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Efficacy and Safety of Dapagliflozin According to Frailty in Patients with Heart Failure: A Prespecified Analysis of the DELIVER Trial

Running Title: Butt et al.; *Dapagliflozin and frailty in HFmrEF and HFpEF*

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Abstract

Background: Frailty is increasing in prevalence and because frail patients are often perceived to have a less favorable benefit/risk profile, they may be less likely to receive new pharmacological treatments. We investigated the efficacy and tolerability of dapagliflozin according to frailty status in patients with heart failure and mildly reduced and preserved ejection fraction randomized in DELIVER.
Methods: Frailty was measured using the Rockwood cumulative deficit approach. The primary endpoint was time to a first worsening heart failure event or cardiovascular death.
Results: Of the 6263 patients randomized, a Frailty Index (FI) was calculable in 6258. In total, 2,354 (37.6%) patients had class 1 frailty (FI <0.210, i.e., not frail), 2,413 (38.6%) were in class 2 (FI 0.211-0.310, i.e., more frail), and 1,491 (23.8%) had class 3 frailty (FI >0.311, i.e., most frail). Greater frailty was associated with a higher rate of the primary endpoint (per 100 person-years): FI class 1, 6.3 (95% CI 5.7-7.1); class 2, 8.3 (7.5-9.1); and class 3, 13.4 (12.1-14.7), P<0.001. The effect of dapagliflozin (as a hazard ratio) on the primary endpoint from FI class 1 to 3 was: 0.85 (95% CI, 0.68-1.06); 0.89 (0.74-1.08); and 0.74 (0.61-0.91), respectively ($P_{interaction}$=0.40). Although frailer patients had worse KCCQ scores at baseline, the improvement with dapagliflozin was greater than in less frail patients: placebo-corrected improvement in KCCQ-OSS at 4 months FI class 1, 0.3 (95% CI -0.9 to 1.4); class 2, 1.5 (0.3-2.7); and class 3, 3.4 (1.7-5.1) [$P_{interaction}$=0.021]. Adverse reactions and treatment discontinuation, while more frequent in frailer patients, were not more common with dapagliflozin than placebo, irrespective of frailty class.
Conclusions: In DELIVER, frailty was common and associated with worse outcomes. The benefit of dapagliflozin was consistent across the range of frailty studied. The improvement in health-related quality of life with dapagliflozin occurred early and was greater in patients with greater frailty.
Clinical Trial Registration: Clinicaltrials.gov; Unique identifier: NCT03619213.

Key words: Heart failure; frailty; clinical trial; outcomes.

Abbreviations

AF: Atrial fibrillation
ATMOSPHERE: Aliskiren Trial of Minimizing OutcomeS in Patients With HEart Failure
DELIVER: Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure
ECG: Electrocardiogram
eGFR: Estimated glomerular filtration rate
FI: Frailty Index
HF: Heart failure
HFmrEF: Heart failure with mildly reduced ejection fraction
HFpEF: Heart failure with preserved ejection fraction
HR: Hazard ratio
KCCQ-CSS: Kansas City Cardiomyopathy Questionnaire Clinical Summary Score
KCCQ-OSS: Kansas City Cardiomyopathy Questionnaire Overall Summary Score
KCCQ-TSS: Kansas City Cardiomyopathy Questionnaire Total Symptom Score
LVEF: Left ventricular ejection fraction
NYHA: New York Heart Association
NT-proBNP: N-terminal pro-B-type natriuretic peptide
PARADIGM-HF: Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure
PARAGON-HF: Prospective Comparison of ARNI With ARB Global Outcomes in Heart Failure With Preserved Ejection Fraction
RR: Rate ratio
TOPCAT: Treatment of Preserved Cardiac Function with an Aldosterone Antagonist

Clinical Perspective

What is new?

- In a prespecified analysis of the DELIVER trial, greater frailty was associated with more impairment of health status and clinical outcomes in patients with heart failure and mildly reduced and preserved ejection fraction.
- The beneficial effects of dapagliflozin, compared with placebo, on clinical outcomes were consistent regardless of frailty class, but the improvements in symptoms, physical function, and quality of life were larger in the frailest patients.
- Adverse events were not more common in individuals randomized to receive dapagliflozin compared with placebo, irrespective of frailty class.

What are the clinical implications?

- The benefit/risk balance related to frailty in patients with heart failure and mildly reduced and preserved ejection fraction was favorable for dapagliflozin.
- These findings should challenge any clinical reluctance to introduce dapagliflozin in patients perceived to be frail.

Introduction

Frailty, a syndrome characterized by a decline in homeostatic reserves across multiple physiological systems and increased vulnerability to endogenous and exogenous stressors, is an increasing health burden globally.[1–4] The implications of frailty are substantial not only for public health, but also for individual patients, who are not only at greater risk of outcomes such as hospital admission and premature death, but also of falls, reduced mobility, impaired quality of life, institutional placement, social isolation, and loneliness.[1–4] Since physiological reserves decline with both age and number of comorbidities, frailty is related to, but not the same as ageing and multimorbidity. Frailty can also occur in younger people and those without comorbidities, and poor appetite, fatigue, reduced mobility, and declining cognition, all of which are manifestations of frailty, are not specific to a particular disease.[1–4]

Although heart failure (HF) and frailty are two distinct conditions, they often coexist, and each increases the likelihood and complicates the course, of the other. Thus, patients with HF are up to six times more likely to be frail than the general population, and the catabolic/anabolic imbalance in HF may accelerate the development of frailty.[5–9] Frail HF patients also have a substantially higher risk of functional decline, hospital admissions, and death, compared to non-frail HF patients.[9–15] Recently, there has also been increasing interest in evaluating the effects of new HF treatments in frail patients. There is a common perception that evidence-based therapies are less effective in frail individuals, and there are concerns that these patients have more treatment intolerance, experience more adverse drug reactions, and drug interactions, and thus are more likely to discontinue treatment.[9,10,16–18] Given the anticipation of a less favorable risk-benefit profile in frail patients, clinicians may be more reluctant to initiate new therapies in such individuals.[9,10,16–18] However, there is little evidence to support this assumption, and frail HF patients may even have greater absolute benefits on worsening HF events and health-related quality of life with certain pharmacological therapies

and aerobic exercise training.[10,11,15,19–23] This is particularly important given the likely role of hospitalization and worsening of HF in accelerating frailty.

In the Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure (DELIVER) trial, dapagliflozin, compared with placebo, reduced the risk of worsening HF events or cardiovascular death, and improved symptoms, in 6,263 patients with HF and mildly reduced and preserved EF.[24] In this pre-specified analysis, we examined the efficacy and safety of dapagliflozin according to frailty status, using the Rockwood cumulative deficit approach.

Methods

DELIVER was randomized, double-blind, controlled trial in patients with HF and mildly reduced and preserved left ventricular ejection fraction (LVEF), comparing the efficacy and safety of dapagliflozin 10 mg once daily compared to matching placebo, in addition to standard care. The design, baseline characteristics, and primary results of DELIVER are published.[24–27] The trial protocol was approved by the Ethics Committee at all participating institutions, and all patients provided written informed consent. The corresponding author had full access to all the trial data and takes responsibility for its integrity and the data analysis. Data underlying the findings described in this manuscript may be obtained following AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

Study patients

Key inclusion criteria were age ≥40 years, HF diagnosis ≥6 weeks with at least intermittent use of diuretic treatment, New York Heart Association (NYHA) functional class II-IV, a LVEF >40%, evidence of structural heart disease (either left atrial enlargement or left ventricular hypertrophy), and an N-terminal pro-B-type natriuretic peptide (NT-proBNP)

concentration ≥300 pg/mL (≥600 pg/mL if atrial fibrillation/flutter on the electrocardiogram [ECG] at enrolment). Both ambulatory and hospitalized patients were eligible. Key exclusion criteria were type 1 diabetes; estimated glomerular filtration rate (eGFR) <25 mL/min/1.73m^2; and systolic blood pressure <95 mmHg. A complete list of exclusion criteria is provided in the design paper.[25]

Frailty Index

In the present analysis, frailty was assessed using the Rockwood cumulative deficit approach, and this approach has been described in detail previously.[10,11,28–30] Standard criteria for constructing a frailty index (FI) using this approach are the following: at least 30 items are required; items must be associated with health status; items must cover a range of body systems and not be isolated to one system; items must not be part of normal ageing or saturate too early (e.g., presbyopia), but they should generally increase with age. We created a 30-item FI, and these items were derived from medical history, vital signs, laboratory data, and the EuroQoL-5 Domain questionnaire (health-related quality of life measures, including functional status) **[Table S1].** A score was assigned for each non-missing item, and the FI score was calculated as the sum of these scores divided by the total number of non-missing items, with higher scores indicating greater frailty. Binary variables (e.g., a history of MI) were scored 0/1 (absent/present); ordinal variables (e.g., quality of life measures) were scored from 0 to 1 (in increments of 0.25, with a score of 1 indicating the greatest severity); and continuous variables (e.g., creatinine) were categorized and scored as 0/1 (normal/abnormal). Patients were excluded if they had ≥20% missing items.[10,11,31–33] Patients were divided into the following three subgroups: FI ≤0.210 (FI class 1) [classified as non-frail patients, as defined previously]; FI 0.211- 0.310 (FI class 2, i.e., more frail), and FI ≥0.311 (FI class 3, i.e., most frail).

Trial outcomes

The primary outcome in DELIVER was the composite of worsening HF (HF hospitalization or urgent HF visit) or cardiovascular death. The secondary outcomes in the trial were total HF events (first and repeat HF hospitalization or an urgent visit for worsening HF) and cardiovascular death; change from baseline to 8 months in the Kansas City Cardiomyopathy Questionnaire (KCCQ) total symptom score (KCCQ-TSS); cardiovascular death; and all-cause mortality. In the present analysis, we also examined the change from baseline to 8 months in the KCCQ overall and clinical summary score (KCCQ-OSS and -CSS, respectively) and the change in KCCQ-scores from baseline to 4 months; worsening HF, HF hospitalization and any hospitalization.

Prespecified safety analyses included serious adverse events, adverse events leading to discontinuation of trial treatment, and selected adverse events, including volume depletion, renal adverse events, amputation, major hypoglycemia, and diabetic ketoacidosis, for consistency across reporting in trials.

Statistical analyses

Baseline characteristics were summarized as frequencies with percentages, means with standard deviation, or medians with interquartile ranges. Differences in baseline characteristics were tested using the Cochran-Armitage trend test for binary variables, the Cochran-Mantel-Haenszel test for categorical variables, and the JonckheereTerpstra test and analysis of variance test for non-normal and normally distributed continuous variables, respectively.

Regardless of treatment allocation, time-to-event data were evaluated using the Kaplan-Meier estimator (all-cause death), the Aalen-Johansen estimator (all outcomes except all-cause death), and Cox proportional-hazards models, stratified according to diabetes mellitus status, and adjusted for treatment assignment, and hazard ratios (HR) with 95% CIs were reported

for FI (with FI class I as the reference). Total (first and recurrent) events were evaluated with semiparametric proportional-rates models,[34] stratified according to diabetes mellitus status and adjusted for treatment assignment, and rate ratios (RR) with 95% CIs were reported. In addition, HRs and RRs, stratified according to diabetes mellitus status, and adjusted for treatment assignment, age, sex, geographical region, a history of HF hospitalization, HF duration, log of NT-proBNP, LVEF, and NYHA functional class were reported; variables which were part of the FI were not adjusted for, since the categorization of FI into the three classes were conditioned on these variables.

To compare the effects of dapagliflozin with placebo, time-to-event data and total (first and recurrent) events were evaluated with Cox proportional-hazards models and semiparametric proportional-rates models, respectively, and these models were stratified according to diabetes mellitus status. HRs and RRs with 95% CI within each FI class were reported. The effect of dapagliflozin was also examined according to continuous FI as a fractional polynomial. The difference between treatment groups in the change in KCCQ-TSS, -CSS, and -OSS from baseline to 8 months was analyzed using mixed-effect models for repeated measurements, adjusted for baseline value, visit (month 1, 4 and 8), treatment assignment, and interaction of treatment and visit. The least-squares mean differences with 95% CI between treatment groups within each FI class were reported. The interaction term between treatment assignment and visit was included to examine the effect of dapagliflozin, compared with placebo, on the mean change in KCCQ scores at 4 and 8 months. To test for interaction between the treatment effect of dapagliflozin and FI, the Wald test was used for the Cox proportional-hazards models, the semiparametric proportional-rates models, and the mixed-effect models for repeated measurements.

All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC) and STATA version 17.0 (College Station, TX).

Results

Patient characteristics

Of the 6,263 patients randomized in DELIVER, FI was calculable for 6,258 patients. The numbers of patients with missing data for individual components of the FI are shown in **Tables S2** and **S3**. The distribution of FI is shown in **Figure S1**. Mean FI was 0.248 (standard deviation, 0.092) and median FI was 0.242 (interquartile range, 0.183-0.308; range 0-0.633). In total, 2,354 (37.6%) patients had class 1 frailty (FI $\leq$0.210, i.e., not frail), 2,413 (38.6%) were in class 2 (FI 0.211-0.310, i.e., more frail), and 1,491 (23.8%) had class 3 frailty (FI $\geq$0.311, i.e., most frail).

Baseline characteristics according to FI class are presented in **Table 1**. Compared to patients with lower FI, those with higher FI (worse frailty) were older, more often White (and less often Asian), more likely to have cardiovascular and non-cardiovascular comorbidities, and more often smokers. They also had higher systolic blood pressure, BMI, NT-proBNP (irrespective of AF on ECG), and hemoglobin A1c, but lower eGFR. Patients with higher FI were more likely to have a longer duration of HF, lower LVEF, and worse NYHA functional class and KCCQ scores than those with lower FI (i.e., less frailty).

Outcomes according to Frailty Index

Compared to patients in FI class 1 (the least frail), those in FI class 3 (the frailest) had a higher risk of worsening HF or cardiovascular death; worsening HF; HF hospitalization; any hospitalization; cardiovascular death; all-cause death; and total HF events and cardiovascular death, even after adjustment for known prognostic variables **(Figure 1, Table 2)**. Compared to individuals in FI class 1, those in FI class 2 also had a higher risk of these outcomes, although the association between FI class 2 and these outcomes were not statistically significant (except for any hospitalization), after adjustment for prognostic variables.

Effects of dapagliflozin on clinical outcomes according to Frailty Index

Primary composite outcome

Compared with placebo, dapagliflozin reduced the risk of worsening HF or cardiovascular death across FI classes – the HRs from lowest to highest FI class were: 0.85 [95% CI, 0.68-1.06], 0.89 [95% CI, 0.74-1.08], and 0.74 [95% CI, 0.61-0.91], respectively. There was no interaction between FI class (as an ordinal variable) and the effect of dapagliflozin on the primary outcome (P for interaction=0.40) **[Table 2]**. The effect of dapagliflozin was also consistent across the spectrum of continuous FI (P for interaction=0.27) **[Figure 2]**.

In the overall trial, the HR for the primary composite endpoint with dapagliflozin compared to placebo was 0.82 (95% CI, 0.73-0.92); applying a relative risk reduction of 18% to the placebo event rate to each FI class resulted in a number of patients needed to treat (NNT) of 40, 31, and 19, respectively, to prevent one primary event over the median follow-up of 2.3 years.

Secondary outcomes

The effect of dapagliflozin was consistent across FI classes for worsening HF; HF hospitalization; cardiovascular death; all-cause death; and the composite of total HF events or cardiovascular death (P for interaction for all outcomes $\geq$0.25) **[Table 2, Figure 3]**. The effect of dapagliflozin on these outcomes was also consistent across the spectrum of continuous FI (P for interaction $\geq$0.11) **[Figure 2]**.

In the overall trial, the HR for HF hospitalization with dapagliflozin compared to placebo was 0.77 (95% CI 0.67-0.89); applying a relative risk reduction of 23% to the placebo event rate in each FI class resulted in NNTs of 48, 37, and 20, in FI classes 1 to 3, respectively, to prevent at least one hospital admission for worsening heart failure over the median follow-up of 2.3 years.

Symptoms and health status measured using the KCCQ

At baseline, 5,793 patients (92.6%) had available KCCQ data. At 8 months, 4,485 patients (71.7% of the study population; 74.3% of the study population alive) had available KCCQ data and 1,773 did not (220 due to death, 1,553 due to other reasons than death). The effect of dapagliflozin on the mean change in KCCQ-scores was modified by FI class; larger increases (improvements) were seen with dapagliflozin, compared to placebo, at 4 and 8 months among patients with a higher FI i.e., greater frailty **[Table 3]**.

Safety analyses

The proportions of patients who discontinued trial treatment or experienced adverse events increased with increasing frailty. However, there were no differences between treatments (dapagliflozin versus placebo) across all FI classes **(Table 4)**.

Discussion

In this pre-specified analysis of DELIVER, approximately 63% of patients were categorized as frail. Greater frailty was associated with more impairment in health status and worse clinical outcomes, including hospitalizations and death. The beneficial effects of dapagliflozin, compared with placebo, on clinical outcomes were consistent regardless of frailty class. Importantly, the improvements in symptoms, physical function, and quality of life were larger in the frailest patients. Adverse events, although more frequent in frailer patients, were not more common in those randomized to dapagliflozin compared with placebo.

Prevalence of and outcomes according to frailty

The mean FI in DELIVER, calculated using the Rockwood cumulative deficits approach, was 0.248 (standard deviation, 0.092). Generally, a FI ≤0.210 is considered non-frail. In people >65 years participating in the UK Biobank, the mean FI was 0.129.[35] Other population

studies have reported a mean FI ranging from 0.14 to 0.16.[36,37] In a trial comparing aspirin with placebo in 19,114 people aged ≥70 living in the United States (≥65 years in U.S. minorities) and Australia, and free of cardiovascular disease, persistent physical disability, and dementia, the mean FI was 0.11 and only 8.1% of participants were frail.[38] Even in patients ≥80 years enrolled in two hypertension trials, the median FI was only 0.17 to 0.18.[39,40]

Clearly, the higher FI among participants in DELIVER, contrasts strikingly with these earlier reports, confirming that frailty is much more prevalent in patients with HFmrEF and HFpEF than in the people participating in the studies mentioned above. The mean FI in DELIVER (0.248) was lower than in patients with HFpEF in TOPCAT-Americas (mean FI 0.37) but similar to that in the much larger and more global (and therefore more comparable) PARAGON-HF trial (mean FI 0.227) which also enrolled patients with HFpEF.[11] Interestingly, using the same approach, the FI in the generally younger patients with HFrEF in the PARADIGM-HF and ATMOSPHERE (mean FI 0.250) and DAPA-HF (0.216) was similar to that in DELIVER and PARAGON-HF, confirming that frailty is common in all HF phenotypes and not confined to the very elderly.[10,15]

Impact of frailty

Increasing frailty was accompanied by a large difference KCCQ scores at baseline (these were16 to 17 points lower in the most compared to least frail patients), showing that greater frailty was associated with much more impairment of health-related quality of life and symptoms. The magnitude of the difference in KCCQ scores between more and less frail patients was similar to that observed in both PARAGON-HF and DAPA-HF.[15]

Increasing frailty was also associated with worse outcomes during follow-up. In DELIVER, as in PARAGON-HF and the three large HFrEF trials described above, there was a graded relationship between FI and the standard outcomes reported i.e., the rates of hospitalization

for HF and cardiovascular death increased with increasing FI.[10,15] However, the gradients in the association between frailty and the broader outcomes of hospital admission for any cause and death from any cause were, if anything, steeper than for the more specific heart failure outcomes, emphasizing the more general impact of frailty on health.

Treatment effect of dapagliflozin according to frailty

As alluded to in the introduction, the benefit-risk profile of pharmacological therapy is often considered less favorable in frail patients, with underutilization and discontinuation of recommended treatments in such individuals.[9,10,16–18] While it was true that greater frailty was associated with higher rates of adverse events and discontinuation of randomized treatment, neither was more common in the dapagliflozin group than in the placebo group. More importantly, the efficacy of dapagliflozin was not diminished in the frailest patients. We found there was no statistically significant interaction between frailty and the effects of dapagliflozin, compared with placebo, for any of the outcomes assessed in our categorical analysis and this was confirmed when FI was analysed as a continuous variable. Indeed, there was a trend towards a greater effect on worsening heart failure events in frailer patients, consistent with what was observed with sacubitril/valsartan in PARAGON-HF. Because of the considerably higher event rate in the frailest patients, the absolute benefit was twice as large in these individuals as in non-frail participants, emphasizing the importance of counteracting any tendency to therapeutic nihilism in patients deemed to be frail.

These findings in DELIVER were consistent with those using dapagliflozin in DAPA-HF and with sacubitril-valsartan in patients with both HFrEF and HFpEF.[15] Although the major effect in patients with HFpEF was on HF hospitalization, this is of potentially great importance given the likely role of hospital admission in accelerating frailty, the prevention and treatment of which has become a key priority in clinical medicine.[9,41]

Improvement of health status is another major goal of treatment in patients with HF and this is all the more so in frailer patients, who have a much greater symptom burden and worse health-related quality of life than non-frail patients. Interestingly, the improvement in symptom burden and quality of life with dapagliflozin was significantly larger in patients with greater frailty. This benefit was apparent as early as 4 months after starting treatment. Symptom control and continuation of daily activities are important, per se, for patients with HF and may help prevent the development of frailty and progression of existing frailty in these most vulnerable individuals.

Limitations

The specific inclusion and exclusion criteria in DELIVER precluded the enrolment of the most frail patients, and it is likely that the participants in DELIVER were less frail than patients with HFmrEF and HFpEF in the general population. Although the effects of dapagliflozin on clinical outcomes were consistent across the range of FI in DELIVER (0-0.633), our results may not be generalizable to all patients with HF, and it is possible that the beneficial effects of this therapy may be attenuated in very frail patients. We were not able to test other frailty scores that include assessments of muscle strength and functional capacity as these measurements were not made in DELIVER. Finally, given the observational nature of the analyses on the association between FI and clinical outcomes, the possibility of residual confounding cannot be fully excluded despite adjustment for measured, known confounders in our analyses.

Conclusions

In DELIVER, greater frailty was associated with more impairment of health status and worse clinical outcomes. The relative risk reduction in clinical events with dapagliflozin was consistent across frailty classes. The improvement in health-related quality of life with

dapagliflozin occurred early and was greater in patients with greater frailty. Adverse events were not more common in individuals randomized to dapagliflozin compared with placebo, irrespective of frailty class. Therefore, the benefit/risk balance related to frailty was favorable for dapagliflozin. These findings should challenge any clinical reluctance to introduce this new therapy in patients perceived to be frail.

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Supplemental Materials

Tables S1 – S3

Figure S1

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Table 1. Baseline Characteristics According to Frailty Index

	FI <=0.210 (not frail) N=2,354	FI 0.211-0.310 (more frail) N=2,413	FI =>0.311 (most frail) N=1,491	P-value
Age (years), mean (SD)	70.1±10.3	72.6±9.0	72.7±8.8	<0.001
Age (years), N (%)				<0.001
<=65	726 (30.8)	486 (20.1)	290 (19.5)	
66-75	843 (35.8)	961 (39.8)	608 (40.8)	
=>76	785 (33.3)	966 (40.0)	593 (39.8)	
Sex, N (%)				0.79
Women	1,046 (44.4)	1,050 (43.5)	650 (43.6)	
Men	1,308 (55.6)	1,363 (56.5)	841 (56.4)	
Race, N (%)				<0.001
White	1,416 (60.2)	1,818 (75.3)	1,201 (80.5)	
Black or African American	50 (2.1)	54 (2.2)	55 (3.7)	
Asian	673 (28.6)	401 (16.6)	199 (13.3)	
Other	215 (9.1)	140 (5.8)	36 (2.4)	
Geographic region, N (%)				<0.001
Europe and Saudi Arabia	900 (38.2)	1,298 (53.8)	803 (53.9)	
Asia	660 (28.0)	381 (15.8)	184 (12.3)	
Latin America	594 (25.2)	441 (18.3)	146 (9.8)	
North America	200 (8.5)	293 (12.1)	358 (24.0)	
Physiological measures				
Systolic blood pressure (mmHg), mean (SD)	123.5±14.0	129.4±14.9	133.8±15.9	<0.001
Diastolic blood pressure (mmHg), mean (SD)	73.8±9.8	74.0±10.3	74.1±11.3	0.34
Heart rate (bpm), mean (SD)	71.9±11.8	71.2±11.5	71.3±12.0	0.10
Body mass index, mean (SD)	28.1±5.8	30.2±5.9	32.1±6.2	<0.001
Atrial fibrillation/flutter on baseline ECG, N (%)	986 (41.9)	1,039 (43.1)	619 (41.5)	0.93
NT-proBNP (pg/mL), median (IQR)	961 (608-1627)	1034 (624-1795)	1084 (642-1897)	<0.001
No atrial fibrillation/flutter on baseline ECG	699 (452-1201)	706 (473-1302)	761 (481-1391)	0.004
Atrial fibrillation/flutter on baseline ECG	1314 (933-2033)	1408 (975-2292)	1510 (1019-2484)	<0.001
Hemoglobin A1c (%), mean (SD)	6.2±1.2	6.6±1.3	7.1±1.6	<0.001
Creatinine (μmol/L), mean (SD)	91.1±24.2	104.4±30.4	117.3±34.8	<0.001
eGFR (mL/min/1.73m^2), mean (SD)	68.7±18.0	59.1±18.3	52.1±17.4	<0.001

eGFR (mL/min/1.73m^2), N (%)				<0.001
<60	697 (29.6)	1,300 (53.9)	1,070 (71.8)	
=>60	1,657 (70.4)	1,112 (46.1)	421 (28.2)	
Smoking status, N (%)				<0.001
Current	172 (7.3)	179 (7.4)	133 (8.9)	
Former	764 (32.5)	887 (36.8)	609 (40.8)	
Never	1,418 (60.2)	1,347 (55.8)	749 (50.2)	
Duration of HF, N (%)				<0.001
0 - 3 months	263 (11.2)	225 (9.3)	80 (5.4)	
>3 - 6 months	240 (10.2)	241 (10.0)	111 (7.4)	
>6 - 12 months	366 (15.6)	328 (13.6)	146 (9.8)	
>1 - 2 years	397 (16.9)	368 (15.3)	230 (15.4)	
>2 - 5 years	549 (23.4)	621 (25.7)	398 (26.7)	
>5 years	534 (22.7)	630 (26.1)	526 (35.3)	
Left ventricular ejection fraction (%), mean (SD)	54.2±9.1	54.2±8.8	54.1±8.3	0.67
Left ventricular ejection fraction (%), N (%)				0.004
<=49	818 (34.7)	816 (33.8)	481 (32.3)	
50-59	794 (33.7)	865 (35.8)	595 (39.9)	
=>60	742 (31.5)	732 (30.3)	415 (27.8)	
NYHA class, N (%)				<0.001
I	1 (0.0)	0 (0.0)	0 (0.0)	
II	1,943 (82.5)	1,810 (75.0)	956 (64.1)	
III	403 (17.1)	597 (24.7)	530 (35.5)	
IV	7 (0.3)	6 (0.2)	5 (0.3)	
KCCQ total symptom score, mean (SD)	76.8±19.7	69.7±21.7	59.7±22.7	<0.001
KCCQ clinical summary score, mean (SD)	75.3±18.5	67.9±20.0	57.9±20.6	<0.001
KCCQ overall summary score, mean (SD)	73.2±18.1	66.3±19.6	56.6±20.2	<0.001
Medical history, N (%)				
Hospitalization for HF	821 (34.9)	966 (40.0)	750 (50.3)	<0.001
Atrial fibrillation/flutter	1,188 (50.5)	1,388 (57.5)	976 (65.5)	<0.001
Stroke	92 (3.9)	225 (9.3)	280 (18.8)	<0.001
Stroke/TIA	115 (4.9)	294 (12.2)	363 (24.3)	<0.001
Angina	227 (9.6)	590 (24.5)	678 (45.5)	<0.001
Myocardial infarction	319 (13.6)	675 (28.0)	643 (43.1)	<0.001

PCI or CABG	354 (15.0)	869 (36.0)	841 (56.4)	<0.001
Any coronary artery disease	694 (29.5)	1,322 (54.8)	1,146 (76.9)	<0.001
Any atherosclerotic disease	812 (34.5)	1,488 (61.7)	1,250 (83.8)	<0.001
Peripheral artery disease	44 (1.9)	171 (7.1)	278 (18.6)	<0.001
Non-coronary revascularization	7 (0.3)	52 (2.2)	81 (5.4)	<0.001
Valvular heart disease	456 (19.4)	674 (27.9)	535 (35.9)	<0.001
Pulmonary embolism	16 (0.7)	35 (1.5)	55 (3.7)	<0.001
Hypertension	1,814 (77.1)	2,275 (94.3)	1,459 (97.9)	<0.001
Type 2 diabetes mellitus	558 (23.7)	1,165 (48.3)	1,081 (72.5)	<0.001
Chronic obstructive pulmonary disease	111 (4.7)	270 (11.2)	310 (20.8)	<0.001
Gout	89 (3.8)	253 (10.5)	287 (19.2)	<0.001
Malignancy	58 (2.5)	106 (4.4)	140 (9.4)	<0.001
Syncope	36 (1.5)	89 (3.7)	135 (9.1)	<0.001
Sleep apnea	57 (2.4)	167 (6.9)	261 (17.5)	<0.001
Neuropathy	33 (1.4)	185 (7.7)	402 (27.0)	<0.001
Dyslipidemia	969 (41.2)	1,725 (71.5)	1,294 (86.8)	<0.001
Osteoporosis	58 (2.5)	139 (5.8)	127 (8.5)	<0.001
Treatment, N (%)				
Loop diuretic	1,696 (72.1)	1,836 (76.1)	1,274 (85.4)	<0.001
Other diuretic (excluding loop and MRA)	489 (20.8)	559 (23.2)	295 (19.8)	0.71
ACEi	800 (34.0)	929 (38.5)	564 (37.8)	0.007
ARB	824 (35.0)	897 (37.2)	550 (36.9)	0.19
ACEI/ARB	1,621 (68.9)	1,811 (75.1)	1,108 (74.3)	<0.001
ARNI	159 (6.8)	94 (3.9)	48 (3.2)	<0.001
Beta-blocker	1,906 (81.0)	2,014 (83.5)	1,253 (84.0)	0.01
MRA	1,134 (48.2)	976 (40.4)	555 (37.2)	<0.001
Digoxin	144 (6.1)	100 (4.1)	52 (3.5)	<0.001
Lipid-lowering medication	1,179 (50.1)	1,750 (72.5)	1,226 (82.2)	<0.001
Antiplatelet	806 (34.3)	1,064 (44.1)	758 (50.8)	<0.001
Anticoagulant	1,160 (49.3)	1,338 (55.4)	883 (59.2)	<0.001
Pacemaker	151 (6.4)	245 (10.2)	265 (17.8)	<0.001
CRT-P/CRT-D	14 (0.6)	42 (1.7)	44 (3.0)	<0.001
ICD	34 (1.4)	48 (2.0)	31 (2.1)	0.12
ICD/CRT-D	43 (1.8)	72 (3.0)	53 (3.6)	<0.001

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BMI, body mass index; CABG, coronary artery bypass graft surgery; CSS, clinical summary score; CRT, cardiac resynchronization therapy; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; FI, frailty index; HF, heart failure; ICD, implantable cardioverter-defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid-receptor antagonist; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OSS, overall summary score; PCI, percutaneous coronary intervention; SD, standard deviation; TIA, transient ischemic attack; TSS, total symptom score.

Table 2. Outcomes According to Frailty Index

	FI ≤0.210 (not frail) N=2,354	FI 0.211-0.310 (more frail) N=2,413	FI ≥0.311 (most frail) N=1,491
Primary composite outcome			
No. of events (%)	309 (13.1)	418 (17.3)	394 (26.4)
Event rate per 100 person-years (95% CI)	6.3 (5.7-7.1)	8.3 (7.5-9.1)	13.4 (12.1-14.7)
HR (95% CI)*	Reference	1.28 (1.10-1.48)	2.00 (1.70-2.34)
HR (95% CI)**	Reference	1.13 (0.97-1.32)	1.53 (1.29-1.81)
Worsening HF			
No. of events (%)	220 (9.3)	295 (12.2)	307 (20.6)
Event rate per 100 person-years (95% CI)	4.5 (3.9-5.1)	5.9 (5.2-6.6)	10.4 (9.3-11.6)
HR (95% CI)*	Reference	1.27 (1.07-1.52)	2.20 (1.83-2.64)
HR (95% CI)**	Reference	1.13 (0.94-1.36)	1.63 (1.33-1.98)
HF hospitalization			
No. of events (%)	198 (8.4)	265 (11.0)	284 (19.0)
Event rate per 100 person-years (95% CI)	4.0 (3.5-4.6)	5.2 (4.6-5.9)	9.5 (8.5-10.7)
HR (95% CI)*	Reference	1.27 (1.06-1.54)	2.28 (1.88-2.76)
HR (95% CI)**	Reference	1.13 (0.93-1.37)	1.68 (1.36-2.07)
Any hospitalization			
No. of events (%)	716 (30.4)	927 (38.4)	820 (55.0)
Event rate per 100 person-years (95% CI)	16.6 (15.4-17.8)	21.5 (20.2-22.9)	35.5 (33.1-38.0)
HR (95% CI)*	Reference	1.29 (1.17-1.43)	2.10 (1.89-2.34)
HR (95% CI)**	Reference	1.26 (1.14-1.40)	1.89 (1.69-2.12)
Cardiovascular death			
No. of events (%)	145 (6.2)	187 (7.7)	160 (10.7)
Event rate per 100 person-years (95% CI)	2.8 (2.4-3.3)	3.5 (3.0-4.0)	4.8 (4.1-5.6)
HR (95% CI)*	Reference	1.22 (0.97-1.52)	1.68 (1.32-2.13)
HR (95% CI)**	Reference	1.04 (0.83-1.30)	1.29 (1.00-1.67)
All-cause death			
No. of events (%)	288 (12.2)	401 (16.6)	334 (22.4)
Event rate per 100 person-years (95% CI)	5.6 (5.0-6.3)	7.4 (6.7-8.2)	10.0 (9.0-11.2)
HR (95% CI)*	Reference	1.32 (1.13-1.53)	1.77 (1.50-2.10)
HR (95% CI)**	Reference	1.13 (0.97-1.33)	1.45 (1.21-1.73)

Total HF events or cardiovascular death			
No. of events	458	675	728
RR (95% CI)*	Reference	1.34 (1.12-1.60)	2.31 (1.92-2.76)
RR (95% CI)**	Reference	1.17 (0.98-1.39)	1.68 (1.39-2.02)

CI, confidence interval; FI, frailty index; HF, heart failure; HR, hazard ratio; RR, rate ratio.
**Stratified by diabetes status and adjusted for treatment assignment.*
***Stratified by diabetes status and adjusted for treatment assignment, age, sex, geographical region, a history of HF hospitalization, HF duration, log of N-terminal pro-B-type natriuretic peptide, left ventricular ejection fraction, and New York Heart Association.*

Table 3. Effects of Dapagliflozin Compared With Placebo on Outcomes According to Frailty Index

Outcome	FI ≤0.210 (not frail) N=2,354		FI 0.211-0.310 (more frail) N=2,413		FI ≥0.311 (most frail) N=1,491		P-value for interaction
	Placebo N=1,157	Dapagliflozin N=1,197	Placebo N=1,207	Dapagliflozin N=1,206	Placebo N=766	Dapagliflozin N=725	
Primary composite outcome							0.40
No. of events (%)	162 (14.0)	147 (12.3)	220 (18.2)	198 (16.4)	227 (29.6)	167 (23.0)	
Event rate per 100 person-years (95% CI)	6.9 (5.9-8.0)	5.8 (5.0-6.8)	8.8 (7.7-10.0)	7.8 (6.8-9.0)	15.4 (13.5-17.5)	11.4 (9.8-13.2)	
HR (95% CI)*	0.85 (0.68-1.06)		0.89 (0.74-1.08)		0.74 (0.61-0.91)		
Worsening HF							0.25
No. of events (%)	114 (9.9)	106 (8.9)	157 (13.0)	138 (11.4)	183 (23.9)	124 (17.1)	
Event rate per 100 person-years (95% CI)	4.8 (4.0-5.8)	4.2 (3.5-5.1)	6.3 (5.4-7.3)	5.5 (4.6-6.4)	12.4 (10.7-14.3)	8.4 (7.1-10.1)	
HR (95% CI)*	0.87 (0.67-1.14)		0.87 (0.69-1.10)		0.69 (0.55-0.86)		
HF hospitalization							0.46
No. of events (%)	105 (9.1)	93 (7.8)	144 (11.9)	121 (10.0)	169 (22.1)	115 (15.9)	
Event rate per 100 person-years (95% CI)	4.4 (3.6-5.3)	3.7 (3.0-4.5)	5.7 (4.8-6.7)	4.7 (4.0-5.7)	11.3 (9.7-13.1)	7.7 (6.5-9.3)	
HR (95% CI)*	0.83 (0.63-1.10)		0.83 (0.65-1.06)		0.69 (0.54-0.87)		
Cardiovascular death							0.44
No. of events (%)	77 (6.7)	68 (5.7)	93 (7.7)	94 (7.8)	91 (11.9)	69 (9.5)	
Event rate per 100 person-years (95% CI)	3.1 (2.5-3.9)	2.6 (2.0-3.3)	3.4 (2.8-4.2)	3.5 (2.9-4.3)	5.4 (4.4-6.6)	4.2 (3.4-5.4)	
HR (95% CI)*	0.84 (0.60-1.16)		1.03 (0.77-1.37)		0.79 (0.58-1.08)		
All-cause death							0.69
No. of events (%)	146 (12.6)	142 (11.9)	201 (16.7)	200 (16.6)	179 (23.4)	155 (21.4)	
Event rate per 100 person-years (95% CI)	5.8 (5.0-6.9)	5.4 (4.6-6.4)	7.4 (6.4-8.5)	7.5 (6.5-8.6)	10.5 (9.1-12.2)	9.5 (8.1-11.1)	
HR (95% CI)*	0.92 (0.73-1.16)		1.01 (0.83-1.23)		0.90 (0.73-1.12)		
Total HF events or cardiovascular death							0.57
No. of events	246	222	376	299	434	294	
RR (95% CI)*	0.85 (0.66-1.10)		0.80 (0.64-1.01)		0.71 (0.55-0.90)		
KCCQ-TSS							0.016
Change from baseline to 4 months (95% CI)**	4.8 (3.8-5.7)	5.1 (4.2-6.0)	5.7 (4.7-6.7)	7.9 (6.8-8.9)	7.8 (6.4-9.2)	11.5 (10.0-12.9)	
Placebo-corrected change at 4 months (95% CI)**	0.4 (-1.0 to 1.7)		2.2 (0.8-3.6)		3.6 (1.6-5.7)		
Change from baseline to 8 months (95% CI)**	4.3 (3.2-5.3)	6.0 (5.0-7.0)	5.0 (3.8-6.1)	8.0 (6.9-9.2)	8.9 (7.4-10.5)	10.8 (9.1-12.4)	
Placebo-corrected change at 8 months (95% CI)**	1.7 (0.2-3.2)		3.1 (1.5-4.7)		1.8 (-0.5 to 4.1)		
KCCQ-OSS							0.021
Change from baseline to 4 months (95% CI)**	4.1 (3.3-5.0)	4.4 (3.5-5.2)	5.5 (4.6-6.4)	7.0 (6.1-7.9)	6.7 (5.5-7.9)	10.1 (8.9-11.4)	
Placebo-corrected change at 4 months (95% CI)**	0.3 (-0.9 to 1.4)		1.5 (0.3-2.7)		3.4 (1.7-5.1)		
Change from baseline to 8 months (95% CI)**	3.8 (2.8-4.7)	5.2 (4.3-6.1)	4.8 (3.8-5.8)	7.1 (6.1-8.1)	7.6 (6.2-9.0)	10.0 (8.6-11.4)	

Placebo-corrected change at 8 months (95% CI)**	1.4 (0.1-2.8)		2.3 (0.9-3.7)		2.4 (0.4-4.4)		
KCCQ-CSS							0.018
Change from baseline to 4 months (95% CI)**	3.9 (3.0-4.7)	4.3 (3.5-5.2)	5.1 (4.2-6.0)	7.2 (6.3-8.1)	6.5 (5.3-7.8)	10.2 (8.9-11.5)	
Placebo-corrected change at 4 months (95% CI)**	0.5 (-0.8 to 1.7)		2.1 (0.8-3.4)		3.7 (1.8-5.5)		
Change from baseline to 8 months (95% CI)**	3.6 (2.6-4.5)	5.2 (4.3-6.2)	4.3 (3.3—5.3)	7.1 (6.1-8.1)	7.4 (6.0-8.9)	9.6 (8.1-11.1)	
Placebo-corrected change at 8 months (95% CI)**	1.6 (0.3-3.0)		2.8 (1.3-4.3)		2.2 (0.1-4.2)		

CI, confidence interval; FI, frailty index; HF, heart failure; HR, hazard ratio; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire – Total Summary Score; RR, rate ratio.
**Stratified by diabetes status.*
***Mixed-effect models for repeated measurements adjusted for baseline value, visit (months 1, 4, and 8), randomized treatment, and interaction of treatment and visit.*

Table 4. Adverse Events in Patients Assigned to Dapagliflozin or Placebo According to Frailty Index

Adverse event	FI ≤0.210 (not frail) N=2,350		FI 0.211-0.310 (more frail) N=2,411		FI ≥0.311 (most frail) N=1,487		P-value for interaction
	Placebo N=1,155	Dapagliflozin N=1,195	Placebo N=1,206	Dapagliflozin N=1,205	Placebo N=764	Dapagliflozin N=723	
Discontinuation of study drug for any reason, N (%)	137 (11.9)	141 (11.8)	151 (12.5)	168 (13.9)	153 (20.0)	135 (18.7)	0.49
Discontinuation of study drug due to adverse event, N (%)	47 (4.1)	58 (4.9)	67 (5.6)	72 (6.0)	66 (8.6)	53 (7.3)	0.40
Volume depletion SAE/DAE, N (%)	9 (0.8)	7 (0.6)	6 (0.5)	19 (1.6)	22 (2.9)	23 (3.2)	0.06
Renal SAE/DAE, N (%)	18 (1.6)	12 (1.0)	28 (2.3)	32 (2.7)	45 (5.9)	40 (4.5)	0.44
Amputation, N (%)	5 (0.4)	1 (0.1)	7 (0.6)	7 (0.6)	14 (1.8)	11 (1.5)	0.31
Major hypoglycemia, N (%)	2 (0.2)	0 (0.0)	1 (0.1)	4 (0.3)	4 (0.5)	4 (0.5)	N/A
Diabetic ketoacidosis*, N (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	N/A

*DAE, adverse event leading to treatment discontinuation; FI, Frailty Index; N/A, not applicable; SAE, serious adverse event. *Confirmed by independent adjudication committee.*

A total of 10 randomized patients were excluded from the safety analysis, as these were performed in patients who had undergone randomization and received at least one dose of dapagliflozin or placebo.

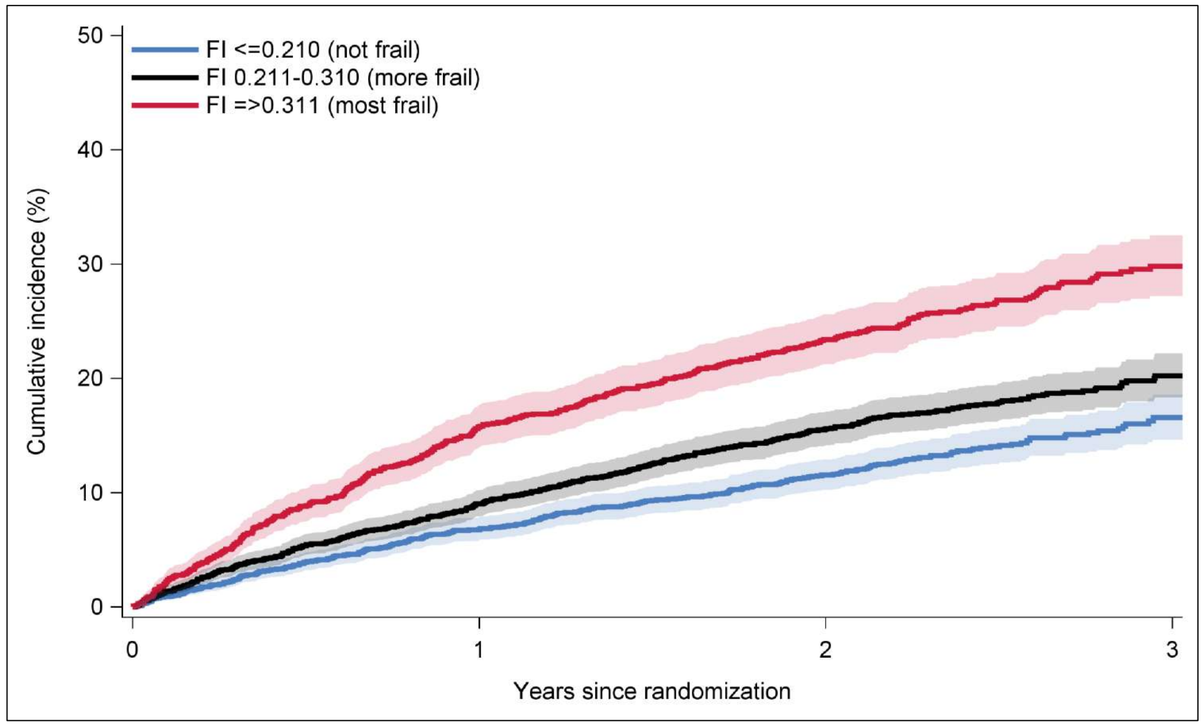
Figure Legends

Figure 1. Cumulative incidence of outcomes according to Frailty Index

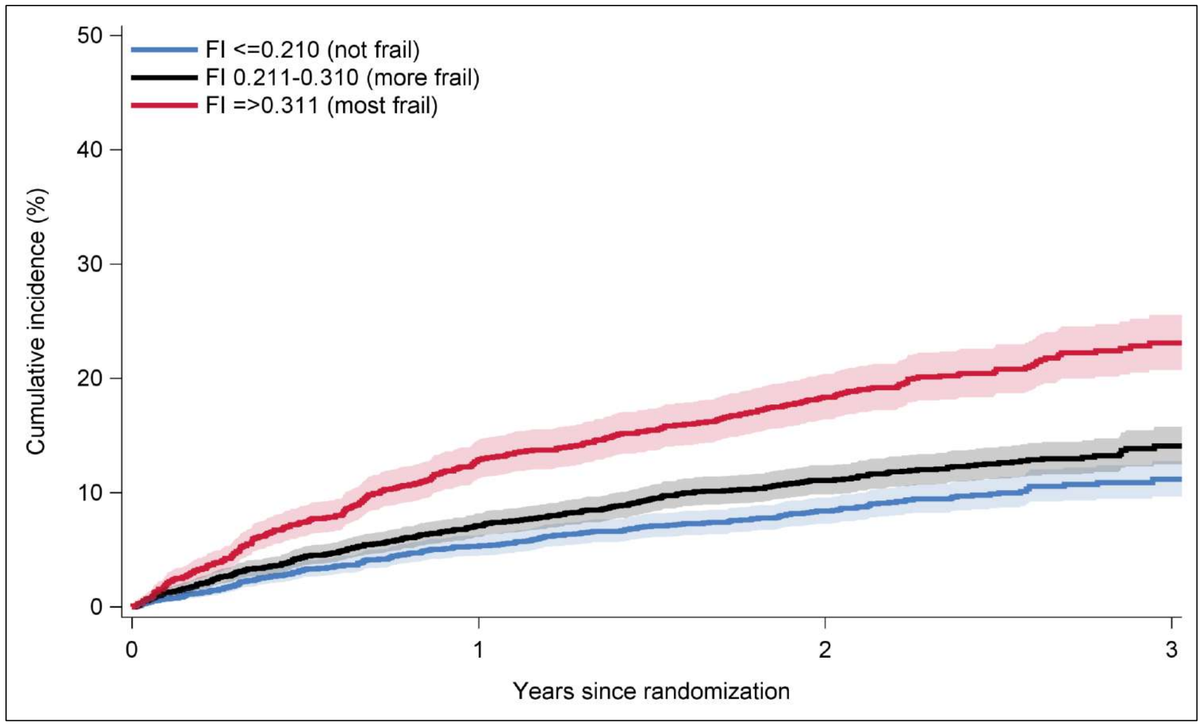
Figure 2. Effects of dapagliflozin compared with placebo on outcomes according to Frailty Index. Hazard and rate ratios are stratified by diabetes status.

Figure 3. Effects of dapagliflozin compared with placebo on clinical events according to Frailty Index. All hazard ratios are stratified by diabetes status.

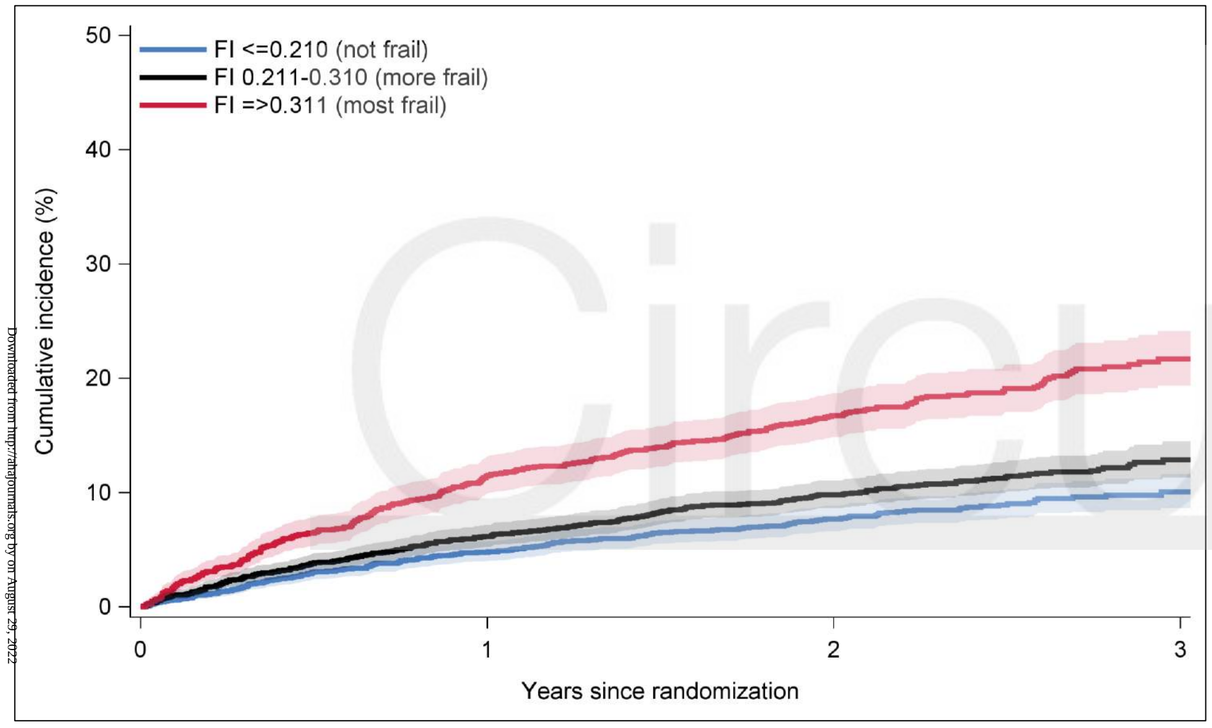
Worsening HF or cardiovascular death



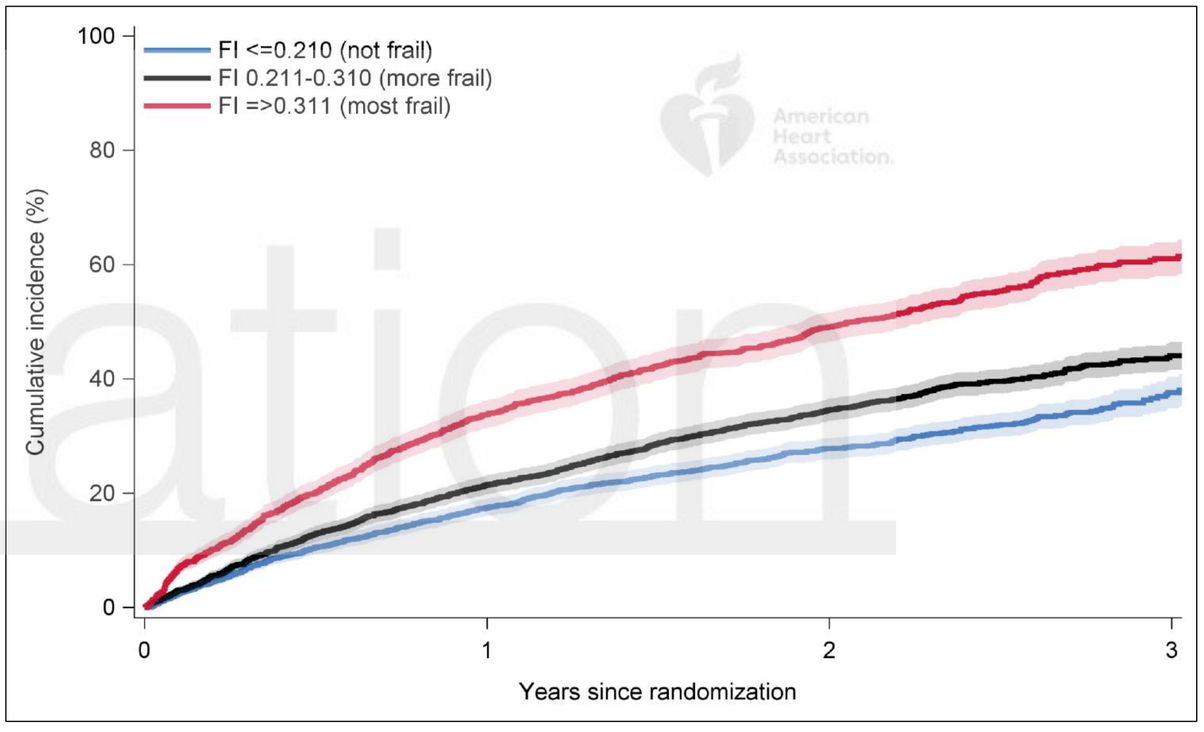
Worsening HF



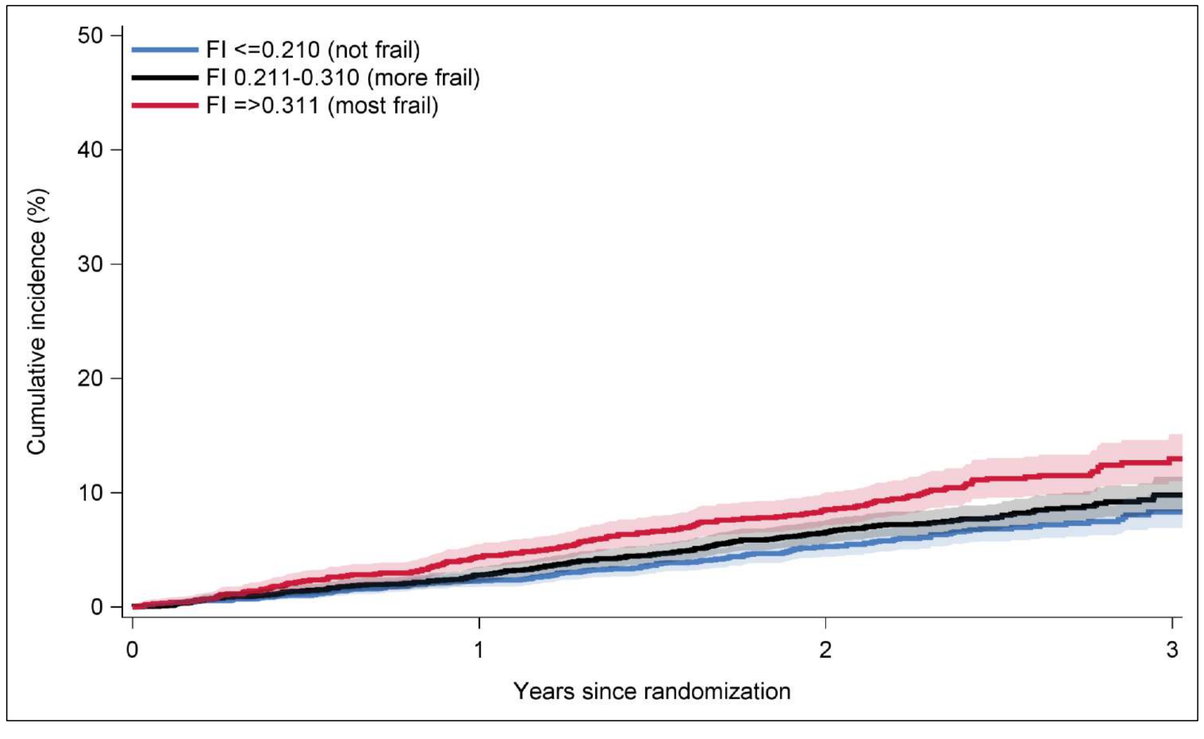
HF hospitalization



Any hospitalization



Cardiovascular death



All-cause death