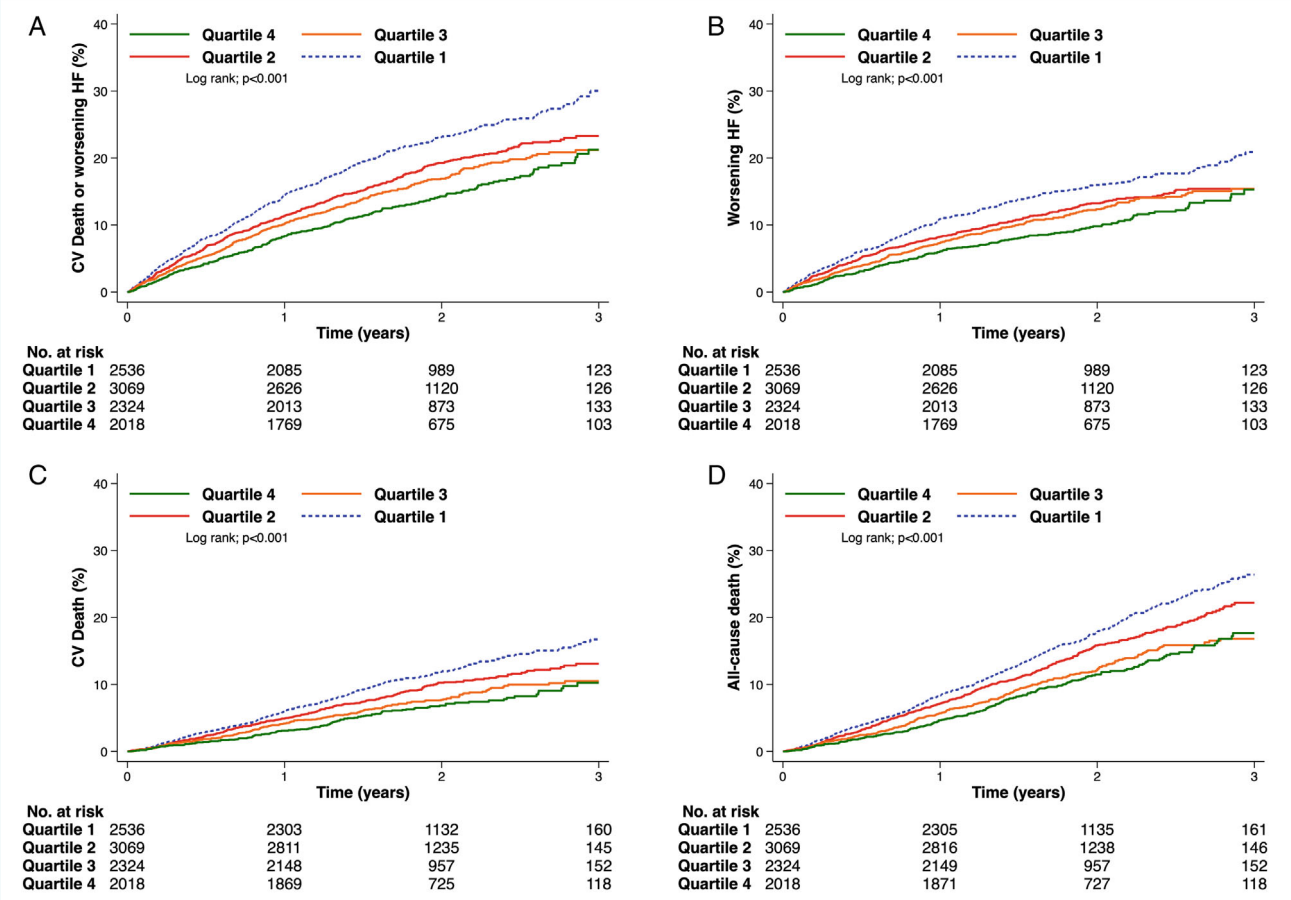


Figure 2 Kaplan–Meier curves for clinical outcome based on the quartile of baseline EuroQol 5-dimension 5-level visual analogue scale (EQ-5D-5L VAS). (*A*) Cardiovascular (CV) death or worsening heart failure (HF); (*B*) worsening HF; (*C*) CV death; (*D*) all-cause death. The number at risk for the event of interest of HF patients at each quartile is shown below each graph.

continuous variable. There was no interaction between LVEF and the effect of dapagliflozin on the VAS score ($p_{interaction} = 0.97$).

Effect of dapagliflozin on the index score

The index score increased from baseline to 8 months by a mean of 0.022 points in the dapagliflozin group and 0.011 points in the placebo group, resulting in a difference of 0.008 (95% CI 0.002–0.014) points (*Graphical Abstract*). *Figure 4B* shows the difference between dapagliflozin and placebo for the change in the index score from baseline to 8 months across the spectrum of LVEF, examined as a continuous variable. There was no interaction between LVEF and the effect of dapagliflozin on the index score ($p_{interaction} = 0.33$).

Effect of dapagliflozin on clinical outcomes according to baseline visual analogue scale and index scores

Figure 5 shows the incidence rate per 100 person-years for the outcomes of interest across the range of VAS scores, analysed as a continuous variable. The risk of the primary composite outcome was lower in the dapagliflozin group, compared to the placebo group, across the range of VAS scores. This difference was explained mainly by the difference in the rate of worsening HF. A similar pattern was observed for the index score analysed as a continuous variable (online supplementary *Figure S3*).

Discussion

In this analysis of the DAPA-HF and DELIVER trials, we found a significant association between EQ-5D VAS and index scores and other measures of health status/symptoms, as well as the occurrence of worsening HF events, CV death and all-cause death, even after extensive adjustment for recognized prognostic variables. Secondly, dapagliflozin improved both scores across the range of LVEF. To our knowledge, this is the first study evaluating the treatment effect of an SGLT2i on the EQ-5D VAS and index scores in HFrEF and HFmrEF/HFpEF. These findings demonstrate the potential value of a general HRQL instrument both in the assessment of patients with HF and in the evaluation of therapies for HF.

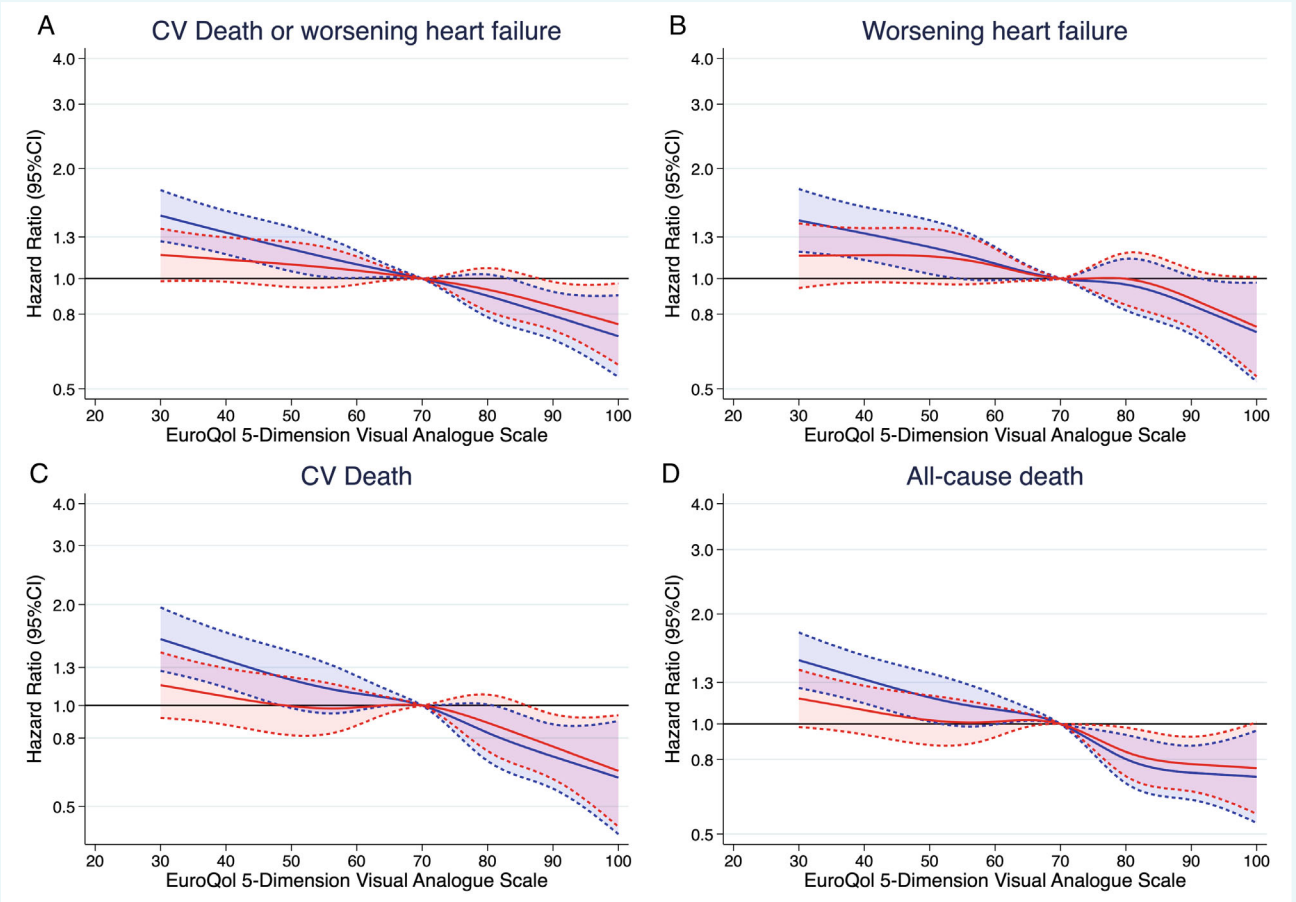


Figure 3 Hazard ratio of each clinical outcome according to baseline EuroQol 5-dimension 5-level visual analogue scale with reference to the population median (70) in patients with heart failure. (*A*) Cardiovascular (CV) death or worsening heart failure; (*B*) worsening heart failure; (*C*) CV death; (*D*) all-cause death. The baseline model (blue) is stratified according to diabetes mellitus status and trial and adjusted for treatment assignment and history of heart failure hospitalization. The adjusted model (red) includes additional adjustment for age, sex, region, heart rate, systolic blood pressure, body mass index, left ventricular ejection fraction, estimated glomerular filtration rate (log-transformed) N-terminal pro-B-type natriuretic peptide, New York Heart Association class, atrial fibrillation, ischaemic aetiology, myocardial infarction, stroke. The shaded area represents 95% confidence interval (CI).

The EQ-5D scores have previously been shown to have a moderate-to-strong correlation with the MLHFQ and KCCQ scores in patients with HF despite the latter being disease-specific.[14,29] Similarly, a significant correlation has been described between EQ-5D scores and NYHA functional class.[35,36] Our findings confirm and extend these prior observations. In particular, we found that both the EQ-5D VAS and index scores were robustly associated, in a linear fashion, with hospitalizations for HF and mortality. The performance of the VAS score is particularly notable, given its simplicity ('thermometer' scale) and consequent ease of use, something that may be important in cross-cultural studies with potential language barriers.

It was also notable that patients with lower EQ-5D VAS and index scores had more comorbidities, e.g. atrial fibrillation, hypertension, obesity and chronic kidney disease, perhaps identifying the contribution of these to HRQL in people with HF.

Compared to patients assigned to placebo, those treated with dapagliflozin showed consistent improvements in the EQ-VAS score (general well-being) and the EQ-5D-5L index score (health utilities) between baseline and 8 months after randomization. There was no interaction between LVEF, examined as a continuous variable, and the effect of dapagliflozin treatment. These findings demonstrate that dapagliflozin improves overall health and not just disease-specific health status, as shown by previous analyses using KCCQ and NYHA class.[37,38] Speculatively, the effects of SGLT2i on associated comorbidities such as anaemia, diabetes, kidney dysfunction, and obesity might contribute to the benefits of such treatment on overall well-being.

It is interesting to compare the EQ-5D VAS and index scores in the present study with those reported in registries.[14,27,28] In the US CHAMP-HF registry of patients with HFrEF, the median VAS score was 62 (50–80) and the median index score was 0.82 (0.73–0.88), compared to 70 (55–80) and 0.87 (0.75–0.95), respectively, in the present study. In the Swedish HF Registry, the median index score was 0.88 (0.34–0.97) among 3495 patients spanning the full range of LVEF. In the Alberta Heart Study (Canada), the median

Table 3 Clinical outcomes according to quartile of EuroQol 5-dimension 5-level index score at baseline

Clinical outcomes	Quartile 1 (very low: −1.026 to 0.751)	Quartile 2 (low: 0.752 to 0.874)	Quartile 3 (moderate: 0.875 to 0.952)	Quartile 4 (high: 0.953 to 1.000)
n (%)	2543 (25.1)	2545 (25.1)	2591 (25.6)	2456 (24.2)
CV death or worsening HF				
n (%)	601 (23.6)	489 (19.2)	417 (16.1)	322 (13.1)
Rate per 100 patient-years (95% CI)	14.00 (12.92–15.16)	10.89 (9.97–11.90)	8.99 (8.17–9.89)	7.22 (6.47–8.05)
Unadjusted HR (95% CI)[a]	Ref.	0.77 (0.68–0.86)	0.63 (0.56–0.72)	0.51 (0.44–0.58)
Additional adjusted HR (95% CI)[b]	Ref.	0.86 (0.76–0.97)	0.79 (0.70–0.90)	0.68 (0.59–0.79)
Worsening HF event				
n (%)	424 (16.7)	341 (13.4)	280 (10.8)	208 (8.5)
Rate per 100 patient-years (95% CI)	9.88 (8.98–10.86)	7.60 (6.83–8.45)	6.04 (5.37–6.79)	4.66 (4.07–5.34)
Unadjusted HR (95% CI)[a]	Ref.	0.76 (0.66–0.88)	0.61 (0.53–0.71)	0.47 (0.40–0.56)
Additional adjusted HR (95% CI)[b]	Ref.	0.91 (0.78–1.05)	0.83 (0.71–0.97)	0.69 (0.58–0.83)
CV death				
n (%)	291 (11.4)	254 (10.0)	208 (8.0)	156 (6.4)
Rate per 100 patient-years (95% CI)	6.15 (5.48–6.90)	5.26 (4.65–5.95)	4.26 (3.72–4.88)	3.35 (2.87–3.92)
Unadjusted HR (95% CI)[a]	Ref.	0.83 (0.70–0.98)	0.66 (0.55–0.79)	0.52 (0.43–0.64)
Additional adjusted HR (95% CI)[b]	Ref.	0.88 (0.74–1.05)	0.77 (0.64–0.92)	0.65 (0.53–0.80)
All-cause death				
n (%)	497 (19.5)	404 (15.9)	341 (13.2)	241 (9.8)
Rate per 100 patient-years (95% CI)	10.48 (9.60–11.44)	8.37 (7.59–9.22)	6.97 (6.27–7.76)	5.18 (4.56–5.87)
Unadjusted HR (95% CI)[a]	Ref.	0.80 (0.70–0.91)	0.66 (0.58–0.76)	0.49 (0.42–0.58)
Additional adjusted HR (95% CI)[b]	Ref.	0.82 (0.72–0.94)	0.72 (0.62–0.83)	0.58 (0.49–0.68)

BMI, body mass index; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure.
[a]Baseline model stratified by diabetes status and trial and adjusted for treatment assignment and history of HF hospitalization (except all-cause death).
[b]Further adjusted for region, age, sex, heart rate, SBP, BMI, NYHA functional class III/IV, LVEF, eGFR, NT-proBNP (log-transformed), atrial fibrillation, myocardial infarction, and stroke.

VAS score in patients with HFrEF was 70 (50–80) and in patients with HFpEF it was 70 (55–80), compared to 70 (57–80) and 70 (54–80), respectively, in the present study. Interestingly, the Alberta Heart Study included non-HF controls who had a median VAS score of 90 (80–95). These reports suggest the impairment in quality of life reported in the present study is consistent with the values observed in 'real-world' outpatient cohorts with generally mild to moderately severe functional impairment (i.e. generally NYHA class II or III). Other studies with recently diagnosed, hospitalized or suboptimally treated patients have reported lower (worse scores).[15,39,40]

The EQ-5D VAS and index scores are also valuable in that they allow comparison of the impact of different diseases since, as generic instruments, they can be utilized in any chronic condition.[41–43] For example, in a study of long-term conditions conducted in 33 primary care practices in the UK, patients with HF had the lowest mean EQ-5D VAS (and index scores): EQ-5D VAS (mean and 95% CI): HF 62.2 (58.9–65.5) versus asthma 73.8 (71.3–76.2), chronic obstructive pulmonary disease 62.3 (59.3–65.3), diabetes 68.2 (65.8–70.5), epilepsy 71.4 (67.1–75.7), and stroke 73.8 (67.2–76.8).[44]

An additional benefit of the EQ-5D index score is that it is the preferred utility measure for health economic assessments conducted by reputable bodies such as the National Institute for Health and Care Excellence (NICE) in the UK and the Institute for Clinical and Economic Review (ICER) in the US.[45,46] Another advantage is that the EQ-5D family of instruments has been widely used in population studies and clinical trials for over 25 years. These instruments are available in both paper and digital versions and can be used online, in postal surveys, and at interviews (face-to-face or telephone). The EQ-5D-5L questionnaire is available in more than 150 languages and is estimated to take only 3–4 min to complete. Value sets allowing comparisons across countries are also available for the index score. All of these aspects of the performance and utilization of the EQ-5D VAS and index scores suggest they should be routinely incorporated in clinical trials evaluating new treatments for HF.

Limitations

This study has some limitations. The participants included in these analyses were enrolled in clinical trials and, as such, were selected according to specific inclusion and exclusion criteria, and our results may not be generalizable to all patients with HF in the general population. There were some missing data in each trial. Although the potential value of the generic nature of the EQ-5D has been highlighted, a potential disadvantage is that it may not capture the specific symptoms and limitations experienced by

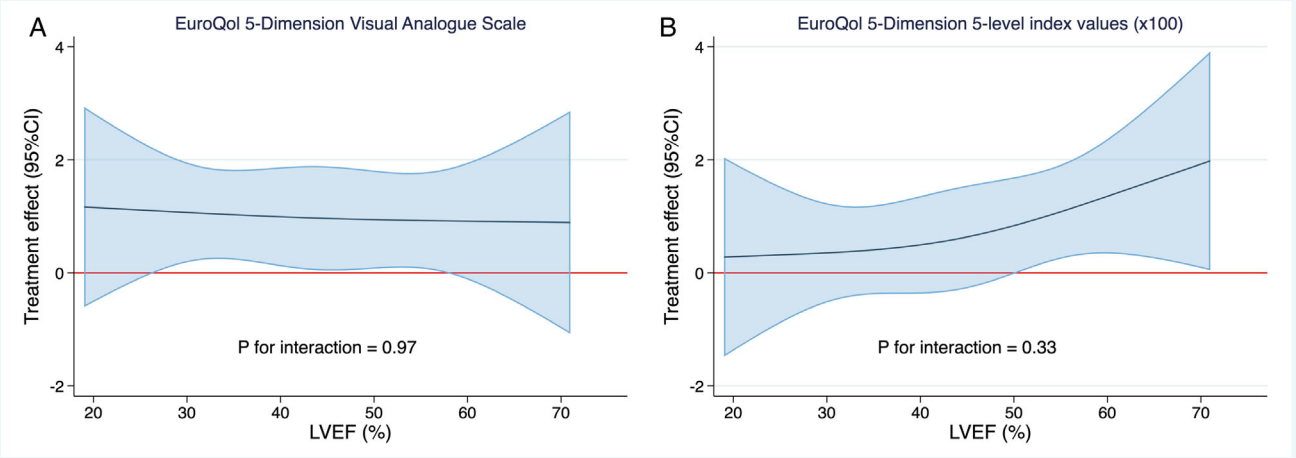


Figure 4 Effects of dapagliflozin versus placebo on the EuroQol 5-dimension 5-level visual analogue scale (EQ-5D-5L VAS) and index score at 8 months across the spectrum of left ventricular ejection fraction (LVEF). Treatment effect refers to placebo-adjusted change in EQ-5D-5L VAS and index score from baseline to 8 months (blue-shaded area represents the 95% confidence interval [CI]). The model was adjusted by baseline visual analogue scale and index score, respectively. *P*-values for interaction are presented.

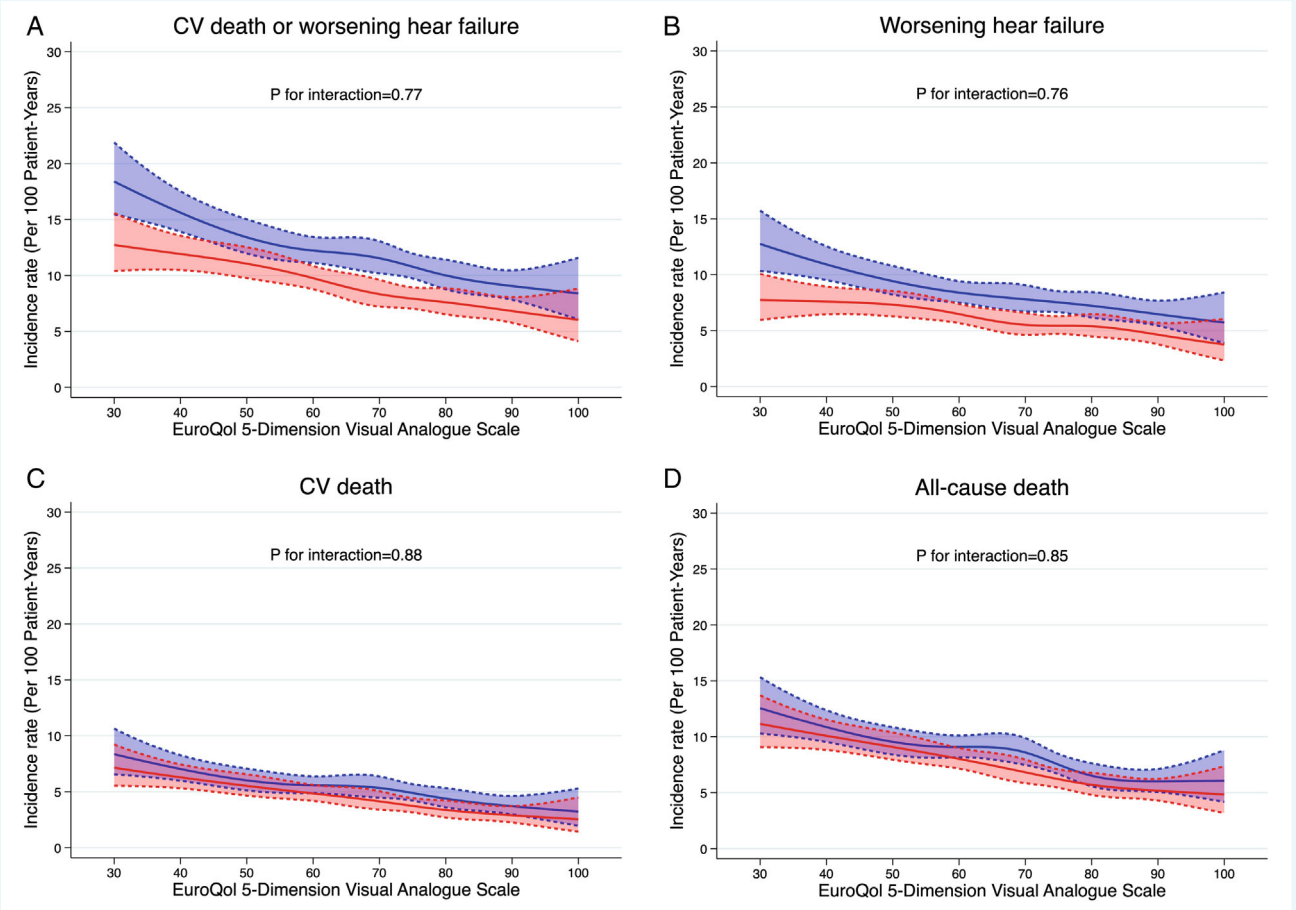


Figure 5 Incidence rates of outcomes across baseline EuroQol 5-dimension 5-level visual analogue scale in heart failure patients with placebo (blue) and dapagliflozin (red). (*A*) Cardiovascular (CV) death or worsening heart failure; (*B*) worsening heart failure; (*C*) CV death; (*D*) all-cause death.

HF patients. Instruments like the EQ-5D VAS may have ceiling and floor effects, which may limit their sensitivity in capturing small changes in HRQL. EQ-5D-5L index value sets were not available for several countries. Furthermore, there are no validated minimally clinically important differences for EQ-5D VAS or index scores, making it difficult to interpret the significance of the changes observed with treatment in the present study. Finally, potential confounders, such as socioeconomic status, education, and cultural factors, were not measured and could not be adjusted for.

Conclusions

The EQ-5D VAS and index scores correlate with other measures of health status/symptoms and have a strong, linear, association with the occurrence of worsening HF events and death. These scores appear sensitive to treatment intervention, showing an improvement following assignment to dapagliflozin, versus placebo, across the spectrum of ejection fraction. The EQ-5D VAS and index scores offer a useful approach to the assessment of HRQL and the response to treatment in patients with both HFrEF and HFmrEF/HFpEF.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Funding

J.J.V.M. and P.S.J. are supported by a British Heart Foundation Centre of Research Excellence Grant RE/18/6/34217 and the Vera Melrose Heart Failure Research Fund.

Conflict of interest: M.Y. has received Global CardioVascular Clinical Trialists (CVCT) Young Trialist Grant and travel grants from AstraZeneca. T.K. reports speaker fees from Abbott, Ono Pharma, Otsuka Pharma, Novartis, AstraZeneca, Bristol Myers Squibb, and Abiomed. A.T. has nothing to disclose. P.S.J. has received speaker fees from AstraZeneca, Novartis, Alkem Metabolics, ProAdWise Communications, Sun Pharmaceuticals, and Intas Pharmaceuticals; has received advisory board fees from AstraZeneca, Boehringer Ingelheim, and Novartis; has received research funding from AstraZeneca, Boehringer Ingelheim, Analog Devices Inc; his employer the University of Glasgow has been remunerated for clinical trial work from AstraZeneca, Bayer AG, Novartis, and Novo Nordisk; and is the Director of Global Clinical Trial Partners (GCTP). K.F.D. reports receiving honoraria from AstraZeneca and a research grant to his institution from Boehringer Ingelheim. B.L.C. has received consulting fees from Boehringer Ingelheim. M.V. has received research grant support, advisory boards or speaker engagements with American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, Boehringer Ingelheim, Chiesi, Cytokinetics, Lexicon Pharmaceuticals, Merck, Novartis, Novo Nordisk, Pharmacosmos, Relypsa, Roche Diagnostics, Sanofi, and Tricog Health; and participated in clinical trial committees for studies sponsored by AstraZeneca, Galmed, Novartis, Bayer AG, Occlutech, and Impulse Dynamics. E.B. is an employee of and shareholder in AstraZeneca. A.F.H. has received research support from American Regent, AstraZeneca, Boehringer Ingelheim, Merck, Novartis, and Verily; and has served as a consultant or on the Advisory Board for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cytokinetics, Myokardia, Merck, Novartis, and Vifor. C.S.P.L. is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from AstraZeneca, Bayer, Boston Scientific, and Roche Diagnostics; has served as a consultant or on the advisory board/steering committee/executive committee for Actelion, Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Cytokinetics, Darma Inc, Us2.ai, Janssen Research & Development LLC, Medscape, Merck, Novartis, Novo Nordisk, Radcliffe Group Ltd, Roche Diagnostics, Sanofi, and WebMD Global LLC; and serves as the co-founder and non-executive director of Us2.ai. S.E.I. has served on clinical trial committees or as a consultant to AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Merck, Pfizer, and Bayer; and has given lectures sponsored by AstraZeneca and Boehringer Ingelheim. F.A.M. has received personal fees from AstraZeneca, Novartis, Gador, Baliarda, Pfizer, Bayer, Bago. R.A.d.B. has received research grants and fees outside the submitted work from AstraZeneca, Abbott, Boehringer Ingelheim, Cardio Pharmaceuticals GmbH, Ionis Pharmaceuticals, Inc, Novo Nordisk, and Roche; has received speaker fees from Abbott, AstraZeneca, Bayer, Cardior Phramaceuticals GmbH, Novo Nordisk, and Roche, outside the submitted work. M.N.K. has received research grant support from AstraZeneca, Boehringer Ingelheim and Pfizer; has served as a consultant or on an advisory board for Alnylam, Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Eli Lilly, Esperion Therapeutics, Janssen, Lexicon, Merck (Diabetes and Cardiovascular), Novo Nordisk, Pfizer, Phrmcosmos, Sanofi, and Vifor Pharma; has received other research support from AstraZeneca; and has received honoraria from AstraZeneca, Boehringer Ingelheim, and Novo Nordisk. A.S.D. reports consulting fees from Abbott, Biofourmis, Boston Scientific, Boehringer Ingelheim, DalCor Pharmaceuticals, and Regeneron, grant support (paid to Brigham and Women's Hospital) and consulting fees from Alnylam Pharmaceuticals and Novartis, and advisory board fees from Corvidia and Relypsa. L.K. reports other support from AstraZeneca and personal fees from Novartis and Boehringer as a speaker. P.P. has received personal fees from Boehringer Ingelheim, AstraZeneca, Servier, Bristol Myers Squibb, Amgen, Novartis, Merck, Pfizer, and Berlin Chemie; and has received grants and personal fees from Vifor Pharma. M.S.S. is a member of the TIMI Study Group, which has also received institutional research grant support through Brigham and Women's Hospital from Abbott, Aralez, Roche, and Zora Biosciences. S.D.S. has received research grants from Actelion, Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, Bristol Myers Squibb, Celladon, Cytokinetics, Eidos, Gilead, GlaxoSmithKline, Ionis, Lilly, Mesoblast, MyoKardia, National Institutes of Health/NHLBI, Neurotronik, Novartis, Novo Nordisk, Respicardia, Sanofi Pasteur, Theracos, and S2.AI; and has consulted for Abbott, Action, Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, GlaxoSmithKline, Lilly, Merck, Myokardia, Novartis, Roche, Theracos, Quantum Genomics, Cardurion, Janssen, Cardiac Dimensions, Tenaya, Sanofi-Pasteur, Dinaqor, Tremeau, CellPro-Thera, Moderna, American Regent, and Sarepta. J.J.V.M. has received payments through Glasgow University from work on clinical trials, consulting and other activities from Amgen, AstraZeneca, Bayer, Cardurion, Cytokinetics, GlaxoSmithKline, KBP Biosciences, and Novartis; has received personal consultancy fees from Alnylam Pharma, Bayer, Bristol Myers Squibb, George Clinical PTY Ltd, Ionis Pharma, Novartis, Regeneron Pharma, and River 2 Renal Corporation; has received personal lecture fees from Abbott, Alkem Metabolics, AstraZeneca, Blue Ocean Scientific Solutions Ltd, Boehringer Ingelheim, Canadian Medical and Surgical Knowledge, Emcure Pharma Ltd, Eris Lifesciences, European Academy of CME, Hikma Pharmaceuticals, Imagica health, Intas Pharma, J.B. Chemicals & Pharma. Ltd, Lupin Pharma, Medscape/Heart, ProAdWise Communications, Radcliffe Cardiology, Sun Pharma, The Corpus, Translation Research Group, and

Translational Medicine Academy; and is a director of Global Clinical Trial Partners Ltd.

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