

## ORIGINAL ARTICLE



# Effect of Dapagliflozin on Accelerometer-Based Measures of Physical Activity in Patients With Heart Failure: An Analysis of the DETERMINE Trials

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**BACKGROUND:** Wearable accelerometers can quantify the frequency and intensity of physical activity during everyday life and may provide complementary data to established functional outcome measures on the effect of heart failure therapies on functional limitations.

**METHODS:** In a voluntary substudy of the DETERMINE trials (Dapagliflozin Effect on Exercise Capacity Using a 6-Minute Walk Test in Patients With Heart Failure), patients wore a waist-worn triaxial accelerometer for as long as possible (ideally for 24 h/d for 7 days) at 3 points during the trial, between the screening visit and randomization (baseline data), and during weeks 8 and 14 to 16. Accelerometer outcomes included the change from baseline to week 16 in the total number of steps, time spent in light-to-vigorous physical activity, time spent in moderate-to-vigorous physical activity, movement intensity during walking, number of vector magnitude units, and total activity counts.

**RESULTS:** Adequate baseline and week 16 accelerometer data were available for 211 of 817 (26%) randomized patients (defined as  $\geq 10$  hours of wear time for  $\geq 3$  days). Dapagliflozin had a favorable effect on the mean change from baseline at 16 weeks in the number of steps (between-group difference, 778 [95% CI, 240–1315]), time spent in moderate-to-vigorous physical activity (0.16 [95% CI, 0.03–0.29] hours), and in the mean vector magnitude units (25 [95% CI, 0.1–49] counts per minute). There were no between-group differences in the other accelerometer outcomes of interest.

**CONCLUSIONS:** In this exploratory analysis of the DETERMINE trials, dapagliflozin had a beneficial effect on selected accelerometer-based measures of physical activity in patients with heart failure across the entire left ventricular ejection fraction spectrum, yet did not improve 6-minute walk distance, as previously reported. These data suggest that accelerometer-based measurements of everyday activity may provide complementary information to 6-minute walk distance and identify beneficial effects of treatment not detected by 6-minute walk distance.

**REGISTRATION:** URL: <https://www.clinicaltrials.gov>; Unique identifiers: NCT03877237 and NCT03877224.

**Key Words:** accelerometry ■ exercise ■ sodium-glucose transporter 2 inhibitors ■ walk test ■ wearable electronic devices

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### WHAT IS NEW?

- In patients with heart failure, wearable accelerometers can assess the degree of physical and functional limitations during day-to-day living.
- Wearable accelerometers can be used to evaluate the effect of a treatment on these limitations.
- In the placebo-controlled DETERMINE trials (Dapagliflozin Effect on Exercise Capacity Using a 6-Minute Walk Test in Patients With Heart Failure), the SGLT2 (sodium-glucose transporter 2) inhibitor dapagliflozin had a favorable effect on several accelerometer-based measures of physical activity in patients with heart failure across the ejection fraction spectrum.

### WHAT ARE THE CLINICAL IMPLICATIONS?

- The finding of a beneficial effect of dapagliflozin on accelerometer-based measures of physical activity, in the context of no effect on 6-minute walk distance, suggests that accelerometers may be able to provide additive information on a treatment's effect on functional limitations in patients with heart failure.

mpairment of physical activity and functional limitations characterize the syndrome of heart failure (HF).<sup>1,2</sup> As well as improving morbidity and mortality outcomes, interventions that improve the degree of physical and functional limitation in daily life are highly valued by patients with HF and are acceptable to regulators for approval. Traditional methods of assessing physical and functional limitations include patient-reported outcome measures (eg, Kansas City Cardiomyopathy Questionnaire [KCCQ]), 6-minute walk distance (6MWD), and cardiopulmonary exercise testing.<sup>3</sup> However, several therapies have demonstrated a beneficial effect on KCCQ scores (and morbidity/mortality outcomes) but have had an inconsistent or no effect on 6MWD or cardiopulmonary exercise testing outcomes such as peak oxygen consumption.<sup>4–8</sup> Wearable accelerometers may provide complementary data on functional limitations, quantifying the frequency and intensity of physical activity during everyday life.<sup>3,9,10</sup>

In this exploratory analysis of the DETERMINE trials (Dapagliflozin Effect on Exercise Capacity Using a 6-Minute Walk Test in Patients With Heart Failure), we examined the effect of the SGLT2 (sodium-glucose transporter 2) inhibitor dapagliflozin on a range of accelerometer-based measures of physical activity in people with HF across the whole spectrum of left ventricular ejection fraction (LVEF).<sup>8</sup>

### METHODS

The DETERMINE double-blind, placebo-controlled, multicenter trials assessed the efficacy of 16 weeks of

### Nonstandard Abbreviations and Acronyms

<b>6MWD</b>	6-minute walk distance
<b>CHIEF-HF</b>	Canagliflozin: Impact on Health Status, Quality of Life and Functional Status in Heart Failure
<b>DETERMINE</b>	Dapagliflozin Effect on Exercise Capacity Using a 6-Minute Walk Test in Patients With Heart Failure
<b>EMPIRE-HF</b>	Empagliflozin in Heart Failure Patients With Reduced Ejection Fraction: A Randomized Clinical Trial
<b>HF</b>	heart failure
<b>HF-ACTION</b>	Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training
<b>KCCQ</b>	Kansas City Cardiomyopathy Questionnaire
<b>LVEF</b>	left ventricular ejection fraction
<b>LVPA</b>	light-to-vigorous physical activity
<b>MVPA</b>	moderate-to-vigorous physical activity
<b>NEAT-HFpEF</b>	Nitrate's Effect on Activity Tolerance in Heart Failure With Preserved Ejection Fraction
<b>NT-proBNP</b>	N-terminal pro-B-type natriuretic peptide
<b>PRESERVED-HF</b>	Dapagliflozin in PRESERVED Ejection Fraction Heart Failure
<b>SGLT2</b>	sodium-glucose transporter 2
<b>VMU</b>	vector magnitude unit
<b>WATCHFUL</b>	Pedometer-Based Walking Intervention in Patients With Chronic Heart Failure With Reduced Ejection Fraction

treatment with dapagliflozin 10 mg once daily, compared with placebo, in addition to standard care on the total symptom score and physical limitation scale of the KCCQ and 6MWD in 313 patients with HF with reduced ejection fraction (DETERMINE-Reduced [https://www.clinicaltrials.gov, NCT03877237]) and in 504 patients with HF with preserved ejection fraction (DETERMINE-Preserved [https://www.clinicaltrials.gov, NCT03877224]). Full details about the trial protocol and primary results of the DETERMINE trials have been published.<sup>8</sup>

### Data Sharing

Data underlying the findings described in this article may be obtained in accordance with AstraZeneca's data-sharing policy

described at <https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure>

## Code Availability

Code for the analyses in this article can be shared on request with the corresponding author if data have been released following the data-sharing policy described at <https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure>.

## Trial Patients

The main inclusion criteria were as follows: age  $\geq 18$  years (DETERMINE-Reduced) or  $\geq 40$  years (DETERMINE-Preserved); LVEF  $\leq 40\%$  (DETERMINE-Reduced) or  $>40\%$  and evidence of structural heart disease (DETERMINE-Preserved); elevated natriuretic peptide levels; a diagnosis of HF for  $>2$  months; and New York Heart Association functional classes II to IV. In addition, there was a minimum 6MWD requirement for eligibility.<sup>8</sup>

Exclusion criteria included systolic blood pressure  $<95$  mm Hg; estimated glomerular filtration rate  $<25$  mL/min $\cdot$ 1.73 m<sup>2</sup>; type 1 diabetes; other conditions likely to prevent patient participation in the trial or greatly limit life expectancy; and any condition precluding exercise testing. The Ethics Committee of each participating institution approved the protocols, and all patients gave written informed consent.

## Accelerometer Substudy

In a voluntary substudy at 67 sites in 10 countries, patients wore a waist-worn triaxial accelerometer with a sampling frequency of 100 Hz (Dynaport MoveMonitor; McRoberts B.V., the Hague, the Netherlands) for as long as possible (ideally for 24 h/d for 7 days) at 3 points during the trial, between the screening visit and randomization (baseline data), and during weeks 8 and 14 to 16 (hereafter referred to week 16) following randomization. Adequate wear time for inclusion in the accelerometer substudy was prespecified as  $\geq 10$  hours of wear time between 6:00 AM and 10:00 PM, for  $\geq 3$  days during the 7-day period.<sup>11</sup>

## Accelerometer Outcomes

Accelerometer outcomes included in this analysis were the total number of steps (excluding those while walking on stairs), time spent in light-to-vigorous physical activity (LVPA), time spent in moderate-vigorous physical activity (MVPA), number of vector magnitude units (VMUs), movement intensity during walking (measured in milligravities [mg]), and the total number of activity counts during worn periods. The time spent in LVPA and MVPA (in hours) is an estimate of the total wear time spent with an energy expenditure  $\geq 1.5$  METs (ie, equivalent to nonsedentary activity) and  $\geq 3.0$  METs (activity at or above the intensity of brisk walking and household chores), respectively, calculated using a validated algorithm.<sup>12</sup> The number of VMUs per minute refers to the mean of the square root of squared values along the vertical axis signal, converted from raw acceleration to counts per minute, and is considered a proxy for the intensity of physical activity.<sup>13</sup> Movement intensity during walking (measured in mg [ $1 \text{ mg} = 9.81 \times 10^{-3} \text{ ms}^{-2}$ ]) was calculated as the root mean square of the sum of the values along the x, y, and z

signals (x axis) during periods classed as walking (defined as at least 3 consecutive steps during a standing period).

## Statistical Analyses

In this exploratory analysis, the study cohort was defined as those patients in DETERMINE-Reduced and DETERMINE-Preserved with paired accelerometer data at baseline and week 16. These patients were pooled to form the DETERMINE-Pooled cohort. The change in these accelerometer measures from baseline to weeks 8 and 16 was calculated in both treatment groups in all participants with available data. For the purpose of this analysis, the change from baseline to week 16 in each accelerometer measure was considered as the primary outcome, with the change from baseline at week 8 as the secondary outcome. The effect of dapagliflozin compared with placebo was examined using ANCOVA adjusted for baseline value of the outcome of interest, LVEF, trial, age, sex, body mass index, NT-proBNP (N-terminal pro-B-type natriuretic peptide), New York Heart Association functional class, and geographic region. No imputation for missing data was performed. The treatment effect estimates were calculated overall in the DETERMINE-Pooled cohort and separately in DETERMINE-Reduced and DETERMINE-Preserved. In the primary results of the DETERMINE trials, all change data were censored at the site-reported date of the start of the COVID-19 pandemic in their region.<sup>8</sup> We did not apply this data censoring for the present study to maximize the number of patients with available data for these exploratory analyses. As the analyses presented were not prespecified and are considered exploratory, no formal testing for statistical significance was performed. All analyses were performed independently by 2 different analysts, 1 using SAS (Statistical Analysis Software, version 9.4; SAS Institute Inc, Cary, NC) and the other using Python programming language (version Python 3.9.5-foss-2021a).

## RESULTS

Of the 817 patients enrolled in the DETERMINE trials (313 in DETERMINE-Reduced and 504 in DETERMINE-Preserved), adequate accelerometer data at both baseline and week 16 were available for 211 (26%) participants (75 in DETERMINE-Reduced and 136 in DETERMINE-Preserved), of whom 107 and 104 were randomized to dapagliflozin and placebo, respectively. Of these 211, 179 (85%) had available data at week 8 (90 and 89 were randomized to dapagliflozin and placebo, respectively). The number of patients with accelerometer data at specified time points during the trials is provided in [Table S1](#).

## Baseline Characteristics

The baseline characteristics of the 211 patients in the accelerometer substudy are presented in [Table 1](#). Patients included in the accelerometer substudy were generally representative of the whole DETERMINE trial population. The mean age was 71 years, the mean LVEF was 43%, and 32% of patients were female. The

**Table 1. Baseline Characteristics in the DETERMINE-Pooled Accelerometer Substudy**

	Dapagliflozin (n=107)	Placebo (n=104)	Total (N=211)
Study, n (%)			
DETERMINE-Preserved	67 (62.6)	69 (66.3)	136 (64.5)
DETERMINE-Reduced	40 (37.4)	35 (33.7)	75 (35.5)
Age, y; mean (SD)	71.4 (8.9)	71.1 (8.8)	71.3 (8.9)
Sex, n (%)			
Male	71 (66.4)	72 (69.2)	143 (67.8)
Female	36 (33.6)	32 (30.8)	68 (32.2)
Race, n (%)			
White	94 (87.9)	98 (94.2)	192 (91)
Black or African American	10 (9.3)	5 (4.8)	15 (7.1)
Other	3 (2.8)	1 (1)	4 (1.9)
Geographic region, n (%)			
West Europe/North America	72 (67.3)	77 (74)	149 (70.6)
Rest of world	35 (32.7)	27 (26)	62 (29.4)
LVEF, mean (SD)	41.8 (12.8)	43.8 (13.3)	42.8 (13)
KCCQ-TSS, median (IQR)	78.1 (63–85.9)	77.6 (65.4–89.6)	78.1 (64.1–87.5)
KCCQ-PLS, median (IQR)	70.8 (56.7–87.5)	70.8 (58.3–87.5)	70.8 (58.3–87.5)
NYHA class, n (%)			
II	89 (83.2)	89 (85.6)	178 (84.4)
III	18 (16.8)	15 (14.4)	33 (15.6)
NT-proBNP, pg/mL; median (IQR)	899 (565–1733)	767 (498–1406)	861 (514–1591)
6MWD, m; median (IQR)	333.0 (280.5–386.0)	339.5 (271.0–384.5)	336 (275–385.5)
BMI, kg/m <sup>2</sup> ; mean (SD)	30.5 (6.1)	29.7 (5.3)	30.1 (5.7)
eGFR, mL/min-1.73 m <sup>2</sup> ; mean (SD)	60.9 (17.3)	62.1 (18.6)	61.5 (17.9)
Systolic blood pressure, mm Hg; mean (SD)	121.2 (16.9)	125.8 (15.6)	123.4 (16.4)
Medical history, n (%)			
Type 2 diabetes	34 (31.8)	44 (42.3)	78 (37)
Atrial fibrillation	60 (56.1)	48 (46.2)	108 (51.2)
Treatment, n (%)			
ACE inhibitor	49 (45.8)	38 (36.5)	87 (41.2)
ARB	35 (32.7)	37 (35.6)	72 (34.1)
ARNI	15 (14)	18 (17.3)	33 (15.6)
β-Blocker	95 (88.8)	95 (91.3)	190 (90)
MRA	56 (52.3)	59 (56.7)	115 (54.5)
Diuretic	92 (86)	88 (84.6)	180 (85.3)

Data are presented as mean±SD or median (IQR) for continuous measures and N (%) for categorical measures.

6MWD indicates 6-minute walk distance; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BMI, body mass index; DETERMINE, Dapagliflozin Effect on Exercise Capacity Using a 6-Minute Walk Test in Patients With Heart Failure; eGFR, estimated glomerular filtration rate; IQR, interquartile range; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PLS, physical limitation scale; and TSS, total symptom score.

proportion of patients with LVEF ≤40% and >40% was 36% and 64%, respectively. Most patients were in the New York Heart Association functional class II (84%), and the median NT-proBNP was 861 pg/mL (interquartile range, 514–1591). Median KCCQ-total symptom score was 78.1 (interquartile range, 64.1–87.5), and median 6MWD was 336 m (interquartile range, 275–386). The

proportion of patients with type 2 diabetes or atrial fibrillation was 37% and 51%, respectively. The majority of patients (91%) were treated with a renin-angiotensin system inhibitor alone (75%) or in combination with a neprilysin inhibitor (16%) and a β-blocker (90%). Pre-trial use of a mineralocorticoid receptor antagonist was recorded in 55% of patients.

## Effect of Dapagliflozin on Accelerometer Outcomes

The effect of dapagliflozin compared with placebo on the accelerometer-based outcomes of interest at weeks 8 and 16 in the DETERMINE-Pooled cohort is displayed in Tables 2 and 3, respectively, and the Figure. From baseline to week 8, levels of accelerometer-recorded physical activity declined in both treatment groups, with no significant between-group differences at week 8 following randomization.

By week 16, measures of physical activity in the placebo group generally continued to fall, whereas, in the dapagliflozin group, there was an attenuation of the initial decline in the accelerometer-measured degree of physical activity. The mean change in the number of steps from baseline to week 16 was 88 (SD, 1945) and  $-846$  (SD, 2350) in patients randomized to dapagliflozin and placebo, respectively; between-group difference was 778 (95% CI, 240–1315). The mean change in time spent in MVPA from baseline to week 16 was 0 (SD, 0.45) hours and  $-0.18$  (SD, 0.58) hours in the dapagliflozin and placebo groups, respectively; between-group difference was 0.16 (95% CI, 0.03–0.29). The mean change in VMU (counts per minute) from baseline to week 16 was  $-3$  (SD, 95) and  $-26$  (SD, 91) in the dapagliflozin and placebo groups, respectively; between-group difference was 25 (95% CI, 0.1–49). There were no between-group differences in the time spent in LVPA, movement intensity during walking, or the total number of activity counts during worn periods.

The effect of dapagliflozin, compared with placebo, on accelerometer outcomes of interest in the 2 individual DETERMINE trials is displayed in Table S2 (DETERMINE-Reduced) and Table S3 (DETERMINE-Preserved). In DETERMINE-Reduced, the mean

between-group difference in the number of steps was 920 (95% CI, 153–1688) in favor of dapagliflozin, with no other between-group differences in the other outcomes. In DETERMINE-Preserved, dapagliflozin had a favorable effect on time in LVPA (between-group difference, 0.31 [95% CI, 0.01–0.61] hours), MVPA (0.2 [95% CI, 0.03–0.37]), VMUs (between-group difference, 39 [95% CI, 4–75] counts per minute), and the total number of activity counts (between-group difference, 42 [95% CI, 3–81] counts $\times 10^3$ ). In tests for a treatment effect interaction between the 2 trials, interaction *P* values for all outcomes were  $>0.10$  except for time spent in LVPA (interaction *P*=0.01).

## DISCUSSION

In this exploratory pooled analysis of the DETERMINE-Reduced and DETERMINE-Preserved trials, 16 weeks of treatment with the SGLT2 inhibitor dapagliflozin had a beneficial effect on accelerometer-measured total daily number of steps, the quantity of MVPA, and VMUs (a measure of movement intensity). Taken together, these data suggest that 16 weeks of treatment with dapagliflozin had a favorable effect on both the quantity (number of steps and time in MVPA) and the intensity (VMUs) of physical activity during daily living among patients who took part in the voluntary accelerometer substudy of the DETERMINE trials and who provided adequate data for analysis.

To our knowledge, this is the first report of a pharmacological therapy for HF having a beneficial effect on accelerometer-based measures of physical activity. While a previous trial has reported on the negative effect of an intervention on an accelerometer-based measure of physical activity, no trials have reported the benefit of a therapy on an accelerometer-based outcome.<sup>14</sup> The

**Table 2. Effect of Dapagliflozin Compared With Placebo on Accelerometer Outcomes at Week 8**

	Dapagliflozin				Placebo				Between-group difference (95% CI)
	n	Baseline	Week 8	Change from baseline	n	Baseline	Week 8	Change from baseline	
No. of steps	90	4286 (2440)	4116 (2433)	$-169$ (1816)	89	4838 (2750)	4307 (2555)	$-530$ (2171)	138 ( $-410$ to 686)
Time in LVPA, h	90	2.94 (1.52)	2.86 (1.46)	$-0.07$ (0.79)	89	3.04 (1.56)	2.97 (1.59)	$-0.08$ (0.74)	$-0.03$ ( $-0.25$ to 0.19)
Time in MVPA, h	90	1.31 (0.62)	1.26 (0.62)	$-0.04$ (0.41)	89	1.37 (0.7)	1.3 (0.72)	$-0.06$ (0.51)	$-0.01$ ( $-0.14$ to 0.12)
Vector magnitude units (counts/min)	90	229 (153)	226 (155)	$-2$ (87)	89	214 (129)	208 (132)	$-6$ (68)	4 ( $-18$ to 27)
Movement intensity during walking, mg	90	173 (34)	171 (32)	$-2$ (26)	89	167 (28)	168 (28)	2 (17)	$-1$ ( $-7.6$ to 4.6)
Total number of activity counts during worn periods (counts $\times 10^3$ )	90	289 (175)	279 (175)	$-10$ (108)	89	286 (172)	271 (167)	$-15$ (76)	5 ( $-21$ to 31)

Data are presented as mean (SD) unless otherwise stated.

The estimated mean between-group difference and 95% CIs were calculated by ANCOVA adjusted for baseline value of outcome, left ventricular ejection fraction, trial (DETERMINE-Reduced or DETERMINE-Preserved), age, sex, body mass index, NT-proBNP, New York Heart Association functional class, and geographic region.

DETERMINE indicates Dapagliflozin Effect on Exercise Capacity Using a 6-Minute Walk Test in Patients With Heart Failure; LVPA, light-to-vigorous physical activity; MVPA, moderate-to-vigorous physical activity; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

**Table 3. Effect of Dapagliflozin Compared With Placebo on Accelerometer Outcomes at Week 16**

	Dapagliflozin				Placebo				Between-group difference (95% CI)
	n	Baseline	Week 16	Change from baseline	n	Baseline	Week 16	Change from baseline	
No. of steps	107	4330 (2457)	4418 (2499)	88 (1945)	104	4812 (2764)	3966 (2674)	-846 (2350)	778 (240 to 1315)
Time in LVPA, h	107	2.95 (1.49)	2.85 (1.44)	-0.1 (0.89)	104	3.1 (1.58)	2.85 (1.5)	-0.25 (1)	0.08 (-0.16 to 0.32)
Time in MVPA, h	107	1.31 (0.62)	1.31 (0.65)	0 (0.45)	104	1.37 (0.68)	1.19 (0.63)	-0.18 (0.58)	0.16 (0.03 to 0.29)
Vector magnitude units (counts/min)	107	235 (153)	233 (162)	-3 (95)	104	222 (137)	196 (121)	-26 (91)	25 (0.1 to 49)
Movement intensity during walking, mg	107	174 (34)	173 (35)	-1 (24)	104	170 (30)	166 (30)	-4 (25)	5 (-1 to 11)
Total number of activity counts during worn periods (counts×10 <sup>3</sup> )	107	294 (174)	282 (172)	-12 (109)	104	294 (182)	255 (160)	-39 (112)	25 (-3 to 53)

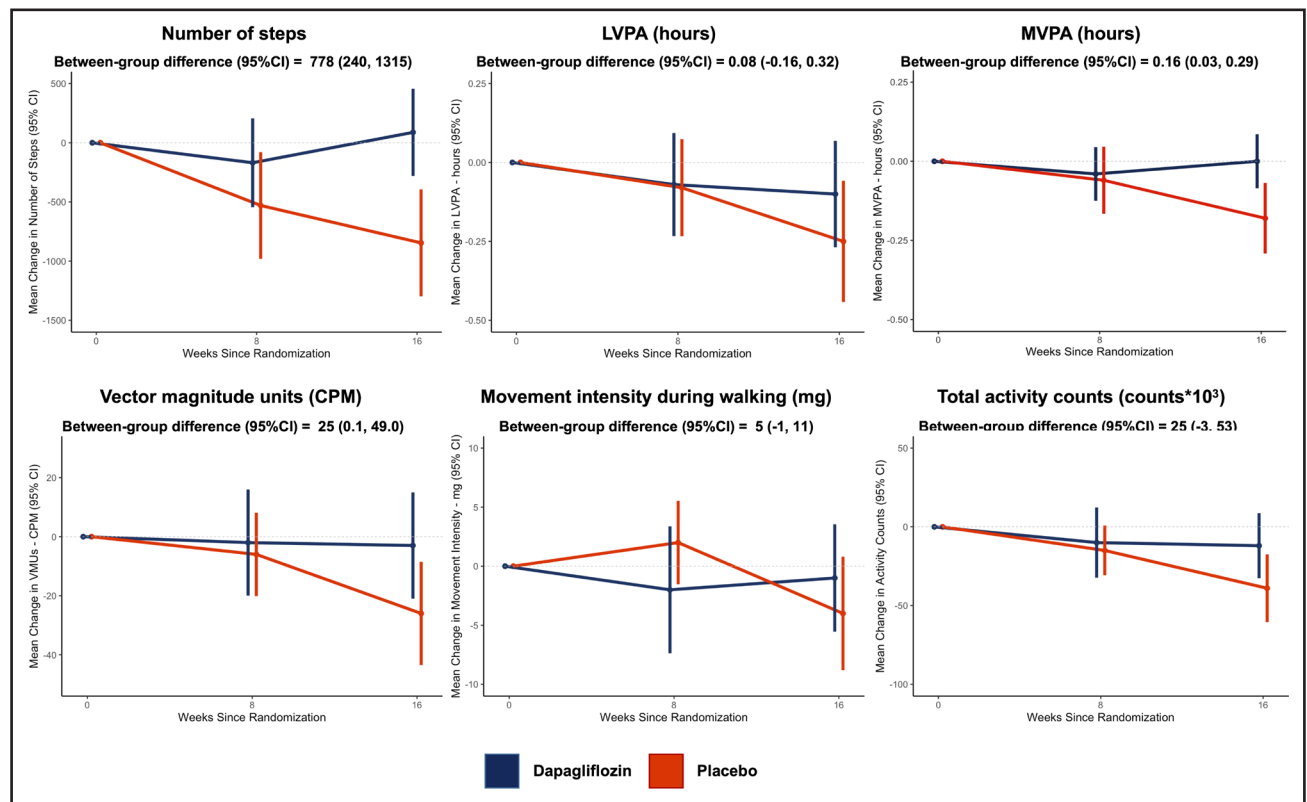
Data are presented as mean (SD) unless otherwise stated.

The estimated mean between-group difference and 95% CIs for the accelerometer outcomes were calculated by ANCOVA adjusted for baseline value of outcome, left ventricular ejection fraction, trial (DETERMINE-Reduced or DETERMINE-Preserved), age, sex, body mass index, NT-proBNP, New York Heart Association functional class, and geographic region.

DETERMINE indicates Dapagliflozin Effect on Exercise Capacity Using a 6-Minute Walk Test in Patients With Heart Failure; LVPA, light-to-vigorous physical activity; MVPA, moderate-to-vigorous physical activity; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

magnitude of the mean between-group difference in number of daily steps (778 [95% CI, 240–1315]) is similar to that suggested to be a minimally important clinical difference in patients with HF. For example, in an analysis

of patients with HF in the National Health and Nutrition Examination Survey, each additional 1000 steps per day were associated with a 15% lower risk of all-cause mortality.<sup>15</sup> Similar results have been reported in the general



**Figure. Effect of dapagliflozin compared with placebo on the change from baseline at week 16 in accelerometer outcomes in DETERMINE-Pooled (Dapagliflozin Effect on Exercise Capacity Using a 6-Minute Walk Test in Patients With Heart Failure).** The estimated mean between-group differences and 95% CIs are the treatment effect estimates at week 16 and were calculated by ANCOVA adjusted for baseline value of outcome, left ventricular ejection fraction, trial (DETERMINE-Reduced or DETERMINE-Preserved), age, sex, body mass index, NT-proBNP (N-terminal pro-B-type natriuretic peptide), New York Heart Association functional class, and geographic region. CPM indicates counts per minute; LVPA, light-to-vigorous physical activity; mg, milligravities; MVPA, moderate-to-vigorous physical activity; and VMU, vector magnitude unit.

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population with a 7% lower risk of cardiovascular mortality per 500 greater number of steps per day.<sup>16</sup> The observed increase in time spent in MVPA of  $\approx 10$  minutes has previously been reported to be associated with a 5% lower risk of death or HF hospitalization in patients following implantation of implantable cardiac devices with activity-measuring capabilities.<sup>17</sup> To our knowledge, no minimally important clinical difference in VMUs has been reported in patients with HF; however, the magnitude of the between-group difference of 25 cpm corresponds to an approximate 10% increase in the mean intensity of movement per minute.

SGLT2 inhibitors, as well as having consistent and meaningful benefits on reducing the risk of worsening HF and mortality, reduce patient-reported symptoms and improve the degree of patient-reported functional limitation as assessed by the KCCQ.<sup>2,8,18–22</sup> Two other trials have examined the effect of SGLT2 inhibition on accelerometer outcomes. Neither the EMPIRE-HF trial (Empagliflozin in Heart Failure Patients With Reduced Ejection Fraction: A Randomized Clinical Trial) nor the CHIEF-HF trial (Canagliflozin: Impact on Health Status, Quality of Life and Functional Status in Heart Failure) reported a significant effect on accelerometer-measured daily activity counts or daily step counts, respectively.<sup>23,24</sup> Direct between-trial comparisons are limited by several between-trial differences. First, the accelerometer devices used varied across trials, and this may have led to differences in the device's sensitivity to detect low-level physical activity, as is common in patients with HF. Furthermore, differences in device placement (ie, whether waist- or wrist-worn) and the analytical methods used mean that the results for the same outcome (eg, steps) may not be directly comparable between trials. Second, the follow-up time in EMPIRE-HF and CHIEF-HF was shorter than that in the DETERMINE trials (12 versus 16 weeks). In DETERMINE, the significant between-group differences at 16 weeks were not present at 8 weeks, so a longer follow-up time may be required to detect a treatment's effect on these outcomes. Finally, there may have been differences in the characteristics of the trial populations studied that influenced the results; there was a substantially lower level of baseline patient-reported health-related quality of life in CHIEF-HF as compared with the DETERMINE trials, and it is possible that this limited the ability of patients in CHIEF-HF to improve in terms of accelerometer-measured step count over the 12 weeks of follow-up.<sup>24</sup>

The benefits seen in this analysis of accelerometer outcomes contrast with the absence of a beneficial effect of dapagliflozin on 6MWD in each individual DETERMINE trial or in an exploratory pooled analysis of both trials (between-group difference, 2.5 [95% CI,  $-3.5$  to 8.4] m), along with a lack of a consistent beneficial effect of SGLT2 inhibitors on 6MWD in several smaller trials, although in 1 of these (PRESERVED-HF [Dapagliflozin

in PRESERVED Ejection Fraction Heart Failure]), dapagliflozin did increase 6MWD in a population that was more obese and had more severely impaired functional capacity at baseline, as discussed elsewhere.<sup>6,8,25–30</sup> This discrepancy between an effect on accelerometer outcomes and 6MWD has been observed in other trials using different interventions. In the randomized WATCHFUL trial (Pedometer-Based Walking Intervention in Patients With Chronic Heart Failure With Reduced Ejection Fraction), a lifestyle walking intervention, combining self-monitoring with an activity tracker and telephone counseling, increased the step count by 1420 per day, the time spent in MVPA (+0.14 hours), and patient-reported health status, as compared with the control group, yet did not have any significant effect on the primary outcome of 6MWD (between-group difference, 7.4 [95% CI,  $-8.0$  to 22.7] m).<sup>31</sup> Notably, the effect of dapagliflozin on time spent in MVPA in DETERMINE-Pooled was the same as the effect of the lifestyle walking intervention in the WATCHFUL trial (0.16 versus 0.14 hours). In the NEAT-HFpEF trial (Nitrate's Effect on Activity Tolerance in Heart Failure With Preserved Ejection Fraction), isosorbide mononitrate reduced accelerometer-measured physical activity but did not affect 6MWD, KCCQ scores, or NT-proBNP concentrations.<sup>14,32</sup>

Except for intravenous iron and cardiac resynchronization therapy, the majority of treatments for HF have had no consistent beneficial effect on 6MWD, despite favorable effects on patient-reported health-related quality of life and clinical outcomes.<sup>33</sup> The data presented here from the DETERMINE trials and the results of the WATCHFUL and NEAT-HFpEF trials suggest that accelerometer-based measurements of everyday activity may provide complementary information to 6MWD and identify beneficial (or negative) effects of treatments or interventions not detected by 6MWD. Additional attractive features of the use of accelerometer-based measures as clinical trial outcomes include their ability to measure activity over longer periods during daily living, as opposed to a single time point as with commonly used assessments of functional capacity in trials such as 6MWD or peak oxygen consumption measured with cardiopulmonary exercise testing and that the measurements provided by accelerometers are more reflective of the intensity of activity at which patients with HF live for the majority of their time on a day-to-day basis.<sup>9,10</sup>

The lack of effect of dapagliflozin on 6MWD may reflect that the magnitude of dapagliflozin's treatment effect on increasing step count, time spent in MVPA, and VMUs was insufficient to result in physiological adaptations, which translated into a measurable increase in an individual's capacity for more metabolically demanding activity and an improved 6MWD. Although there are suggested mechanisms of action of SGLT2 inhibitors that could specifically improve aerobic exercise performance (eg, increase in erythropoiesis and hematocrit, enhanced

skeletal muscle and myocardial iron utilization, and favorable cardiac remodeling), the magnitude of these effects and the limited training stimulus effect of an increase in steps and movement intensity may not have been sufficient to improve aerobic capacity (and 6MWD).<sup>25,26,34,35</sup> Indeed, even in the HF-ACTION trial (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training), structured aerobic exercise training at >60% of heart rate reserve resulted in only an ≈15-m increase in 6MWD at 6 months (ie, less than what is thought to be a clinically meaningful change) with no between-group difference at 12 months.<sup>36</sup>

Furthermore, noncardiac factors such as comorbidities that impair the oxygen cascade and are not modifiable by treatment with an SGLT2 inhibitor may have limited the scope for improvement in 6MWD, which for many patients with HF is not a test of submaximal exercise capacity (as is commonly thought) but often requires maximal or even supramaximal effort above anaerobic threshold.<sup>37,38</sup> Nevertheless, the observed increase in step count, time spent in MVPA, and VMUs provide an objective validation for the improvements in patient-reported functional limitations previously reported with dapagliflozin.<sup>2,19,20</sup>

There are limitations to this exploratory post hoc analysis that should be recognized. The accelerometer substudy of the DETERMINE trials was voluntary; therefore, the patients who chose to take part and who provided adequate data for these analyses (26% of the total DETERMINE population) may not necessarily be representative of all patients with HF. Less than half of the patients with any accelerometry data provided adequate data for this study, highlighting a challenge with the use of wearable devices in clinical trials. Furthermore, the requirement for a minimum 6MWD for inclusion in the DETERMINE trials may limit the generalizability of the results. The definition of the amount of accelerometer data provided by a patient to be eligible for this study was the definition prespecified in the DETERMINE trials' statistical analysis plan. We did not examine alternative data filter definitions, which may have provided alternative results. The use of a waist-worn device may have underestimated the time spent in stationary activities such as household chores, which may have been detected using a wrist-worn device. Wearable accelerometers may have limited sensitivity to detect low levels of activity as compared with more intense activity; however, the device used in the DETERMINE trials has been shown to perform favorably to other devices at lower levels of activity.<sup>39</sup> Additionally, there are limitations to the use of categories of activity intensity that are not specific for patients with HF who expend more energy at any given level of activity as compared with patients without HF (and, therefore, the use of non-HF-specific cutoffs may underestimate the amount of activity).<sup>40,41</sup> The small sample size may have limited our ability to detect smaller treatment effects on time in LVPA, movement intensity during walking, and the

total number of activity counts. Due to the relatively short follow-up time and small number of clinical events, we were unable to examine the association between changes in accelerometer-based measures of physical activity and outcomes in the DETERMINE trials. Measurements relating to changes in cardiac function, filling pressures, and remodeling were not performed in the DETERMINE trials, so we were unable to examine the relationship between these and the observed changes in accelerometer-based measures of physical activity.

## CONCLUSIONS

In this exploratory analysis of the DETERMINE trials, dapagliflozin had a beneficial effect on selected accelerometer-based measures of physical activity in patients with HF across the entire LVEF spectrum. Dapagliflozin increased the total daily number of steps, the time spent in MVPA, and VMUs per minute (a measure of movement intensity) in patients with HF, yet it did not improve 6MWD, as previously reported. Accelerometer-based measurements of everyday activity may provide complementary information to 6MWD and identify beneficial effects of treatment not detected by 6MWD.

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Dr Docherty's employer, the University of Glasgow, has been remunerated by AstraZeneca for his work on clinical trials; he has received speaker fees from AstraZeneca, Boehringer Ingelheim, Pharmacosmos, Translational Medical Academy, and Radcliffe Cardiology; has served on Advisory Boards for Us2.ai and holds stock in the company; has served on an advisory board and served on a clinical end point committee for Bayer AG; has performed consultancy for FIRE-1; and has received research grant support (paid to his institution) from AstraZeneca, Roche,



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## Supplemental Material

Tables S1–S3

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