Dapagliflozin for heart failure according to body mass index: the DELIVER trial

Running title: Dapagliflozin and BMI in HFmrEF and HFpEF

Carly Adamson, MBChBa
Toru Kondo, MD PhDab
Pardeep Jhund, MBChB MSc PhDa
Rudolf A. de Boer, MDc
Jose Walter Cabrera Honorio, MDD
Brian Claggett, PhDe
Akshay S. Desai, MDf
Marco Antonio Alcocer Gamba, MDF
Waleed Al Habeeb, MDG
Adrian F. Hernandez, MDF
Silvio E. Inzucchi, MDI
Mikhail N. Kosiborod, MDI
Carolyn S.P. Lam, MDCk
Anna Maria Langkilde, MD PhDlj
Daniel Lindholm, MD, PhD l
Erasmus Bachus, MD,PhD l
Sheldon E Litwin, MDm
Felipe Martinez, MDn

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Magnus Petersson, MD, PhD
Sanjiv J. Shah, MD
Muthiah Vaduganathan, MD MPH
Pham Nguyen Vinh, MD
Ulrica Wilderäng, PHD
Scott D. Solomon, MD
John JV McMurray MD

a British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, UK;
b Department of Cardiology, Nagoya University Graduate School of Medicine, Nagoya, Japan
c University of Groningen, University Medical Center Groningen, department of Cardiology, Groningen, the Netherlands
d Clínica Vesalio, San Borja, Peru
e Cardiovascular Division, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts, USA;
f Centro de Estudios Clínicos de Querétaro (CECLIQ), Querétaro, México
g Cardiac Sciences Department, King Saud University, Riyadh, Saudi Arabia;
h Duke University Medical Center, Durham, North Carolina, USA
i Yale School of Medicine, New Haven, Connecticut, USA
j Saint Luke’s Mid America Heart Institute, University of Missouri-Kansas City, Kansas City, Missouri, USA;
k National Heart Centre Singapore & Duke-National University of Singapore, Singapore

l Late-Stage Development, Cardiovascular, Renal, and Metabolism, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden.

m Division of Cardiology Medical University of South Carolina and Ralph H. Johnson, Veterans Affairs Medical Center, Charleston, South Carolina

n University of Cordoba, Cordoba, Argentina

o Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

p Cardiovascular Center, Tam Anh hospital, Tan Tao University, Vietnam

Address for Correspondence:
Professor John J.V. McMurray
British Heart Foundation Cardiovascular Research Centre
University of Glasgow
126 University Place, Glasgow, G12 8TA, United Kingdom
Tel: +44 141 330 3479
Fax: +44 141 330 6955
Email: john.mcmurray@glasgow.ac.uk
ABSTRACT

**Background and Aims:** Obesity is common and associated with unique phenotypic features in heart failure with preserved ejection fraction (HFpEF). Therefore, understanding the efficacy and safety of new therapies in HFpEF patients with obesity is important. The effects of dapagliflozin were examined according to body mass index (BMI) among patients in DELIVER.

**Methods:** BMI was analyzed by World Health Organization (WHO) categories and as a continuous variable using restricted cubic splines.

**Results:** BMI ranged from 15.2 to 50 kg/m² with a mean value of 29.8 (SD ± 6.1) kg/m². The proportions, by WHO category, were: normal weight 1343 (21.5%); overweight 2073 (33.1%); class I obesity 1574 (25.2%); class II obesity 798 (12.8%); class III obesity 415 (6.6%). Compared to placebo, dapagliflozin reduced the risk of the primary outcome to a similar extent across these categories: hazard ratio (95% confidence interval) 0.89 (0.69-1.15), 0.87 (0.70-1.08), 0.74 (0.58-0.93), 0.78 (0.57-1.08), and 0.72 (0.47-1.08), respectively (P-interaction=0.82). The placebo-corrected change in Kansas City Cardiomyopathy Questionnaire total symptom score with dapagliflozin at 8 months was: 0.9 (-1.1, 2.8), 2.5 (0.8, 4.1), 1.9 (-0.1, 3.8), 2.7 (-0.5, 5.8), and 8.6 (4.0, 13.2) points, respectively (P-interaction=0.03). The placebo-corrected change in weight at 12 months was: -0.88 (-1.28, -0.47), -0.65 (-1.04, -0.26), -1.42 (-1.89, -0.94), -1.17 (-1.94, -0.40), and -2.50 (-4.4, -0.64) kg (P-interaction=0.002).

**Conclusions:** Obesity is common in patients with HFpEF and is associated with higher rates of heart failure hospitalization and worse health status. Treatment with dapagliflozin improves cardiovascular outcomes across the spectrum of BMI, leads to greater symptom improvement in patients with obesity, compared to those without, and has the additional benefit of causing modest weight loss.

**Keywords:** Heart failure, obesity, body mass index, SGLT2 inhibitor
Key Question
Obesity is common in heart failure with preserved ejection fraction (HfPpEF), affecting younger patients and women especially. Therefore, it is important to find treatments that are efficacious and safe in this population. The effect of dapagliflozin in the DELIVER trial was examined according to body mass index (BMI).

Key Finding
45% of patients in the DELIVER trial were obese. The relative risk reduction in the primary composite outcome (worsening heart failure or cardiovascular death) was consistent across BMI categories ($p$ interaction = 0.82), with a larger absolute risk reduction in the higher-risk patients with obesity. There was improvement in KCCQ-TSS and modest weight loss in all BMI categories, although both were greater in more obese patients.

Take Home Message
Obesity is very common in contemporary patients with HfPpEF. The efficacy and safety of dapagliflozin is consistent across the spectrum of BMI, with substantial absolute benefits in patients with obesity.
INTRODUCTION

Obesity is a risk factor for the development of heart failure (HF), especially HF with preserved ejection fraction (HFpEF), more so in women than men. Consequently, many patients with HF are obese and obesity is more often a concomitant problem in patients with HFpEF. Indeed, in the United States, more than 80% of patients with HFpEF are overweight or obese and in contemporary clinical trials, the proportion of HF patients with severe obesity (World Health Organization [WHO] Class III) is almost 20%. Obese patients generally have worse symptoms and greater functional limitations than their non-obese counterparts. Recent studies have highlighted several potential explanations for this, including a variety of systemic effects of inflammatory cytokines and other mediators secreted by adipose tissue, direct cardiac consequences such as pericardial restraint due to local deposition of adipose tissue, greater concentric left ventricular remodelling and right ventricular dilatation and dysfunction, and even renal dysfunction due to excess adipose tissue in and around the kidney. Consequently, finding treatments that are efficacious in HFpEF patients with concomitant obesity is important. Sodium-glucose cotransporter 2 (SGLT2) inhibitors may be a particularly attractive treatment in these patients, especially as obesity is part of a common triad which includes dysglycemia and hypertension and SGLT2 inhibitors lead to modest reductions in weight, glycated haemoglobin and blood pressure, in addition to their benefits on HF symptoms and outcomes. Therefore the effect of SGLT2 inhibition was examined according to body mass index (BMI) in the Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure (DELIVER) trial. DELIVER included 6,263 patients with HF and mildly reduced and preserved ejection fraction and showed that dapagliflozin, compared with placebo, reduced the risk of worsening HF events or cardiovascular death, and improved symptoms.
METHODS

DELIVER was a double-blind, placebo-controlled trial which examined the efficacy and safety of dapagliflozin 10 mg once daily compared to matched placebo in patients with HF and mildly reduced and preserved ejection fraction. Randomization was stratified by the presence or absence of type 2 diabetes. The design, baseline characteristics and primary results are published.\textsuperscript{19,21,22} The protocol was approved by an Ethics Committee at each participating centre and all patients provided written informed consent.

\textit{Study patients}

Key inclusion criteria included age \(\geq 40\) years, HF diagnosis \(\geq 6\) weeks and a requirement for treatment with at least intermittent diuretic, New York Heart Association (NYHA) functional class II to IV, left ventricular ejection fraction (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 \(\geq 300\) pg/mL (\(>600\) pg/mL if atrial fibrillation/flutter on the electrocardiogram at enrolment). Patients could be enrolled in both the outpatient and inpatient setting. Patients were excluded if body mass index (BMI) was \(>50\) kg/m\(^2\). Other key exclusion criteria included type 1 diabetes; estimated glomerular filtration rate (eGFR) \(<25\) mL/min/1.73 m\(^2\); and systolic blood pressure \(<95\) mmHg. A complete list of inclusion and exclusion criteria is provided in the design paper.\textsuperscript{21}

\textit{Body mass index}

BMI was calculated as weight in kilograms divided by height in meters squared, using measurements made at the trial enrollment visit. Patients categorized using WHO definitions i.e., underweight (<18.5

\textit{Chat patients}
kg/m$^2$); normal weight (18.5-24.9 kg/m$^2$); overweight (25.0-29.9 kg/m$^2$); obesity class I (30.0-34.9 kg/m$^2$); obesity class II (35.0-39.9 kg/m$^2$) and obesity class III (≥40 kg/m$^2$).  

Outcomes

The primary outcome in DELIVER was the composite of time to the first occurrence of a worsening HF event (HF hospitalization or urgent outpatient HF visit requiring intravenous diuretic therapy) or cardiovascular death. The primary outcome was assessed in the full population and patients with an ejection fraction of <60% in a dual primary analysis. Secondary outcomes included in this analysis were the total number of worsening HF events (including first and recurrent events) and cardiovascular deaths; change in self-reported severity of HF symptoms at 8 months based on the Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TSS); worsening HF events, cardiovascular death and all-cause death.

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. These analyses included only patients who had taken at least one dose of study medication.

Statistical analyses

Baseline characteristics are reported for each BMI category as means ± standard deviation (SD), median with interquartile range (Q1-Q3) and proportions, as appropriate. The Cochran-Armitage test was used to test-for-trend across groups for binary variables and the Jonckheere-Terpstra test for continuous variables.
The association between BMI category and each outcome, adjusted for randomized treatment, was compared between BMI groups in a Cox regression model with overweight as the reference. This was repeated with additional adjustments for age, sex, race, region, heart rate, systolic blood pressure, glycated haemoglobin (HbA1c), creatinine, history of HF hospitalization, NYHA class, LVEF, atrial fibrillation/flutter, hypertension, myocardial infarction, coronary artery bypass graft, stroke, and (log-transformed) NT-proBNP. The associations between BMI, as a continuous variable, and outcomes were modelled using restricted cubic splines with adjustment for randomized treatment with median population BMI as reference. The 5 knots were placed at default positions according to percentiles of BMI (5, 27.5, 50, 72.5 and 95 centile). This was repeated with the additional adjustments listed above, in both the whole population and in males and females separately.

The efficacy of dapagliflozin, compared with placebo, in each BMI category, was examined using Kaplan-Meier estimates and Cox regression models. Event rates per 100 person-years and hazard ratios (HRs) are reported for each BMI category (these and all other models were stratified by diabetes status). The presence of an interaction between BMI category and treatment on the occurrence of each outcome was examined using a likelihood ratio test. The effect of randomized treatment across baseline BMI as a continuous variable was modelled flexibly using restricted cubic splines with three knots (at 10th, 50th and 90th percentile of BMI), in the whole population and subgroups of interest (males and females; LVEF <60 and ≥ 60; presence or absence of diabetes; and patients of White and Asian race). Analysis of recurrent events was by the Lin, Wei, Ying and Yang (LWYY) method, a semi-parametric proportional-rates model. Mean change in KCCQ-TSS at 8 months was calculated using a mixed model for repeated measurements including all time points within each BMI category.
A three way interaction between treatment, time and BMI was assessed in the mixed model at 8-month follow-up.

A mixed model for repeated measurement was used to examine change in weight over time according to baseline BMI (adjusted for baseline values, randomized treatment, and interaction of treatment and visit, with a random intercept and slope per patient). A three way interaction between treatment, time and BMI was assessed at 12-month follow-up.

The interaction between BMI category and randomized treatment on the occurrence of the safety outcomes was tested in a logistic regression model.

All analyses were conducted using STATA version 17.0 (College Station, TX, USA).

RESULTS

Of the 6,263 patients randomized in DELIVER, 6 had missing data for BMI. BMI ranged from 15.2 to 50 kg/m² with a mean value of 29.8 (SD ± 6.1) kg/m² and a median value of 29.1 (Q1-Q3 25.4-33.4) kg/m² and an approximately normal distribution (Supplementary Figure 1). In total, 54 (0.9%) patients were classified as underweight, 1343 (21.5%) as normal weight, 2073 (33.1%) as overweight, 1574 (25.2%) as class I obesity, 798 (12.8%) as class II obesity and 415 (6.6%) as class III obesity.

Due to the small number of patients in the underweight category, these participants were not included in the main results but are presented in the Supplementary Appendix.

Patient characteristics

Baseline characteristics according to BMI class are presented in Table 1. Compared to patients with normal BMI, those with obesity were younger, more often female and more likely to be White (and less
likely to be of Asian race). They had higher systolic and diastolic blood pressure, a higher HbA1c and were more likely to have a diagnosis of type 2 diabetes than patients with a normal weight. There was an inverse association between BMI and NT-proBNP with the lowest level of NT-proBNP in class III obesity - 862 [IQR 539-1311] ng/L compared to 1155 [IQR 667-2055] ng/L in patients in the normal weight category. A higher proportion of patients with obesity were in NYHA class III or IV and patients with obesity had lower (worse) KCCQ scores. Patients with higher BMI had a higher mean LVEF compared to those with normal weight. Patients with greater obesity had more hypertension but less coronary heart disease. Patients with obesity were more often treated with a beta-blocker, renin-angiotensin system blocker, calcium channel blocker, and a loop diuretic, but were less often treated with a mineralocorticoid receptor antagonist.

-Outcomes according to BMI-

There was a J-shaped relationship between BMI categories and the crude (unadjusted) incidence of the primary outcome and worsening HF events. The crude incidence of both outcomes was lowest in the overweight category and increased with increasing BMI category above this, driven by an increasing incidence of worsening HF events (Table 2, Figures 1 and 2). The relationship between BMI category and cardiovascular and all-cause death was different, with the lowest crude rates among patients with class III obesity (Table 2, Figures 1 and 2). Examination of BMI as a continuous variable confirmed these patterns.

Adjustment for prognostically important variables, including NT-proBNP, did not fundamentally alter the patterns observed in the unadjusted categorical or continuous analyses described above (Table 2 and Figure 2).
Repeating this analysis in males and females separately showed the nadir in risk for the primary endpoint and HF hospitalization occurred at a slightly lower BMI in men compared to women (Supplementary Figure 2). There was no difference between sexes for mortality outcomes.

Effects of dapagliflozin on clinical outcomes according to BMI

The hazard ratio for the primary outcome was 0.82 (95% CI 0.73-0.92) in the full population and 0.83 (95% CI 0.73-0.95) in the <60% ejection fraction subgroup. Dapagliflozin reduced the risk of the primary outcome to a similar extent across BMI categories: hazard ratio (95%CI) 0.89 (0.69-1.15) for normal weight, 0.87 (0.70-1.08) for overweight; 0.74 (0.58-0.93) for obesity class I, 0.78 (0.57-1.08) for obesity class II and 0.72 (0.47-1.08) for obesity class III (P interaction = 0.82) (Table 3). Examined as a continuous variable, there was no significant interaction between BMI and randomised treatment on the primary outcome (p interaction = 0.68) (Figure 3). Results in the subgroup of patients with ejection fraction <60% were consistent with that of the full population (Supplementary Table 5, Supplementary Figure 3).

The effects of dapagliflozin on the other outcomes (cardiovascular death, a worsening HF event, all-cause mortality, total HF events and cardiovascular death) were also consistent across BMI categories (P for interaction for all outcomes ≥ 0.6) (Table 3). The results were also consistent when BMI was modelled as a continuous variable (p for interaction all ≥ 0.2) (Figure 3). There was no treatment-by-sex-by-BMI interaction (p=0.76 for the primary endpoint). The effect of treatment in men and women separately is shown in Supplementary Figure 4 and of other subgroups of interest in Supplementary Figure 5, with no significant variation of treatment effect by BMI in these subgroups.

Change in KCCQ-TSS according to baseline BMI
Overall, 5792 patients (93%) had KCCQ-TSS recorded at baseline, and 4485 (71.7%) had a measurement at 8 months (219 missing due to death). The improvement in KCCQ-TSS at 8 months with dapagliflozin, compared to placebo, was greater in patients with higher BMI: placebo-corrected change 0.9 (-1.1, 2.8), 2.5 (0.8, 4.1), 1.9 (-0.1, 3.8), 2.7 (-0.5, 5.8), and 8.6 (4.0, 13.2) points, in normal weight, overweight, class I obesity, class II obesity, and class III obesity, respectively, \( P \text{-interaction}=0.03 \). (Table 3).

**Change in weight according to baseline BMI**

Patients with a higher baseline BMI lost a greater amount of weight (at 12 months) with dapagliflozin. The placebo-corrected weight loss with dapagliflozin was: normal weight -0.88 (-1.28, -0.47) kg; overweight -0.65 (-1.04, -0.26) kg; class I obesity -1.42 (-1.89, -0.94) kg; class II obesity -1.17 (-1.94, -0.40) kg; and class III obesity -2.5 (-4.4, -0.64) kg (\( P \) for interaction = 0.002).

**Safety analyses**

There was no significant interaction between BMI categories and the occurrence of adverse events according to randomized treatment (Table 4).

**DISCUSSION**

The key finding of this study was that dapagliflozin was equally efficacious in reducing the primary composite outcome of worsening HF or cardiovascular death across the spectrum of BMI in DELIVER, including among participants who were obese. Treatment with dapagliflozin also led to an improvement in symptoms measured with he KCCQ-TSS and which was greater in patients with a
higher BMI. In addition, dapagliflozin treatment led to a modest but significantly larger reduction in weight in more obese patients than others (Structured Graphical Abstract).

In keeping with epidemiological observations, 45% of participants in this study were found to be obese and 78% were obese or overweight, despite the exclusion of patients with a BMI >50 kg/m². As expected, the prevalence of diabetes and history of hypertension was higher (as was blood pressure) in patients with obesity. Participants with obesity had less evidence of coronary disease, which might also appear paradoxical but has been described previously and may reflect their younger age and the higher proportion of women. The association between higher BMI and lower NT-proBNP was confirmed and LVEF tended to be higher in participants with a higher BMI. Notably, patients with obesity had worse NYHA class, with almost twice as many in functional class III or IV compared to participants with a normal weight. This was mirrored in self-reported symptoms and health-related quality of life, with a striking difference of over 20 points between patients with class III obesity, compared to a normal weight, at baseline.

Regarding clinical outcomes during follow-up, a “U-” or J-shaped” relationship was found between BMI and mortality in patients with HFpEF (as in HF with reduced ejection fraction) with the nadir in crude risk among patients with class I obesity (BMI range 30.0-34.9 kg/m²) and the highest risk of death in patients who were normal or underweight (although there were very few patients in the latter category). Interestingly, the pattern was different for worsening HF, where risk increased with increasing obesity, and was highest in patients with class II/III obesity. Why the relationships between BMI and fatal, compared with non-fatal, outcomes diverged in this way is uncertain. The well-known, but poorly understood association between higher BMI and lower natriuretic peptides is a confounding factor relevant to these findings and in a fully adjusted analysis, including NT-proBNP, the association
of obesity with lower mortality was eliminated. By contrast, the association with higher rates of worsening HF were not, possibly because the relationship between natriuretic peptides and plasma volume in patients with obesity may be different than in non-obese patients (obesity, unusually, is associated with low natriuretic peptide levels despite a greater expansion of plasma volume and higher filling pressures, especially during exercise). 28

Dapagliflozin reduced the risk of the primary composite endpoint (worsening HF or cardiovascular death), with no interaction between the effect of treatment and BMI, examined as either a categorical or continuous variable, for this or any other outcome. Conservatively, applying the hazard ratio for the trial overall to each BMI category gave an NNT for the primary outcome in patients with class III obesity of only 22 (over the median DELIVER follow-up of 2.3 years), compared to 31 in patients with a normal weight, indicating a greater absolute benefit in obese individuals because of their higher absolute risk of this outcome.

As described above, patients with greater obesity had markedly worse health status at baseline and, importantly, this was improved following randomization to dapagliflozin. Indeed, the improvement in KCCQ-TSS was greatest in patients with the highest BMI. This finding is consistent with the hypothesis that the results of the PRESERVED-HF were more positive than EMPERIAL-Preserved because of the much higher prevalence of obesity in the former trial. 29,30

While the main reason to use SGLT2 inhibitors in HFpEF is to improve symptoms and reduce worsening HF, their modest weight-reducing effect may be a useful additional attribute in patients with obesity. By increasing urinary excretion of glucose and calories, these agents have been shown to reduce weight in a range of patient populations, including patients with HF. 14,15,27 The overall weight reduction at 12 months in DELIVER was just over 1 kg, slightly larger than in DAPA-HF. 27 The
reduction in DELIVER was greater in patients with a higher BMI; the most obese participants with
nearly three times the loss of those who had a normal weight (2.5 versus 0.88 kg). Although modest,
this additional benefit of SGLT2 inhibition may augment other strategies to reduce weight in HFpEF
patients with obesity. One example is caloric restriction and aerobic exercise training which was shown
to lead to a larger decrease in weight, and improvement in peak oxygen consumption but no consistent
improvement in health-related quality of life. 31,32 Glucagon-like peptide-1 receptor agonists and related
treatments are currently under investigation as weight-loss treatments in HFpEF patients with obesity

As with similar reports, our study had some limitations. BMI does not take into account the location of
body fat or its amount, relative to muscle, or the weight of the skeleton, which may often differ
according to sex, age, and race. 33,34 Therefore, the conventional definition of obesity based on this
metric may not account for these differences across populations, although our models were adjusted for
race and region. Patients with extreme obesity (a BMI >50 kg/m²) were excluded and only 54 patients
who were “underweight” were enrolled, precluding any meaningful analysis, although this is a rare
group of patients, at least in most countries.

In conclusion, the benefit of dapagliflozin on clinical outcomes was consistent across the spectrum of
BMI in DELIVER, without any safety concerns. Treatment with dapagliflozin led to an improvement
in symptoms and a modest reduction in weight, both of which were amplified in patients with a higher
BMI.

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Conflict of interest

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**Data availability statement**

The data sharing policy of the DELIVER trial sponsor, AstraZeneca, is described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.


Figure Legends

Structured Graphical Abstract

Summary of the key background and findings of this study.

BMI, body mass index; CV, cardiovascular; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score

Figure 1. Cumulative incidence of key outcomes according to BMI

Risk of each outcome in patients grouped by baseline body mass index.

Figure 2. Effect of BMI as continuous variable on the hazard of each outcome

Risk of each outcome according to body mass index with reference to the population median (29kg/m²).

The baseline (blue) line is adjusted for randomized treatment and stratified for diabetes status (blue shaded area represents the 95%CI). The red line includes additional adjustment for age, sex, race, heart rate, pulse, systolic blood pressure, HbA1c, creatinine, history of HF hospitalization, NYHA class, LVEF, AF, hypertension, MI, CABG, stroke and (log-transformed) NT-proBNP.

Figure 3 – Treatment effect of dapagliflozin on the main study outcomes according to baseline BMI.

Baseline BMI (5-95 centile) is shown on the X-axis and the hazard ratio (HR) for the effect of dapagliflozin compared with placebo is shown on the Y-axis. The horizontal black line shows a HR of one (unity). The blue line represents a continuous HR and the blue shaded areas the 95% confidence interval. A HR less than one indicates a benefit of dapagliflozin over placebo.
1. Table 1. Baseline characteristics according to BMI category

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<th>Normal weight</th>
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<th>Obesity class III</th>
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<td>N=1343</td>
<td>N=2073</td>
<td>N=1574</td>
<td>N=798</td>
<td>N=415</td>
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</tr>
<tr>
<td>Age (years)</td>
<td>73.3±10.0</td>
<td>72.4±9.5</td>
<td>71.4±9.0</td>
<td>69.3±9.1</td>
<td>67.8±9.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female sex</td>
<td>578 (43.0)</td>
<td>828 (39.9)</td>
<td>676 (42.9)</td>
<td>380 (47.6)</td>
<td>255 (61.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race</td>
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<td>&lt;0.001</td>
</tr>
<tr>
<td>White</td>
<td>587 (43.7)</td>
<td>1,427 (68.8)</td>
<td>1,333 (84.7)</td>
<td>711 (89.1)</td>
<td>362 (87.2)</td>
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<tr>
<td>Asian</td>
<td>633 (47.1)</td>
<td>453 (21.9)</td>
<td>119 (7.6)</td>
<td>24 (3.0)</td>
<td>8 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>24 (1.8)</td>
<td>47 (2.3)</td>
<td>32 (2.0)</td>
<td>30 (3.8)</td>
<td>25 (6.0)</td>
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</tr>
<tr>
<td>Other</td>
<td>99 (7.4)</td>
<td>146 (7.0)</td>
<td>90 (5.7)</td>
<td>33 (4.1)</td>
<td>20 (4.8)</td>
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</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>0.58</td>
</tr>
<tr>
<td>Current</td>
<td>115 (8.6)</td>
<td>158 (7.6)</td>
<td>116 (7.4)</td>
<td>65 (8.1)</td>
<td>21 (5.1)</td>
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<tr>
<td>Former</td>
<td>475 (35.4)</td>
<td>750 (36.2)</td>
<td>579 (36.8)</td>
<td>281 (35.2)</td>
<td>158 (38.1)</td>
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</tr>
<tr>
<td>Never</td>
<td>753 (56.1)</td>
<td>1,165 (56.2)</td>
<td>879 (55.8)</td>
<td>452 (56.6)</td>
<td>236 (56.9)</td>
<td></td>
</tr>
</tbody>
</table>

Vital signs

<p>| | | | | | | |</p>
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</tr>
</thead>
<tbody>
<tr>
<td>Pulse (beats/min)</td>
<td>71.2±12.1</td>
<td>70.9±11.8</td>
<td>71.7±11.2</td>
<td>72.4±11.7</td>
<td>72.8±12.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>124.9±15.6</td>
<td>127.8±14.7</td>
<td>130.1±14.7</td>
<td>130.6±15.9</td>
<td>130.6±16.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>72.1±10.4</td>
<td>73.5±9.8</td>
<td>75.1±10.1</td>
<td>75.6±10.3</td>
<td>75.4±11.9</td>
<td>&lt;0.001</td>
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</table>

Laboratory values

<p>| | | | | | | |</p>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>6.0 (5.6-6.5)</td>
<td>6.1 (5.7-6.8)</td>
<td>6.2 (5.8-7.1)</td>
<td>6.4 (5.9-7.6)</td>
<td>6.5 (5.9-7.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>100.0±30.4</td>
<td>102.4±30.5</td>
<td>103.8±31.4</td>
<td>105.1±32.7</td>
<td>100.3±30.8</td>
<td>0.01</td>
</tr>
<tr>
<td>eGFR</td>
<td>62.1±19.4</td>
<td>61.2±19.0</td>
<td>60.2±18.5</td>
<td>60.0±19.4</td>
<td>62.0±20.6</td>
<td>0.03</td>
</tr>
</tbody>
</table>
### (mL/min/1.73m²)

- **eGFR < 60**
  - 643 (47.9)  1,004 (48.4)  786 (49.9)  405 (50.8)  201 (48.4)  0.28

- **NT-proBNP (ng/L)**
  - **NT-proBNP (ng/L) if baseline ECG in AF/flutter**
    - 1606.0  1447.0  1404.5  1242.0  1108.0  <0.001
  - **NT-proBNP (ng/L) if baseline ECG not in AF/flutter**
    - 810.0  757.0  663.0  627.0  612.0  <0.001

### Heart failure characteristics

- **Prior HF hospitalization**
  - 586 (43.6)  817 (39.4)  625 (39.7)  309 (38.7)  173 (41.7)  0.10

- **NYHA class**
  - **II**
    - 1,064 (79.2)  1,633 (78.8)  1,160 (73.7)  560 (70.2)  245 (59.0)
  - **III/IV**
    - 279 (20.8)  439 (21.2)  414 (26.3)  238 (29.8)  170 (41.0)

- **KCCQ-TSS**
  - 80.2 (62.5-93.8)  75.0 (59.4-89.6)  69.8 (54.2-84.4)  66.7 (50.0-83.3)  58.3 (38.5-72.9)  <0.001

- **Baseline LVEF(%)**
  - 53.0 (46.0-60.0)  53.0 (46.0-60.0)  54.0 (47.0-60.0)  55.0 (47.0-60.0)  55.0 (49.0-60.0)  0.02

### Clinical history

- **T2DM**
  - 421 (31.3)  885 (42.7)  782 (49.7)  463 (58.0)  240 (57.8)  <0.001

- **Atrial fibrillation**
  - 720 (53.6)  1,060 (51.1)  929 (59.0)  486 (60.9)  235 (56.6)  <0.001

- **Hypertension**
  - 1,071 (79.7)  1,812 (87.4)  1,474 (93.6)  750 (94.0)  398 (95.9)  <0.001

- **Myocardial infarction**
  - 344 (25.6)  635 (30.6)  398 (25.3)  180 (22.6)  71 (17.1)  <0.001

- **CABG**
  - 126 (9.4)  283 (13.7)  207 (13.2)  89 (11.2)  37 (8.9)  0.97
<table>
<thead>
<tr>
<th>Stroke</th>
<th>147 (10.9)</th>
<th>220 (10.6)</th>
<th>140 (8.9)</th>
<th>66 (8.3)</th>
<th>22 (5.3)</th>
<th>&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Beta blocker</strong></td>
<td>1,033 (77.0)</td>
<td>1,694 (81.7)</td>
<td>1,353 (86.0)</td>
<td>699 (87.6)</td>
<td>352 (84.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Calcium channel blockers</strong></td>
<td>353 (26.3)</td>
<td>594 (28.7)</td>
<td>491 (31.2)</td>
<td>313 (39.2)</td>
<td>150 (36.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>ACEi, ARB or ARNI</strong></td>
<td>941 (70.2)</td>
<td>1,594 (76.9)</td>
<td>1,289 (81.9)</td>
<td>644 (80.7)</td>
<td>329 (79.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Mineralocorticoid receptor antagonist</strong></td>
<td>618 (46.1)</td>
<td>869 (41.9)</td>
<td>679 (43.1)</td>
<td>308 (38.6)</td>
<td>167 (40.2)</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Loop diuretics</strong></td>
<td>980 (73.1)</td>
<td>1,513 (73.0)</td>
<td>1,227 (78.0)</td>
<td>674 (84.5)</td>
<td>373 (89.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Other (non-loop) diuretics</strong></td>
<td>243 (18.1)</td>
<td>448 (21.6)</td>
<td>356 (22.6)</td>
<td>189 (23.7)</td>
<td>95 (22.9)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

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

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CABG, coronary artery bypass graft; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HF, heart failure; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire – Total Symptom Score; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus.
Table 2. – Outcomes according to BMI category

<table>
<thead>
<tr>
<th></th>
<th>Normal weight (n =1343)</th>
<th>Overweight (n =2073)</th>
<th>Obesity class I (n =1574)</th>
<th>Obesity class II (n =798)</th>
<th>Obesity class III (n =415)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No(%)</td>
<td>233 (17.4)</td>
<td>331 (16.0)</td>
<td>298 (18.9)</td>
<td>154 (19.3)</td>
<td>92 (22.2)</td>
</tr>
<tr>
<td>Rate (95% CI)</td>
<td>8.7 (7.6-9.9)</td>
<td>7.7 (6.9-8.6)</td>
<td>9.1 (8.1-10.2)</td>
<td>9.2 (7.9-10.8)</td>
<td>11.0 (9.0-13.6)</td>
</tr>
<tr>
<td>Unadjusted (95% CI) *</td>
<td>1.17 (0.99-1.38)</td>
<td>REF</td>
<td>1.16 (0.99-1.36)</td>
<td>1.15 (0.95-1.39)</td>
<td>1.37 (1.09-1.73)</td>
</tr>
<tr>
<td>Additional adjustment † (95% CI)</td>
<td>1.12 (0.94-1.34)</td>
<td>REF</td>
<td>1.21 (1.03-1.43)</td>
<td>1.26 (1.03-1.54)</td>
<td>1.68 (1.32-2.15)</td>
</tr>
<tr>
<td><strong>Worsening heart failure event</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No(%)</td>
<td>163 (12.1)</td>
<td>227 (11.0)</td>
<td>234 (14.9)</td>
<td>122 (15.3)</td>
<td>72 (17.4)</td>
</tr>
<tr>
<td>Rate (95% CI)</td>
<td>6.1 (5.2-7.1)</td>
<td>5.3 (4.6-6.0)</td>
<td>7.1 (6.3-8.1)</td>
<td>7.3 (6.1-8.7)</td>
<td>8.6 (6.9-10.9)</td>
</tr>
<tr>
<td>Unadjusted (95% CI) *</td>
<td>1.19 (0.97-1.45)</td>
<td>REF</td>
<td>1.33 (1.11-1.60)</td>
<td>1.34 (1.07-1.67)</td>
<td>1.57 (1.20-2.04)</td>
</tr>
<tr>
<td>Additional adjustment † (95% CI)</td>
<td>1.07 (0.86-1.32)</td>
<td>REF</td>
<td>1.42 (1.17-1.71)</td>
<td>1.48 (1.18-1.87)</td>
<td>1.94 (1.47-2.57)</td>
</tr>
<tr>
<td><strong>Cardiovascular death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No(%)</td>
<td>125 (9.3)</td>
<td>149 (7.2)</td>
<td>110 (7.0)</td>
<td>67 (8.4)</td>
<td>29 (7.0)</td>
</tr>
<tr>
<td>Rate (95% CI)</td>
<td>4.4 (3.7-5.2)</td>
<td>3.3 (2.8-3.8)</td>
<td>3.1 (2.6-3.7)</td>
<td>3.7 (2.9-4.7)</td>
<td>3.1 (2.2-4.5)</td>
</tr>
<tr>
<td>Unadjusted (95% CI) *</td>
<td>1.39 (1.09-1.76)</td>
<td>REF</td>
<td>0.93 (0.72-1.19)</td>
<td>1.09 (0.81-1.45)</td>
<td>0.92 (0.62-1.38)</td>
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<tr>
<td>Additional adjustment † (95% CI)</td>
<td>1.48 (1.15-1.90)</td>
<td>REF</td>
<td>0.98 (0.76-1.26)</td>
<td>1.27 (0.94-1.71)</td>
<td>1.25 (0.82-1.89)</td>
</tr>
<tr>
<td><strong>All-cause death</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No(%)</td>
<td>239 (17.8)</td>
<td>325 (15.7)</td>
<td>255 (16.2)</td>
<td>125 (15.7)</td>
<td>63 (15.2)</td>
</tr>
<tr>
<td>Rate (95% CI)</td>
<td>8.4 (7.4-9.5)</td>
<td>7.1 (6.4-7.9)</td>
<td>7.2 (6.3-8.1)</td>
<td>6.8 (5.7-8.2)</td>
<td>6.8 (5.3-8.7)</td>
</tr>
<tr>
<td>Unadjusted (95% CI) *</td>
<td>1.29 (1.02-1.43)</td>
<td>REF</td>
<td>0.99 (0.84-1.16)</td>
<td>0.93 (0.75-1.14)</td>
<td>0.92 (0.70-1.20)</td>
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</tbody>
</table>
### Additional adjustment † (95% CI)

<table>
<thead>
<tr>
<th>No</th>
<th>385</th>
<th>511</th>
<th>514</th>
<th>283</th>
<th>155</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate (95% CI)</td>
<td>13.6 (11.7-15.8)</td>
<td>11.2 (9.9-12.8)</td>
<td>14.5 (12.6-16.8)</td>
<td>15.6 (12.9-18.9)</td>
<td>16.8 (13.4-21.3)</td>
</tr>
<tr>
<td>Unadjusted (95% CI) *</td>
<td>1.25 (1.02-1.53)</td>
<td>REF</td>
<td>1.26 (1.04-1.53)</td>
<td>1.33 (1.05-1.67)</td>
<td>1.42 (1.09-1.85)</td>
</tr>
<tr>
<td>Additional adjustment † (95% CI)</td>
<td>1.14 (0.94-1.39)</td>
<td>REF</td>
<td>1.35 (1.11-1.64)</td>
<td>1.52 (1.21-1.91)</td>
<td>1.83 (1.38-2.41)</td>
</tr>
</tbody>
</table>

1. Rates are given per 100 patient years
2. *baseline model adjusted for randomized treatment and stratified by diabetes status
3. †age, sex, race, region, heart rate, systolic blood pressure, HbA1c, creatinine, history of heart failure hospitalization, NYHA class, LV ejection fraction, atrial fibrillation, hypertension, MI, CABG, stroke, NT-proBNP(log-transformed)
Table 3. Effect of randomized treatment on outcomes according to BMI category

<table>
<thead>
<tr>
<th></th>
<th>Overall (n=6263)</th>
<th>Normal weight (n = 1343)</th>
<th>Overweight (n = 2073)</th>
<th>Obesity class I (n = 1574)</th>
<th>Obesity class II (n = 798)</th>
<th>Obesity class III (n = 415)</th>
<th>P-int</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Dapa-gliflozin</td>
<td>Placebo</td>
<td>Dapa-gliflozin</td>
<td>Placebo</td>
<td>Dapa-gliflozin</td>
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<tr>
<td>N</td>
<td>3132</td>
<td>3131</td>
<td>670</td>
<td>673</td>
<td>1048</td>
<td>1025</td>
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<td>Primary endpoint</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>No (%)</td>
<td>610 (19.5)</td>
<td>512 (16.4)</td>
<td>122 (18.2)</td>
<td>111 (16.5)</td>
<td>176 (16.8)</td>
<td>155 (15.1)</td>
<td></td>
</tr>
<tr>
<td>Rate (95%CI)</td>
<td>9.6 (8.9-10.4)</td>
<td>7.8 (7.2-8.5)</td>
<td>9.2 (7.7-11.0)</td>
<td>8.2 (6.8-9.9)</td>
<td>8.2 (7.1-9.5)</td>
<td>7.2 (6.1-8.4)</td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>0.82 (0.73-0.92)</td>
<td>0.89 (0.69-1.15)</td>
<td>0.87 (0.70-1.08)</td>
<td>0.74 (0.58-0.93)</td>
<td>0.78 (0.57-1.08)</td>
<td>0.72 (0.47-1.08)</td>
<td>0.82</td>
</tr>
<tr>
<td>Worsening heart failure event</td>
<td></td>
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</tr>
<tr>
<td>No (%)</td>
<td>455 (14.5)</td>
<td>368 (11.8)</td>
<td>83 (12.4)</td>
<td>80 (11.9)</td>
<td>126 (12.0)</td>
<td>101 (9.9)</td>
<td></td>
</tr>
<tr>
<td>Rate (95%CI)</td>
<td>7.2 (6.5-7.8)</td>
<td>5.6 (5.1-6.2)</td>
<td>6.3 (5.0-7.8)</td>
<td>5.9 (4.7-7.3)</td>
<td>5.9 (5.0-7.0)</td>
<td>4.7 (3.8-5.7)</td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>0.79 (0.69-0.91)</td>
<td>0.94 (0.69-1.28)</td>
<td>0.79 (0.61-1.03)</td>
<td>0.72 (0.56-0.94)</td>
<td>0.80 (0.56-1.14)</td>
<td>0.63 (0.39-1.00)</td>
<td>0.66</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (%)</td>
<td>261 (8.3)</td>
<td>231 (7.4)</td>
<td>66 (9.9)</td>
<td>59 (8.8)</td>
<td>81 (7.7)</td>
<td>68 (6.6)</td>
<td></td>
</tr>
<tr>
<td>Rate (95%CI)</td>
<td>3.8 (3.3-4.3)</td>
<td>3.3 (2.9-3.8)</td>
<td>4.7 (3.7-5.9)</td>
<td>4.1 (3.2-5.3)</td>
<td>3.5 (2.8-4.4)</td>
<td>3.0 (2.4-3.8)</td>
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</tr>
<tr>
<td>HR</td>
<td>0.88 (0.74-1.05)</td>
<td>0.88 (0.62-1.25)</td>
<td>0.84 (0.61-1.16)</td>
<td>0.75 (0.52-1.10)</td>
<td>1.00 (0.62-1.61)</td>
<td>1.17 (0.56-2.44)</td>
<td>0.89</td>
</tr>
<tr>
<td>All-cause death</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (%)</td>
<td>526 (16.8)</td>
<td>497 (15.9)</td>
<td>126 (18.8)</td>
<td>113 (16.8)</td>
<td>171 (16.3)</td>
<td>154 (15.0)</td>
<td></td>
</tr>
<tr>
<td>Rate (95%CI)</td>
<td>7.6 (9.7-8.3)</td>
<td>7.2 (6.6-7.8)</td>
<td>8.9 (7.5-10.6)</td>
<td>7.9 (6.5-9.5)</td>
<td>7.4 (6.4-8.6)</td>
<td>6.8 (5.8-8.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.4 (6.2-8.7)</td>
<td>6.9 (5.8-8.3)</td>
<td>6.4 (5.0-8.3)</td>
<td>7.2 (5.7-9.2)</td>
<td>6.8 (4.8-9.7)</td>
<td>6.7 (4.7-9.5)</td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>0.94 (0.83-1.07)</td>
<td>0.88 (0.69-1.14)</td>
<td>0.91 (0.73-1.13)</td>
<td>0.94 (0.74-1.20)</td>
<td>1.13 (0.79-1.60)</td>
<td>0.97 (0.59-1.60)</td>
<td>0.82</td>
</tr>
<tr>
<td>-------------</td>
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<td>------------------</td>
<td>------------------</td>
<td>------------------</td>
<td>------------------</td>
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<td>------</td>
</tr>
</tbody>
</table>

**Total heart failure hospitalizations and cardiovascular deaths**

<table>
<thead>
<tr>
<th>No (%)</th>
<th>1057</th>
<th>815</th>
<th>198</th>
<th>187</th>
<th>288</th>
<th>223</th>
<th>323</th>
<th>191</th>
<th>154</th>
<th>129</th>
<th>89</th>
<th>66</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate (95%CI)</td>
<td>15.3 (13.9-16.9)</td>
<td>11.8 (10.7-13.1)</td>
<td>14.0 (11.4-17.5)</td>
<td>13.1 (10.6-16.3)</td>
<td>12.6 (10.6-15.1)</td>
<td>9.9 (8.2-12.0)</td>
<td>17.8 (14.6-21.9)</td>
<td>11.0 (9.1-13.4)</td>
<td>17.2 (13.5-22.2)</td>
<td>14.0 (10.5-19.1)</td>
<td>19.8 (14.8-27.1)</td>
<td>13.9 (9.8-20.4)</td>
</tr>
<tr>
<td>Rate ratio</td>
<td>0.77 (0.67-0.89)</td>
<td>0.93 (0.69-1.25)</td>
<td>0.78 (0.60-1.01)</td>
<td>0.62 (0.47-0.82)</td>
<td>0.80 (0.55-1.18)</td>
<td>0.71 (0.45-1.12)</td>
<td>0.44</td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

**KCCQ-TSS**

<table>
<thead>
<tr>
<th>Mean change in KCCQ at 8m</th>
<th>5.6 (4.9, 6.3)</th>
<th>7.9 (7.2, 8.6)</th>
<th>3.9 (2.6, 5.3)</th>
<th>4.8 (3.5, 6.2)</th>
<th>5.6 (4.4, 6.7)</th>
<th>8.0 (6.9, 9.2)</th>
<th>6.1 (4.7, 7.5)</th>
<th>8.0 (6.6, 9.4)</th>
<th>7.2 (5.0, 9.5)</th>
<th>9.9 (7.7, 12.1)</th>
<th>5.9 (2.6, 9.1)</th>
<th>14.5 (11.3, 17.7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo corrected change at 8m**</td>
<td>2.4 (1.4, 3.4)</td>
<td>0.9 (-1.1, 2.8)</td>
<td>2.5 (0.8, 4.1)</td>
<td>1.9 (-0.1, 3.8)</td>
<td>2.7 (-0.5, 5.8)</td>
<td>8.6 (4.0, 13.2)</td>
<td>0.03</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Rates are given per 100 patient years.
2. *Full trial population, including the 6 patients with missing BMI at baseline.
3. **Mixed-effect models for repeated measurements adjusted for baseline value, visit (months 1, 4, and 8), randomized treatment, and interaction of treatment and visit.
4. **
### Table 4 – Adverse events

<table>
<thead>
<tr>
<th></th>
<th>Normal weight</th>
<th>Overweight</th>
<th>Obesity class I</th>
<th>Obesity class II</th>
<th>Obesity class III</th>
<th>P-interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Dapagliflozin</td>
<td>Placebo</td>
<td>Dapagliflozin</td>
<td>Placebo</td>
<td>Dapagliflozin</td>
</tr>
<tr>
<td>N</td>
<td>669</td>
<td>673</td>
<td>1046</td>
<td>1023</td>
<td>801</td>
<td>770</td>
</tr>
<tr>
<td>AE leading to discontinuation of randomized treatment</td>
<td>42 (6.3)</td>
<td>41 (6.1)</td>
<td>61 (5.8)</td>
<td>54 (5.3)</td>
<td>45 (5.6)</td>
<td>53 (6.9)</td>
</tr>
<tr>
<td>Amputation</td>
<td>2 (0.3)</td>
<td>2 (0.3)</td>
<td>9 (0.9)</td>
<td>9 (0.9)</td>
<td>8 (1.0)</td>
<td>5 (0.6)</td>
</tr>
<tr>
<td>Definite or probable DKA*</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Major hypoglycemic event</td>
<td>0 (0.0)</td>
<td>1 (0.1)</td>
<td>4 (0.4)</td>
<td>3 (0.3)</td>
<td>0 (0.0)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Volume depletion SAE/DAE</td>
<td>9 (1.3)</td>
<td>8 (1.2)</td>
<td>14 (1.3)</td>
<td>18 (1.8)</td>
<td>9 (1.1)</td>
<td>14 (1.8)</td>
</tr>
<tr>
<td>Renal SAE/DAE</td>
<td>16 (2.4)</td>
<td>16 (2.4)</td>
<td>27 (2.6)</td>
<td>23 (2.2)</td>
<td>23 (2.9)</td>
<td>28 (3.6)</td>
</tr>
</tbody>
</table>

AE = adverse event; SAE = serious adverse event; DAE = adverse event leading to discontinuation of randomized treatment; DKA = diabetic ketoacidosis

*Confirmed by independent adjudication committee.
Figure 1
227x187 mm (.88 x DPI)
Figure 2
265x190 mm (.88 x DPI)
Figure 3
326x187 mm (.88 x DPI)