Title: Efficacy and Safety of Dapagliflozin in Patients with Heart Failure with Mildly Reduced or Preserved Ejection Fraction by Baseline Glycemic Status in DELIVER: Subgroup Analysis from a Multi-Centre Randomised Double Blind Placebo Controlled Trial

Short title: Glycaemic Status and Dapagliflozin in HFmrEF/HFpEF

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Summary (253 words)

Background: Type 2 diabetes and prediabetes are risk factors for heart failure and adverse heart failure outcomes. We assessed the efficacy and safety of oral dapagliflozin across glycaemic categories in patients with heart failure with mildly reduced/preserved ejection fraction (HFmrEF/HFpEF) in the DELIVER trial, which recently demonstrated reduction in the primary outcome of worsening heart failure or cardiovascular mortality in the overall population.

Methods: Patients with NYHA class II-IV, left ventricular ejection fraction >40%, elevated natriuretic peptides, and evidence of structural heart disease were randomised to dapagliflozin or placebo, administered orally, and followed for a median of 2·3 years. Outcomes in participants with diabetes (history of or identified by HbA1c ≥6·5% [48 mmol/mol] at baseline) or prediabetes (HbA1c 5·7-<6.5% [39-<48mmol/mol] at baseline) were compared to those with normoglycaemia and also examined based on HbA1c as a continuous measure.

Findings: Among 6259 randomised patients, the incidence of the primary outcome (worsening heart failure or cardiovascular death) increased progressively with advancing dysglycaemic category. Dapagliflozin reduced risk of the primary outcome versus placebo in each subgroup (normoglycaemia, 0·77 [95% CI , 0·57, 1·04]; prediabetes HR 0·87 [CI 0·69, 1·08]; diabetes HR 0·81 [0·69, 0·95]) ($p_{interaction}$=0·82) and across the continuous HbA1c spectrum ($p_{interaction}$=0·85). In none of the glycaemic categories were adverse events differentially affected by treatment.

Interpretation: In patients with HFmrEF/HFpEF, oral dapagliflozin improved heart failure outcomes to a similar extent in three glycaemic subgroups: normoglycaemia, prediabetes, and type 2 diabetes. Moreover, the heart failure benefits of dapagliflozin appear to be consistent across a continuous glycaemic spectrum.

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Key Words: SGLT2 inhibitors, dapagliflozin, type 2 diabetes, prediabetes, heart failure with preserved ejection fraction, heart failure with mildly reduced ejection fraction

Research in context

Evidence before this study

We searched PubMed for publications in English between January 1, 2012, and September 1, 2022, using the search terms “SGLT2 inhibitor”, “heart failure”, and “randomised controlled clinical trial”. In large cardiovascular outcome trials involving patients with type 2 diabetes at high cardiovascular risk, SGLT2 inhibitors, originally developed as glucose-lowering medications, have been shown reduce hospitalisations for heart failure. The DAPA-HF and EMPEROR-Reduced trials subsequently demonstrated that the SGLT2 inhibitors dapagliflozin and empagliflozin, respectively, reduced the risk of heart failure hospitalisation or cardiovascular death in individuals with heart failure with left ventricular ejection fraction (LVEF) of 40% or less. The EMPEROR-Preserved trial (using empagliflozin) extended these findings to heart failure with a LVEF above 40%, a category of heart failure highly prevalent in type 2 diabetes populations and for which there were no prior clear evidence-based therapies. Notably, the benefits of SGLT2 inhibitors were consistent in patients with and without type 2 diabetes in all three trials. In the DELIVER trial, dapagliflozin reduced the risk of worsening heart failure or cardiovascular death by 18% in 6263 patients with heart failure and mildly reduced or preserved ejection fraction. In a follow-up meta-analysis of DAPA-HF and DELIVER, the effects of dapagliflozin were consistent across the spectrum of LVEF.

Added value of this study

Our results show that the heart failure benefits of dapagliflozin in DELIVER were consistent across three glycaemic subgroups: normoglycaemia, prediabetes, and type 2 diabetes and, within these subgroups, along the trial’s entire range of LVEF. In the type 2 diabetes subgroup, the effects of dapagliflozin were also similar in those using versus not using metformin or insulin at baseline, those with longer versus shorter duration of diabetes, and those with higher versus lower glycated hemoglobin levels at baseline.

Implications of all the available evidence

In patients with heart failure with mildly reduced or preserved ejection, dapagliflozin imparts substantial cardiovascular benefits across a broad range of glycaemia.

Introduction

The prevalence of heart failure, particularly heart failure with preserved ejection fraction (HFpEF) is higher in patients with type 2 diabetes compared to the general population.[1] HFpEF and diabetes in fact share several risk factors, including obesity, insulin resistance, hypertension, and coronary artery disease. Patients with HFpEF and diabetes are also at increased risk of adverse outcomes compared to those without diabetes.[1] While more stringent control of blood glucose alone in these individuals does not appear to improve heart failure outcomes,[2] epidemiological studies have shown a clear relationship between glycated hemoglobin (HbA1c) levels and the incidence of heart failure as well as hospitalisations and mortality in those with prevalent heart failure. [3] These trends appear to extend to more mildly elevated ranges of HbA1c, not yet diagnostic of diabetes.

Sodium–glucose co-transporter 2 (SGLT2) inhibitors, originally developed as oral glucose-lowering medications for type 2 diabetes, were subsequently found to have unexpected benefits in reducing heart failure hospitalisations. These data emerged from large cardiovascular outcome trials involving type 2 diabetes patients at high cardiovascular risk, which had been assembled to meet regulatory requirements for the demonstration of cardiovascular safety of newer antihyperglycemic therapies.[4] Such findings quickly led to dedicated large, randomized heart failure trials, including both participants with or without diabetes, in which SGLT2 inhibitors demonstrated clear efficacy in reducing adverse heart failure outcomes including in patients with either reduced and preserved ejection fraction.[5-8] As a result, SGLT2 inhibitors are now considered foundational therapy in heart failure, endorsed by multiple guideline statements from both international cardiology[9-10] and diabetology[11] professional societies and national regulatory agencies. Dapagliflozin specifically was recently demonstrated to be highly efficacious and safe in both heart failure with reduced ejection fraction (HFrEF) in the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial[5] and, more recently, in HFpEF in DELIVER (Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure), which included patients with HFpEF and with heart failure and mildly reduced ejection fraction (HFmrEF).[8] How well the observed benefits of dapagliflozin might apply to HFpEF/HFmrEF patients across glycaemic categories has not been previously reported. This is of interest in those with diabetes and prediabetes, given their higher risk of adverse cardiac outcomes, but also in individuals with normoglycaemia who, while at relatively lower risk, would not be expected to experience any glucose-lowering effect from an SGLT2 inhibitor.

In the DELIVER trial, oral dapagliflozin was compared to placebo in 6263 patients with HFmrEF or HFpEF, defined as having a clinical diagnosis of heart failure with a left ventricular ejection fraction >40%.[8] The main findings from DELIVER has been previously reported, with dapagliflozin reducing the risk of the primary outcome (worsening heart failure or cardiovascular death) by 18% (hazard ratio [HR],

0·82; 95% confidence interval [CI], 0·73 to 0·92; P< 0·001.) Reflecting the known increased prevalence of diabetes in heart failure populations – especially in HFpEF[12] – more than half of the DELIVER study population had either a prior history of type 2 diabetes or were newly identified on the basis of an elevated HbA1c at enrolment. Among the no diabetes group, nearly two-thirds had evidence of prediabetes by HbA1c levels (comprising nearly one-third of the entire trial cohort.) With diabetes status being a pre-specified subgroup in DELIVER, we took this opportunity to conduct an in-depth analysis of overall event rates as well as the efficacy and safety of dapagliflozin in the population of trial participants with various stages of dysglycaemia, and compared them to those in the normoglycaemic group. Our primary objective was to determine if there was any differential effect on the primary outcome between baseline glycaemic categories.

Methods

Study Design and Patients

The design and baseline characteristics of the DELIVER trial has been previously described.[13] Briefly, DELIVER was an international, randomised, double-blind, event-driven trial comparing dapagliflozin with placebo, both administered orally, in patients with HFpEF or HFmrEF. Randomizing sites numbered 350 across 20 countries. Eligibility criteria included either ambulatory and hospitalised adult patients, aged 40 years or older who had an LVEF >40%, New York Heart Association functional class II-IV, evidence of structural heart disease (such as left atrial enlargement or left ventricular hypertrophy), and elevation in natriuretic peptides (N-terminal pro B-type natriuretic peptide ≥300 pg/mL or ≥600 pg/mL for patients in atrial fibrillation/flutter) were eligible. The trial recruited patients irrespective of their glycaemic status, i.e. both those with or without type 2 diabetes were eligible. Key exclusion criteria included probable alternative diagnoses potentially accounting for the patients' symptoms; uncontrolled hypertension (systolic blood pressure ≥160 mmHg if not on ≥3 antihypertensive medications, or ≥180 mmHg regardless of number of medications); estimated glomerular filtration rate (eGFR) <25 mL/min/1·73 m^2; type 1 diabetes (owing to the known risk of diabetic ketoacidosis); treatment with any SGLT2 inhibitor within 4 weeks of randomisation or prior intolerance to an SGLT2 inhibitor. For purposes of this analysis, the trial population was divided as prespecified in the trial's Statistical Analysis Plan[13] into the following categories based on glycaemic status at baseline, derived from criteria of the American Diabetes Association (ADA)[14]: (1) normoglycemia (no history of diabetes and baseline HbA1c <5·7% [39 mmol/mol]); (2) prediabetes (no history of diabetes and baseline HbA1c 5·7 - <6·5% [39 - <48 mmol/mol]; and (3) type 2 diabetes (history of and/or prevalent use of a glucose lowering agent [unless specifically prescribed for an indication other than diabetes]) or baseline HbA1c ≥6·5% [48 mmol/mol].) The protocol was approved by institutional review boards or ethics committees at each study site, and

every patient provided written informed consent. The trial has been registered in ClinicalTrials.gov, NCT03619213.

Study Procedures

After informed consent and a 21-day screening period, patients were randomised to dapagliflozin 10 mg or matching placebo, taken orally once daily. Randomisation was stratified by type 2 diabetes status at baseline. Concomitant medical treatment for diabetes, hypertension, dyslipidemia and other comorbidities including heart failure management was recommended according to the local standard of care. Following randomisation, study visits took place at 30, 120, 240, 360, and 480 days after randomisation, and then every 120 days thereafter until the final study visit. More details about the study protocol is in appendix 2. Because of the intervening COVID-19 pandemic, several accommodations needed to be made during conduct of the trial in order to ensure data quality and integrity. These adaptations included the conversion, when necessary, of in-person to virtual study site visits, remote data collection for patient-reported outcomes, and also the collection and reporting of all COVID-19 related adverse events and adjudication of COVID-19 related hospitalisations and deaths. A sensitivity analysis was performed with patients being censored at the time of a COVID-19 diagnosis; we then assessed for competing risk for non-cardiovascular death. This did not change the primary results of the DELIVER trial. [8]

Study Outcomes

All prespecified study outcomes were adjudicated by a Clinical Events Committee, which was blinded to treatment assignment. The primary outcome was the composite of time to first worsening heart failure events (defined as an unplanned hospitalisation or urgent heart failure visit requiring intravenous therapy) or cardiovascular death. Key secondary outcomes included *total* number of worsening heart failure events (i.e. first and subsequent hospitalisations for heart failure and/or urgent heart failure visits or cardiovascular death), cardiovascular death, and all-cause mortality. Other outcomes included time to first worsening heart failure event, time to first hospitalisation for heart failure, and all-cause mortality. Heart failure outcomes may be in part influenced by the duration and severity of diabetes, and also conceivably by concurrent anti-hyperglycaemic therapy. We therefore analyzed (post hoc) the primary outcome by several other subgroups and reported treatment effect hazard ratios among patients with previously diagnosed diabetes by (a) duration of diabetes < 10 vs ≥ 10 years, (b) baseline HbA1c $\leq$ 7·1% [54 mmol/mol] (median) vs > 7·1% [54 mmol/mol], (c) baseline metformin use versus no metformin use, (d) baseline use of a sulfonylurea versus no sulfonylurea use, (e) baseline use of a DPP-4 inhibitors versus no DPP-4 inhibitor use, and (f) baseline insulin use versus no insulin use. We also assessed efficacy of dapagliflozin within each glycaemic subgroup by left ventricular ejection fraction. In light of the prior extensive safety data regarding dapagliflozin, only collection of serious adverse events (SAE) and adverse events leading to discontinuation of study drug (SAE/DAE) were required; these included volume

depletion and renal events. Additionally, events related to major hypoglycemic events, diabetic ketoacidosis, and amputation were collected. Accordingly, we did not collect and cannot report other non-serious adverse events such as genital mycotic infections which are already known to be increased by SGLT2 inhibition.

Statistical Analyses

Details of DELIVER Statistical Analysis Plan (SAP) have been previously published,[8,13] and the main analysis reported herein was prespecified (See academic SAP version 1.3 in appendix 2). Baseline characteristics were compared between the three glycaemic subgroups using ANOVA for continuous variables and chi-square or Fisher exact tests for categorical variables. For the overall trial, a sample size of 6100 participants followed for a minimum of 13·5 and a maximum of 39 months was estimated to provide 1117 events. This resulted in 93% power to detect a 20% relative risk reduction for the primary endpoint with a two-sided alpha of 0·024; the HR of 0.80 was prespecified and felt to be a relevant target treatment effect. The current subgroup analyses had no formal statistical considerations, however. The primary and secondary event-based objectives were evaluated under the treatment policy estimand, including differences in outcomes over the entire study period until the primary analysis censoring date, in order to reflect the effect of the initial treatment assignment, irrespective of exposure to concomitant treatment with or subsequent treatment discontinuation of the investigational product. The analysis was performed for the Full Analysis Set (FAS) including all events that occurred on or prior to primary analysis censoring date, including events following premature discontinuation of investigational product. The Full Analysis Set comprised all patients who were randomised to study treatment (i.e., 'intent to treat'), irrespective of their protocol adherence and continued participation in the study. Patients were analysed according to their randomised treatment assignment, irrespective of the treatment actually received. The FAS was therefore the primary analysis set for the intention to treat analysis of primary and secondary variables. The Safety Analysis Set (SAS) comprised those patients who were randomly assigned to study treatment and who took at least 1 dose of investigational product, with patients analysed according to the treatment actually received. Safety events included those on or prior to last dose of study drug + 30 days. The SAS was the primary analysis set for all safety outcomes. For these analyses, time-to-event data were evaluated using Kaplan–Meier estimates and Cox proportional hazards models, with the treatment-group assignment as a fixed-effect factor. Event rates were further assessed across the HbA1c spectrum (as a continuous variable) by Poisson regression using restricted cubic splines with knot placement at the 10th, 50th, and 90th percentiles. A similar technique was used to assess event rates across the left ventricular ejection fraction spectrum in each of the glycaemic subgroup. As in the primary DELIVER analysis, treatment effects were examined by Cox proportional hazards models stratified by type 2 diabetes at baseline and including interaction terms for effect modification by glycaemic category. Statistical analyses were conducted using STATA version 16·1 (StataCorp, College Station, TX, USA).

P-values of <0·05 were considered statistically significant. The p-values for the subgroup analyses were not adjusted for multiple comparisons as the tests are exploratory and are interpreted descriptively.

Results

Patient Characteristics

Between September 1, 2018, and January 18, 2021, 10,418 patients were screened for the DELIVER trial, with 6263 being randomized to oral dapagliflozin or placebo. For additional details about patient flow during the trial, see the CONSORT diagram (appendix 1, p. 11) At baseline, clinical characteristics were balanced between the randomized groups. The mean age was 71·7 years (SD 9·6) and mean body mass index (BMI) of 29·8 kg/m^2 (SD 6·1) 44·5% obese); 43·9% were women, and 71·7% were white. The mean of the most recent LVEF was 54·2% (SD 8·8) and the mean baseline estimated glomerular filtration rate (eGFR) was 61·0 mL/min per 1·73 m^2 (SD 19·1) (49·0% eGFR <60 mL/min per 1·73 m^2.) Baseline HbA1c was available in 6247 and an additional 12 patients were identified has having type 2 diabetes at baseline (i.e., did not need HbA1c criteria), yielding a total of 6259 patients, which form the basis of this analysis. In all patients with HbA1c available, the mean value was 6·6% (SD 1·4) [54 mmol/mol] (range, 4·2% - 17·2% [22 - 165 mmol/mol]) and the median value was 6·2% [44 mmol/mol] (interquartile range, 5·7%, 7·0% [39, 53 mmol/mol]) As for glycaemic status at baseline, 3150 (50·3%) had type 2 diabetes (2806 (44·8%) based on prior history, 26 (0·4%) based on medication use, and 318 (5·1%) newly identified by baseline HbA1c level), 1934 (30.9%) had prediabetes, and 1175 (18·8%) were normoglycaemic. (Using the more restrictive criteria of the International Expert Committee[14] that defines pre-diabetes as HbA1c 6.0 - <6.5% [42-48 mmol/mol], the groupings were: type 2 diabetes: 3150 [50·3%], prediabetes: 1033 [16·5%], and normoglycaemic: 2076 [33·2%]). Baseline characteristics by glycaemic subgroups are shown in Table 1. Baseline characteristics by treatment assignment in each glycaemic subgroup are in appendix 1, p. 1-3. Patients with diabetes had higher BMI, somewhat worse kidney function, and had a greater prevalence of atherosclerotic disease, including coronary artery disease. They tended to have a higher New York Heart Association (NYHA) class and had also been more frequently hospitalised for heart failure over the year prior to study enrolment, but had a lower prevalence of atrial fibrillation/flutter as compared with the normoglycaemic subgroup. In general, the prediabetes subgroup had features intermediate between the other two, with the exception of atrial fibrillation which had the highest prevalence in this group. There was more angiotensin receptor blocker and less loop diuretic and mineralocorticoid receptor antagonist use in those with diabetes compared to the other subgroups. Treatment with devices such as pacemakers and implantable cardioverter-defibrillators was similar across the subgroups. The median duration of follow-up was 2·3 years (interquartile range, 1·7, 2·8 years). The trial was stopped when the required number of primary outcome events was reached.

Clinical Outcomes Based on Glycaemic Status

Crude event rates for the primary composite outcome of first worsening heart failure event or cardiovascular death and most of the secondary outcomes varied across the three glycaemic subgroups, with the diabetes group being statistically significantly higher than the normoglycaemic group (Figure 1; appendix 1, p. 4). The primary outcome rate was 6·9 per 100 patient-years in the normoglycaemic group (referent), increasing to 7·6 per 100 patient-years in the prediabetes group (hazard ratio [HR] 1·09 [95% confidence intervals (CI) 0·90, 1·31]) and 10·1 per 100 patient-years in the type 2 diabetes group (HR 1·46 [95% CI, 1·24, 1·73]) ($p<0.001$ for trend). The same trends were observed for heart failure-specific components of the primary outcome, such as worsening heart failure events. CV death and all-cause death occurred at similar frequency across the subgroups with a trend towards higher all-cause mortality in the diabetes group only. For mortality, there was no evidence of any intermediate outcome rates in those with prediabetes. Finally, using HbA1c as a continuous variable, all event rates generally increased at higher levels (Figure 3).

Efficacy of Dapagliflozin Versus Placebo According to Glycaemic Status

Compared with placebo, oral dapagliflozin therapy consistently reduced the risk for the primary outcome (time to first worsening heart failure event or cardiovascular death) across the glycaemic categories. In the normoglycemic subgroup, the primary outcome rate was 7·8 per 100 patient-years in those randomized to placebo and 6·0 per 100 patient-years in the dapagliflozin group, for an absolute risk reduction of 1·8 per 100 patient-years and a HR in favor of dapagliflozin of 0·77 (95% CI , 0·57, 1·04). In comparison, the corresponding values (placebo versus dapagliflozin) in the dysglycaemic categories were as follows: prediabetes: 8·2 versus 7.1 per 100 patient-years (absolute risk reduction, 1·1 per 100 patient-years; HR 0·87 [95% CI 0·69, 1·08]) and diabetes: 11.2 versus 9.0 per 100 patient-years (absolute risk reduction, 2.2 per 100 patient-years; HR 0·81 [95% CI 0·69, 0·95]) ($p_{interaction}$=0·82; Table 2, Figure 2). Similarly, dapagliflozin's treatment effect did not differ statistically significantly across the glycaemic subgroups for the following components of the primary outcome and key secondary outcomes: cardiovascular death; worsening heart failure events; hospitalisations for heart failure; the composite of CV death and all heart failure events (including recurrent); and all-cause mortality (all interaction p-values > 0.10) (Table 2; appendix 1, pp. 5-7, 13-15.) Consistent with the categorical analysis, results were similar with HbA1c modeled as a continuous variable ($p_{interaction}$>0·20 for all; Figure 4.)

Efficacy of dapagliflozin within specific diabetes subgroups

Our post hoc analyses of several diabetes subgroups examined dapagliflozin treatment effect by duration, severity and baseline treatment of established diabetes as follows: diabetes duration less than 10 years

(N=1505 [53.6% of participants with history of type 2 diabetes]) versus 10 years or longer (N=1296 [46.2%]); HbA1c at baseline below (N=1471 [52.4%]) versus above (N=1323 [47.1%]) the median of 7·1% [54 mmol/mol]; and baseline use of the most prevalent glucose-lowering agents in the DELIVER population, metformin (N=1641 [58·5%]), insulin (N=843 [30·0%]), DPP-4 inhibitors (N=471 [16·8%]), and sulphonylureas (N=603 [21·5%]), and GLP-1 receptor agonists (N=61 [2·2%]). As seen in the appendix 1, p. 16, there proved to be generally no statistical heterogeneity across the subgroups on the primary outcome, indicating similar benefits from dapagliflozin. The sole exception was for sulfonylureas where those taking these medications at baseline had statistically significantly more benefit from dapagliflozin (HR 0·50, 95% CI 0·35-0·72) than those not taking these medications (HR 0·94, 95% CI 0·79-1·13) (Pinteraction=0·003). Finally, we conducted a post-hoc analysis of the effect of dapagliflozin on the primary outcome rates within each glycaemic subgroup, based on left ventricular ejection fraction as a continuous variable, and found no significant heterogeneity ($p_{interaction}$=0·92 for all subgroups; appendix 1, p. 17.)

Safety Outcomes

Serious adverse events (SAE) as well as amputations, hypoglycemia, and diabetic ketoacidosis (the latter two being rare in the trial) were more frequent in the diabetes subgroup (appendix 1, p. 8). However, there was no evidence of any influence by treatment assignment (appendix 1, pp. 9-11.) Specifically, those randomized to dapagliflozin had no differences in volume related SAE/DAE, renal SAE/DAE, hypoglycemia or amputations versus placebo.

Discussion

In patients with HFmrEF/HFpEF enrolled in the multinational DELIVER trial and undergoing contemporary therapy, there was a stepwise increase in heart failure outcomes across the three glycaemic categories (normoglycaemia, prediabetes, type 2 diabetes). The SGLT2 inhibitor dapagliflozin, administered orally, reduced the composite primary outcome of time-to-first worsening heart failure events or cardiovascular mortality in the three glycaemic subgroups, without heterogeneity, as well as across the entire range of baseline HbA1c. Given the higher absolute risk of the primary outcome observed in those with diabetes, the absolute risk reduction with dapagliflozin tended to be most favorable for this subgroup (2·2 per 100 patient-years; numbers needed to treat (NNT) 46) than in the other two (normoglycaemia, 1·8 per 100 patient-years [NNT 56]; prediabetes, 1·1 per 100 patient-years [NNT 91].) These results extend the efficacy of dapagliflozin in patients with HFrEF from DAPA-HF to those with HFmrEF/HFpEF. DAPA-HF[5] demonstrated an overall 26% relative risk reduction (95% CI 15%, 35%; p<0·001) for the same primary outcome, with hazard ratios of 0·73 (95% CI 0·60, 0·88) in patients without diabetes (including prediabetes) versus 0·75 (95% CI 0·63, 0·90) in the diabetes subgroup

($P_{interaction}$=0·80.)[15] Taken together, these data confirm that the clinical benefits of dapagliflozin in heart failure patients not only extend over the entire range of ejection fractions but also across the glycaemic spectrum, including those with neither diabetes nor prediabetes and considered to be normoglycaemic. The results are also generalisable as the DELIVER cohort appears representative of the broader HFmrEF/HFpEF population seen in clinical practice.

Additional post hoc analyses within DELIVER's diabetes subgroup also found generally no interaction with dapagliflozin's treatment effect based on duration, severity, diabetes treatment, or ejection fraction. The interaction regarding baseline sulfonylurea therapy has not been reported before in other SGLT2 inhibitor trials and is likely a chance finding. For example, in DAPA-HF, the HRs for the primary endpoint in favor of dapagliflozin was 0·77 and 0·75 in those taking versus not taking sulfonylureas (Pinteraction=0.93).[16] Similar data from the EMPEROR trials are not available. If this finding is confirmed in EMPEROR-Preserved, further investigation would be warranted. An obvious mechanism is not apparent.

Trials testing other SGLT2 inhibitors in heart failure populations have found similar effects. In EMPEROR-Reduced,[6] involving 3730 HFrEF patients, empagliflozin lowered the risk of the primary outcome of time-to-first heart failure hospitalisation or cardiovascular death by 25% (p<0·001), with HRs in participants without diabetes and those with diabetes subgroups of 0·72 (95% CI 0·60, 0·87) and 0·78 (95% CI 0·64, 0·97), respectively ($P_{interaction}$=0·57.)[17] In the EMPEROR-Preserved trial[7] involving 5988 HFpEF/HFmrEF patients, empagliflozin reduced risk of the same primary outcome by 21% (95% CI 10%, 31%; p<0·001), with nearly identical HRs in those without versus with diabetes: 0·78 (95% CI 0.64, 0.95) and 0·79 (95% CI 0·67, 0·94), respectively ($P_{interaction}$=0·92).[18] (For direct comparison, risk of first heart failure hospitalisation or cardiovascular death in DELIVER was reduced by 20% with dapagliflozin in the overall population [HR 0·80 (95% CI 0·71, 0·91)]. Finally, in SOLOIST, which involved 1222 patients with type 2 diabetes and recent hospitalisation for heart failure, treatment with sotagliflozin, and inhibitor of both SGLT2 and SGLT1 resulted in a 29% risk reduction (HR 0·71 [95% CI 0·56, 0·89]) in the same composite outcome.[19]

Regarding safety concerns, we observed more frequent serious adverse events in the diabetes subgroup but no increased risk based on randomised treatment. This is in keeping with prior heart failure studies,[5-8] and is notable, given the frequently frail nature of a heart failure population, commonly treated with multiple vasoactive therapies and potent diuretics that can substantially alter plasma volume and blood pressure.

Our findings are particularly important for medical professionals involved in diabetes care. Heart failure, particularly HFpEF is extremely common in this condition. In the United States, it has been one of the leading causes for hospital admission in the Medicare population (age >65 years),[20] with similar reports from other parts of the world.[21] Once heart failure is established, adverse clinical outcomes, including hospitalisations and mortality, are worse when diabetes coexists.[21,22] Reducing hyperglycemia by itself does not appear to improve heart failure outcomes.[2] Indeed, several glucose-lowering agents have been found to increase the heart failure hospitalizations.[23] Accordingly, understanding the optimal management of heart failure, especially HFmrEF/HFpEF, which is highly prevalent in obese, hypertensive patients with type 2 diabetes, is critically important. Reflecting the known epidemiology of HFpEF,[12] most of the patients enrolled in DELIVER had dysglycaemia, with more than 50% having type 2 diabetes and more than 30% having prediabetes. Indeed, only 2 out of every 10 DELIVER participants were normoglycaemic. These proportions are consistent with other recent HFpEF trials, including EMPEROR-Preserved[7] and PARAGON-HF.[24] These findings reinforce the importance of the awareness amongst clinicians about the frequency of HFpEF in dysglycaemic states (and vice versa).

The role of SGLT2 inhibitors as heart failure therapies is now solidified. In contrast to the original cardiovascular outcome trials with these agents, which involved only those with type 2 diabetes, the heart failure trials have included both patients with and without diabetes, clearly demonstrating that these medications extend to those with prediabetes and normoglycemia.[16-18] In heart failure guidelines, SGLT2 inhibitors are now endorsed in both HFrEF and HFpEF.[9,10] Initial trials documenting their substantive benefits involved patients with left ventricular ejection fractions ≤40%.[5,6] EMPEROR-Preserved[7] and now DELIVER[8] have extended these to heart failure patients with higher ejection fractions. Previously, there remained considerable uncertainty as to whether this class of medication would be effective in HFpEF, given the extensive prior history of clinical trial failures in this space, involving evidence-based therapies known to be effective in HFrEF.[25] Actually, in a meta-analysis of the EMPEROR trials, there appeared to be attenuation of treatment benefit from empagliflozin at the highest ejection fractions.[26] We found no such trends in DELIVER, neither in the overall cohort nor in the individual glycaemic subgroups, when analyzed with left ventricular ejection fraction as a continuous variable. Indeed, in a recent pooled analysis of data from both EMPEROR-Preserved and DELIVER, the hazard ratios for the primary outcomes were nearly identical in all three ejection fraction subgroups (<50%, HR 0.78 [95% CI 0.67, 0.90]; 50-59%, HR 0.79 [95% CI 0.68, 0.93], and >60%, 0.81 [95% CI 0.69, 0.96]).[27] In fact, the SGLT2 inhibitors are now the only category of medication with clear heart failure benefits throughout the full ejection fraction range in both HFpEF and in HFrEF.

There remains uncertainty as to the manner through which they exert their cardiac effects; it certainly does not appear to be mediated through glucose reduction. Theories include reductions in plasma volume

and interstitial fluid with concurrent improvements in ventricular afterload and preload; improved myocardial energetics through altered fuel supply involving ketone bodies; direct cardiac effects via the sodium-hydrogen ion exchanger; reductions in sympathetic and/or vascular tone, improvements in cardiac remodeling, among others.[28]

Limitations

Our analysis has several limitations. First, given the nature of DELIVER as a large global heart failure outcome trial, we did not obtain fasting plasma glucose levels nor did we perform oral glucose tolerance testing. More precise classification of newly identified diabetes, prediabetes and even normoglycaemia would have necessitated these tests for a more rigorous assessment. The number of patients with prediabetes by HbA1c who may actually have had diabetes based on FPG or OGTT is considerable.[29,30] Conversely, some patients with prediabetes by HbA1c may not have met criteria for prediabetes by FPG or by OGTT.[30,31] Accordingly, the numbers and individuals in our subgroups may have changed if these additional tests had been employed. Second, HbA1c was determined only on a single blood sample. While this is adequate for identifying prediabetes, official policies are for the HbA1c to be repeated and confirmed before establishing a diagnosis of diabetes.[14] Accordingly, it is possible that some participants in the small group of newly identified diabetes may have had lower HbA1c on a second determination, leading to re-categorisation. Third, <5% of our study population self-identified as being of Black race. This constitutes an under-represented group in DELIVER, a concern in many heart failure trials. Given the higher prevalence of diabetes in Blacks, it is important to study this group further, perhaps through meta-analyses, to ensure no heterogeneity in effect, although one has not emerged across SGLT2 inhibitors trial to date. In the regard, we would also point out that several investigators have found a higher mean HbA1c in Blacks versus whites for a given degree of hyperglycemia.[14] So, any such future study would ideally entail complementary measures of glycemia to confirm proper assignment of baseline glycaemic status. Finally, we did not measure HbA1c in follow-up, so could not determine the impact of dapagliflozin on this glycemic measure nor analyze outcomes based on the degree of HbA1c lowering.

Conclusions

Oral dapagliflozin reduced the composite of worsening heart failure and cardiovascular death regardless of glycaemic category or baseline HbA1c in HFmrEF/HFpEF patients enrolled in DELIVER, the largest SGLT2 inhibitor heart failure trial to date. Moreover, the lack of any effect modification by baseline glycaemia adds to the growing evidence that the heart failure benefits from dapagliflozin are independent of glycaemic status of the patient. These results are consistent with those demonstrated among patients with HFrEF in the DAPA-HF trial. The benefits dapagliflozin on adverse heart failure outcomes are robust across the spectra of both ejection fraction and glycaemia.

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Author Contributions

SEI, BLC, JJVM, & SDS conceived of and designed the study SEI drafted the manuscript. SEI and SDS had final responsibility for the decision to submit for publication. BLC and BO had access to the raw data, conducted the analyses, and verified the data. All authors contributed to data interpretation and writing of the final version of the manuscript and take responsibility for the accuracy and integrity of the data.

Data sharing statement

The sponsor of this trial is committed to sharing access to patient-level data and supporting clinical documents from eligible studies by qualified external researchers. Such requests are reviewed by an independent review panel and approved based on scientific merit. All data eventually provided will be anonymised to respect the privacy of patients who have participated in the trial, in keeping with applicable laws and regulations. The trial data availability is according to previously published criteria and processes at: https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

Declaration of interests

SEI has served on clinical trial committees or as a consultant to AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Merck, Pfizer, Bayer, Abbott, Lexicon, vTv Therapeutics and Esperion; and has delivered lectures sponsored by AstraZeneca and Boehringer Ingelheim. BLC has received consulting fees from Boehringer Ingelheim. MV has received research grant support or served on advisory boards for American Regent, Amgen, AstraZeneca, Bayer, Baxter Healthcare, Boehringer Ingelheim, Cytokinetics, Lexicon Pharmaceuticals, Novartis, Pharmacosmos, Relypsa, Roche Diagnostics, and Sanofi; received speaker fees from AstraZeneca, Novartis, and Roche Diagnostics; and participates on clinical trial committees for studies sponsored by Galmed, Novartis, Bayer, Occlutech, and Impulse Dynamics. ASD has received research grants (to his institution) from Abbott, AstraZeneca, Alnylam, Bayer, and Novartis and consulting fees/honoraria from Abbott, Alynylam, AstraZeneca, Axon Therapeutics, Biofourmis, Boston Scientific, Bayer, Cytokinetics, GlaxoSmithKline, Lupin Pharma, Merck, Medpace, Novartis, Parexel, Regeneron, Roche, and Verily. PSJ's employer has been remunerated by AstraZeneca, Bayer, and Novo Nordisk for clinical trial work. PSJ also reports consulting and speakers' fees from Novartis, AstraZeneca, and Boehringer Ingelheim; and research funding Boehringer Ingelheim. RadB has received

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FIGURE LEGENDS

Figure 1. Kaplan-Meier curves for key outcomes by baseline glycaemic status. Primary composite outcome, worsening heart failure events, cardiovascular death and all-cause death in the major glycaemic subgroups (no DM [normoglycaemic], prediabetes, and type 2 diabetes.) Outcomes rates for mortality were similar but for those outcomes primarily driven by heart failure hospitalisations (primary outcome and worsening heart failure event), those in the diabetes subgroup had the worse outcomes, with prediabetes being intermediate.

Figure 2. Kaplan-Meier curves (panels A-C) and Forest plot (panel D) for the primary outcome, dapagliflozin versus placebo in the three glycaemic subgroups. Event rates with dapagliflozin were lower in each subgroup, with no statistical heterogeneity. On Panel D, hazard ratios and 95% confidence intervals for each subgroup is shown on the right. No statistical heterogeneity is demonstrated ($P_{interaction}$ = 0.82), indicating similar treatment benefit across each glycaemic category, from normoglycaemia to prediabetes to type 2 diabetes.

Figure 3. HbA1c distribution, incidence rates and dapagliflozin treatment effect by baseline HbA1c (%). Incidence rates (dark line) with 95% confidence intervals (dashed lines) for the primary composite outcome, worsening heart failure event, cardiovascular death and all-cause death by baseline HbA1c as a continuous variable. In general, a positive relationship is demonstrated. Data have been adjusted by sex, age and region).

Figure 4. Treatment effect (ratio, dapagliflozin versus placebo) by baseline HbA1c(%). Restricted cubic spline analyses of the effect of dapagliflozin on the above four key outcomes across the range of baseline HbA1c. The solid black line represents a continuous hazard ratio and the dashed lines show the 95% confidence intervals around the hazard ratio. The hazard ratio is generally under 1.0, indicating a treatment benefit across all HbA1c levels.

Figure 1. Kaplan-Meier curves for key outcomes by baseline glycaemic status

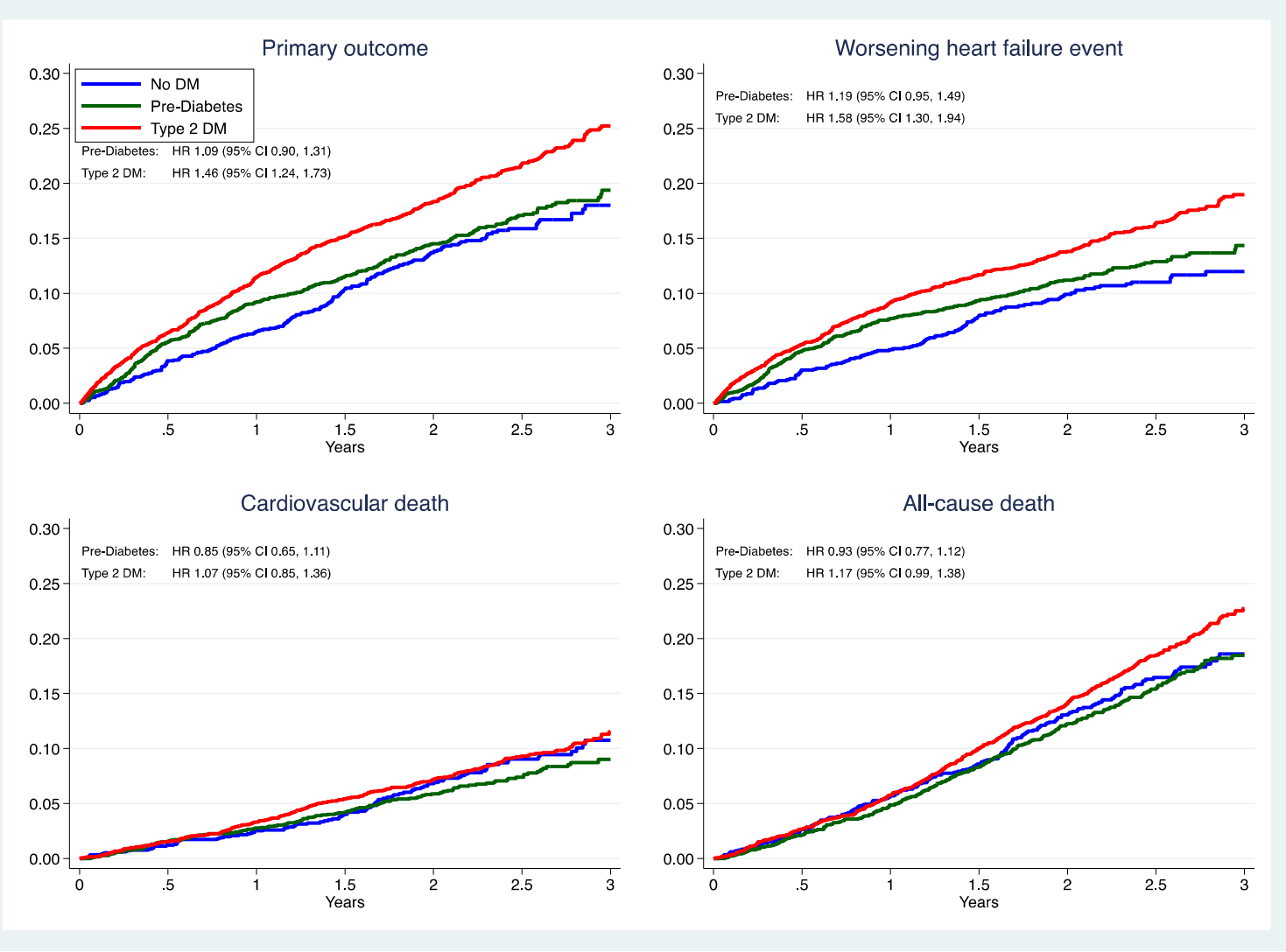


Figure 2. Kaplan-Meier curves (panels A-C) and Forest plot (panel D) for the primary outcome, dapagliflozin versus placebo, in the three glycaemic subgroups

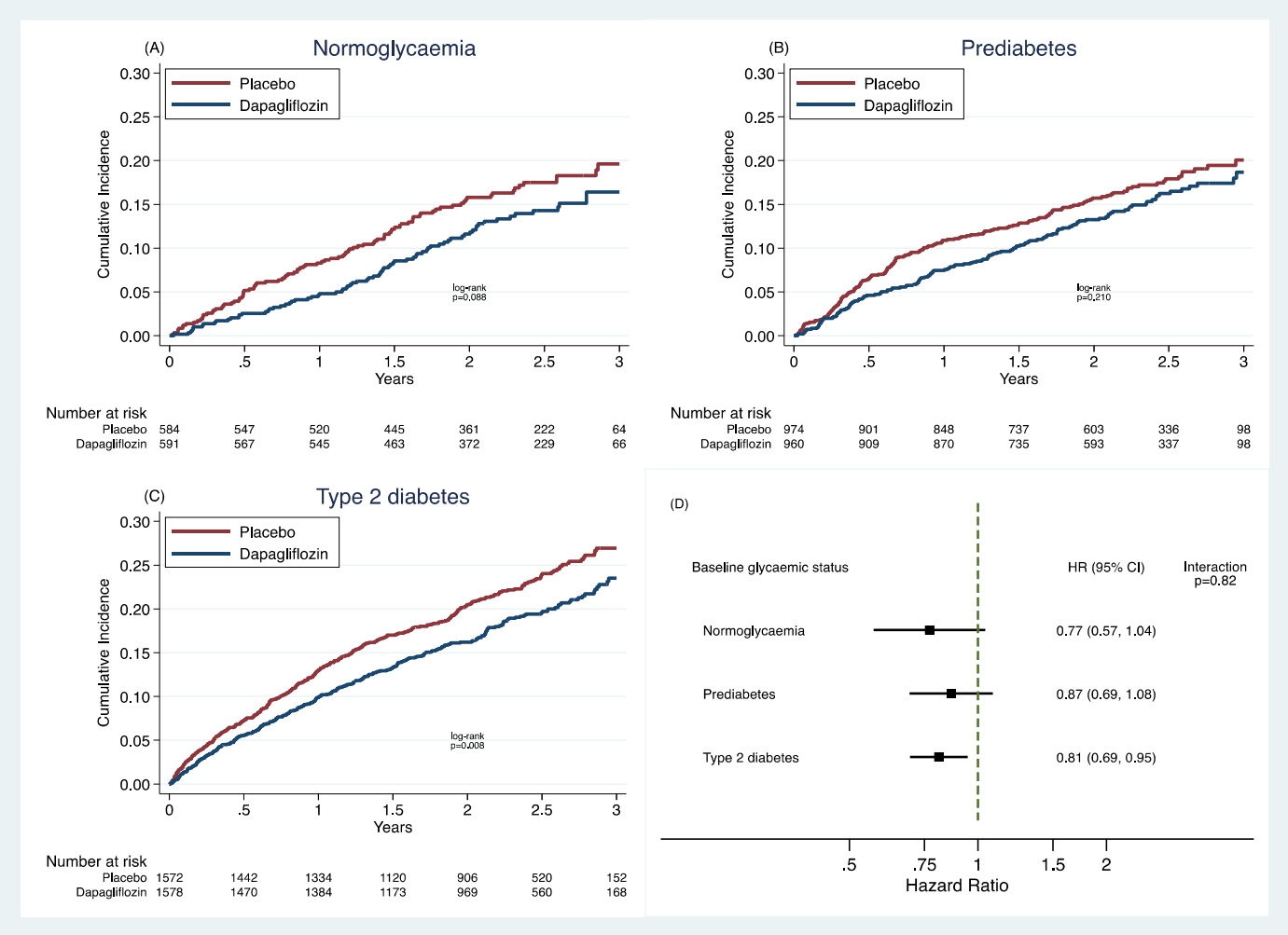


Figure 3. HbA1c distribution and incidence rates by baseline HbA1c (%) (Adjusted by sex, age and region)

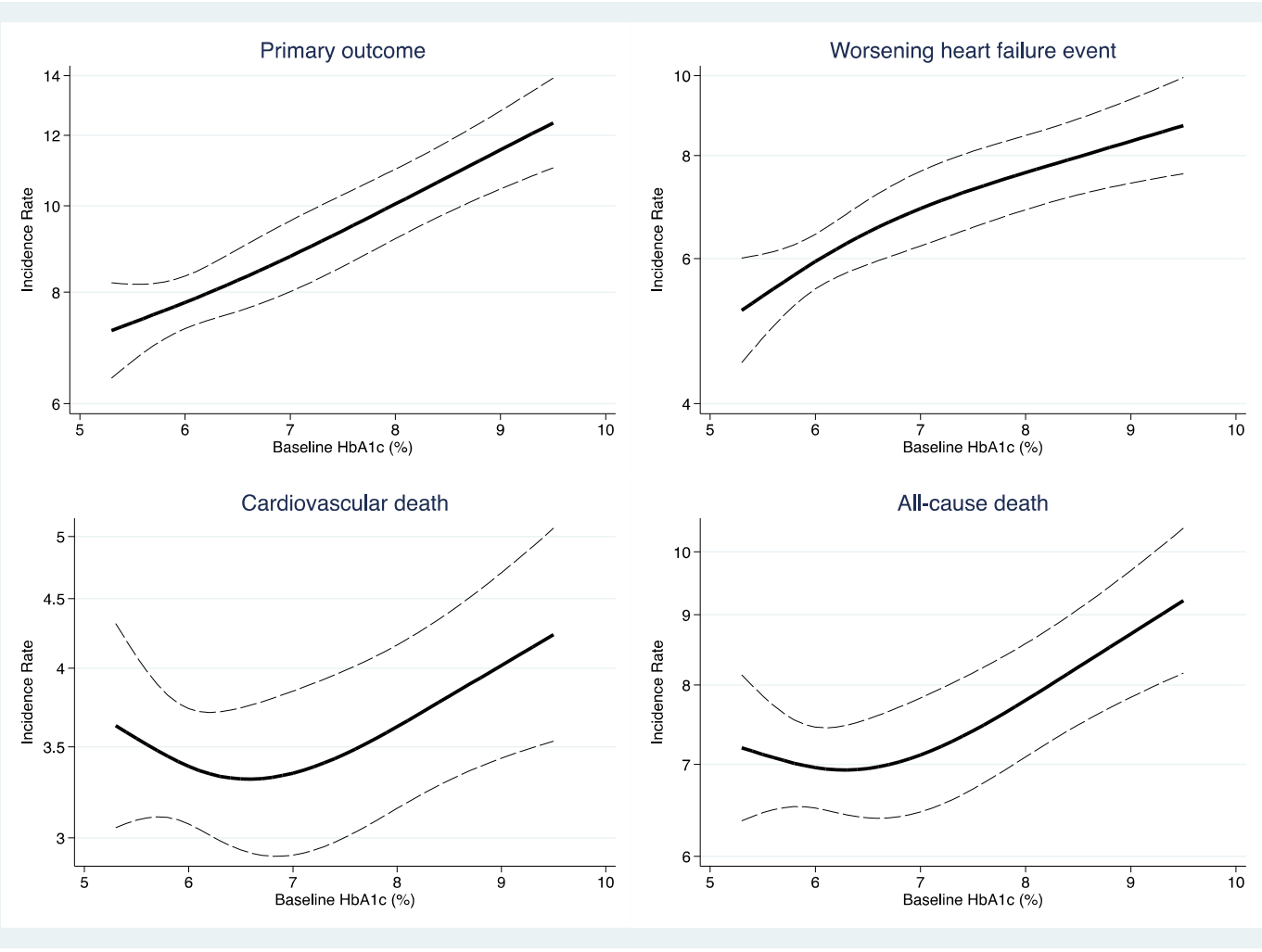


Figure 4. Treatment effect (ratio, dapagliflozin versus placebo) by baseline HbA1c (%)

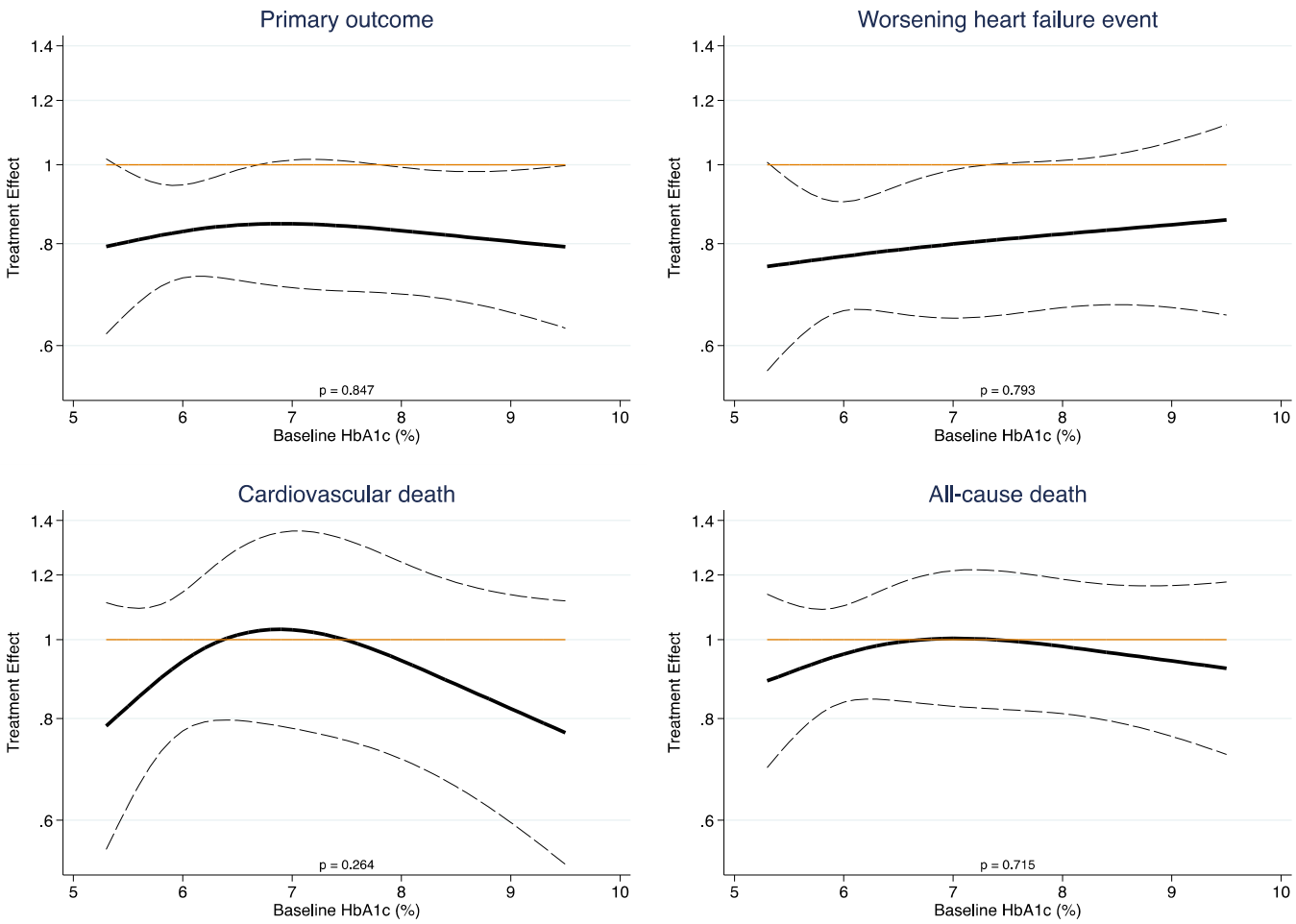


Table 1: Baseline characteristics by glycaemic status (Full Analysis Set)

	Normoglycaemia n=1175	Prediabetes n=1934	Type 2 diabetes n=3150
Age	71.3 (SD 10.5)	73.0 (SD 9.5)	71.0 (SD 9.1)
Diabetes Duration (median [IQR], years)	N/A	N/A	9.2 (3.8, 17.0)
Men	660 (56.2%)	1037 (53.6%)	1818 (57.7%)
Women	515 (53.8%)	897 (46.4%)	1332 (42.3%)
Race			
White	793 (67.5%)	1364 (70.5%)	2278 (72.3%)
Asian	265 (22.6%)	422 (21.8%)	587 (18.6%)
Black Or African American	29 (2.5 %)	37 (1.9 %)	93 (3.0 %)
American Indian Or Alaska Native	33 (2.8 %)	57 (2.9 %)	99 (3.1 %)
Other	55 (4.7 %)	54 (2.8 %)	93 (3.0 %)
Ethnicity			
Hispanic	237 (20.2%)	329 (17.0%)	662 (21.0%)
Geographic Region			
Europe and Saudi Arabia	528 (44.9%)	933 (48.2%)	1543 (49.0%)
Asia	262 (22.3%)	412 (21.3%)	552 (17.5%)
Latin America	228 (19.4%)	313 (16.2%)	638 (20.3%)
North America	157 (13.4%)	276 (14.3%)	417 (13.2%)
Baseline medical history			
Type 2 diabetes	0 (0.0 %)	0 (0.0 %)	2806 (89.1%)
Myocardial Infarction	234 (19.9%)	456 (23.6%)	949 (30.1%)
Any coronary artery disease	462 (39.3%)	882 (45.6%)	1819 (57.7%)
Any atherosclerotic cardiovascular disease	540 (46.0%)	997 (51.6%)	2014 (63.9%)
Prior heart failure hospitalisation	446 (38.0%)	764 (39.5%)	1327 (42.1%)
Atrial fibrillation/flutter	688 (58.6%)	1198 (61.9%)	1663 (52.8%)
Stroke	95 (8.1 %)	158 (8.2 %)	344 (10.9%)
Dyslipidaemia	648 (55.1%)	1107 (57.2%)	2233 (70.9%)
Smoking Status			
Current	97 (8.3 %)	153 (7.9 %)	234 (7.4 %)
Former	389 (33.1%)	697 (36.0%)	1172 (37.2%)
Never	689 (58.6%)	1084 (56.0%)	1744 (55.4%)

Baseline Body Mass Index	28.4 (SD 5.7)	29.0 (SD 6.0)	30.9 (SD 6.2)
Body Mass Index Group (kg/m2)			
<18.5 (Underweight)	15 (1.3 %)	23 (1.2 %)	16 (0.5 %)
18.5-24.9 (Normal weight)	351 (29.9%)	492 (25.5%)	500 (15.9%)
25.0-29.9 (Overweight)	399 (34.0%)	680 (35.2%)	993 (31.5%)
30.0-34.9 (Class I obesity)	264 (22.5%)	446 (23.1%)	863 (27.4%)
35.0-39.9 (Class II obesity)	101 (8.6 %)	187 (9.7 %)	508 (16.1%)
>=40 (Class III obesity)	45 (3.8 %)	102 (5.3 %)	268 (8.5 %)
Time since heart failure diagnosis			
0 – 3 Months	108 (9.2 %)	187 (9.7 %)	273 (8.7 %)
>3 – 6 Months	123 (10.5%)	168 (8.7 %)	301 (9.6 %)
>6 – 12 Months	175 (14.9%)	281 (14.5%)	386 (12.3%)
>1 – 2 Years	178 (15.2%)	310 (16.0%)	505 (16.0%)
>2 – 5 Years	259 (22.1%)	511 (26.4%)	798 (25.3%)
>5 Years	330 (28.1%)	475 (24.6%)	886 (28.1%)
Baseline New York Heart Associaton Class			
I	1 (0.1 %)	0 (0.0 %)	0 (0.0 %)
II	911 (77.5%)	1491 (77.1%)	2308 (73.3%)
III	261 (22.2%)	440 (22.8%)	829 (26.3%)
IV	2 (0.2 %)	3 (0.2 %)	13 (0.4 %)
Baseline Left Ventricular Ejection Fraction (LVEF) (%)	54.3 ± 8.8	54.3 ± 8.9	54.0 ± 8.7
LVEF Group			
<= 40	2 (0.2 %)	1 (0.1 %)	1 (0.0 %)
>=41-49	383 (32.6%)	645 (33.4%)	1083 (34.4%)
50-59	431 (36.7%)	684 (35.4%)	1140 (36.2%)
>= 60	359 (30.6%)	604 (31.2%)	926 (29.4%)
Baseline ECG Atrial Fibrillation/Flutter	491 (41.8%)	939 (48.6%)	1211 (38.5%)
Baseline Systolic Blood Pressure (mmHg)	127.2 (SD 15.5)	126.8 (SD 15.0)	129.5 (SD 15.4)
Baseline Diastolic Blood Pressure (mmHg)	74.3 (SD 10.4)	74.0 (SD 10.2)	73.7 (SD 10.4)
Baseline HbA1c (%)	5.4 (SD 0.2)	6.0 (SD 0.2)	7.4 (SD 1.6)
Baseline eGFR (mL/min/1.73m^2)	65.4 (SD 19.1)	60.9 (SD 18.2)	59.5 (SD 19.5)

eGFR >=60 mL/min/1.73m^2	707 (60.2%)	996 (51.5%)	1488 (47.2%)
Baseline NT-proBNP (median [IQR], ng/L)	1012 [608, 1790]	1104 [656, 1904]	951 [606, 1673]
Baseline heart failure therapies			
Loop diuretics	846 (72.1%)	1480 (76.6%)	2481 (78.8%)
ACE inhibitor (ACEi)	431 (36.7%)	709 (36.7%)	1152 (36.6%)
Angiotensin receptor blocker (ARB)	393 (33.5%)	636 (32.9%)	1243 (39.5%)
Neprilysin inhibitor/ARB (ARNI)	68 (5.8 %)	94 (4.9 %)	139 (4.4 %)
Beta blocker	952 (81.1%)	1587 (82.1%)	2634 (83.6%)
Mineralocorticoid receptor antagonist (MRA)	508 (43.3%)	883 (45.7%)	1275 (40.5%)
Pacemaker	135 (11.5%)	210 (10.9%)	316 (10.0%)
Implantable cardioverter defibrillators (ICD)	18 (1.5 %)	38 (2.0 %)	57 (1.8 %)

Table 2. Treatment effect estimates (dapagliflozin versus placebo) on primary and secondary outcomes by baseline glycaemic status (Full Analysis Set)

Outcome	Normoglycaemic N = 1175		Prediabetes N = 1934		Type 2 diabetes N = 3150		$P_{interaction}$
	Dapagliflozin	Placebo	Dapagliflozin	Placebo	Dapagliflozin	Placebo	
Primary composite	172 events [6.0/100py] HR=0.77 (0.57, 1.04)	[7.8/100py]	305 events [7.1/100py] HR=0.87 (0.69, 1.08)	[8.2/100py]	644 events [9.0/100py] HR=0.81 (0.69, 0.95)	[11.2/100py]	0.82
Cardiovascular death	93 events [3.2/100py] HR=0.82 (0.54, 1.23)	[3.9/100py]	132 events [3.1/100py] HR=1.02 (0.72, 1.43)	[3.1/100py]	266 events [3.5/100py] HR=0.85 (0.67, 1.08)	[4.1/100py]	0.63
Worsening heart failure event	118 events [4.1/100py] HR=0.76 (0.53, 1.10)	[5.4/100py]	229 events [4.8/100py] HR=0.73 (0.56, 0.95)	[6.6/100py]	475 events [6.7/100py] HR=0.83 (0.69, 0.99)	[8.2/100py]	0.74
Hospitalisation for heart failure	113 events [3.7/100py] HR=0.69 (0.47, 1.00)	[5.3/100py]	204 events [4.7/100py] HR=0.74 (0.56, 0.98)	[5.8/100py]	429 events [5.9/100py] HR=0.81 (0.67, 0.98)	[7.4/100py]	0.72
Urgent heart failure visit	11 events [0.5/100py] HR=1.73 (0.51, 5.91)	[0.3/100py]	41 events [0.7/100py] HR=0.59 (0.31, 1.11)	[1.2/100py]	86 events [1.1/100py] HR=0.78 (0.51, 1.19)	[1.4/100py]	0.38
Composite of cardiovascular death and all heart failure events (including recurrent)	284 events [9.0/100py] RR=0.71 (0.50, 1.01)	[12.7/100py]	502 events [9.7/100py] RR=0.70 (0.54, 0.92)	[13.8/100py]	1084 events [14.1/100py] RR=0.82 (0.68, 0.99)	[17.2/100py]	0.58
All-cause death	181 events [6.1/100py] HR=0.80 (0.60, 1.07)	[7.7/100py]	284 events [7.1/100py] HR=1.14 (0.90, 1.44)	[6.2/100py]	556 events [7.6/100py] HR=0.91 (0.77, 1.07)	[8.4/100py]	0.14

HR= hazard ratio (presented with 95% confidence intervals); py=patient-years

Appendix 1

Table S1. Baseline characteristics by treatment assignment across 3 glycaemic subgroups(Full Analysis Set)

	Normoglycaemia		Prediabetes		Type 2 Diabetes	
	Placebo n=584	Dapagliflozin n=591	Placebo n=974	Dapagliflozin n=960	Placebo N=1572	Dapagliflozin N=1578
Age	71.5 ± 10.6	71.1 ± 10.5	72.7 ± 9.7	73.4 ± 9.3	70.9 ± 9.0	71.1 ± 9.3
Age Group						
<= 65	149 (25.5%)	166 (28.1%)	199 (20.4%)	181 (18.9%)	413 (26.3%)	396 (25.1%)
> 75	224 (38.4%)	235 (39.8%)	410 (42.1%)	431 (44.9%)	508 (32.3%)	536 (34.0%)
>65 - 75	211 (36.1%)	190 (32.1%)	365 (37.5%)	348 (36.3%)	651 (41.4%)	646 (40.9%)
Men	334 (57.2%)	326 (55.2%)	517 (53.1%)	520 (54.2%)	897 (57.1%)	921 (58.4%)
Female	250 (42.8%)	265 (44.8%)	457 (46.9%)	440 (45.8%)	XXX (xx.x%)	XXX (xx.x%)
Race						
White	393 (67.3%)	400 (67.7%)	688 (70.6%)	676 (70.4%)	1142 (72.6%)	1136 (72.0%)
Asian	146 (25.0%)	119 (20.1%)	207 (21.3%)	215 (22.4%)	291 (18.5%)	296 (18.8%)
Black Or African American	13 (2.2 %)	16 (2.7 %)	22 (2.3 %)	15 (1.6 %)	43 (2.7 %)	50 (3.2 %)
American Indian Or Alaska Native	14 (2.4 %)	19 (3.2 %)	30 (3.1 %)	27 (2.8 %)	52 (3.3 %)	47 (3.0 %)
Other	18 (3.1 %)	37 (6.3 %)	27 (2.8 %)	27 (2.8 %)	44 (2.8 %)	49 (3.1 %)
Ethnicity						
Hispanic	108 (18.5%)	129 (21.8%)	153 (15.7%)	176 (18.3%)	335 (21.3%)	327 (20.7%)
Geographic Region						
Europe and Saudi Arabia	264 (45.2%)	264 (44.7%)	476 (48.9%)	457 (47.6%)	771 (49.0%)	772 (48.9%)
Asia	143 (24.5%)	119 (20.1%)	202 (20.7%)	210 (21.9%)	274 (17.4%)	278 (17.6%)
Latin America	99 (17.0%)	129 (21.8%)	155 (15.9%)	158 (16.5%)	323 (20.5%)	315 (20.0%)
North America	78 (13.4%)	79 (13.4%)	141 (14.5%)	135 (14.1%)	204 (13.0%)	213 (13.5%)
History: Atrial Fib/Flutter	337 (57.7%)	351 (59.4%)	602 (61.8%)	596 (62.1%)	853 (54.3%)	810 (51.3%)
History of stroke	51 (8.7 %)	44 (7.4 %)	85 (8.7 %)	73 (7.6 %)	163 (10.4%)	181 (11.5%)
History: Dyslipidaemia	336 (57.5%)	312 (52.8%)	573 (58.8%)	534 (55.6%)	1118 (71.1%)	1115 (70.7%)
History: Type 2 Diabetes Mellitus	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	1405 (89.4%)	1401 (88.8%)
ry: Chronic Obstructive Pulmonary Disease	45 (7.7 %)	46 (7.8 %)	124 (12.7%)	113 (11.8%)	171 (10.9%)	193 (12.2%)
/: Non-Coronary Revascularization	12 (2.1 %)	10 (1.7 %)	19 (2.0 %)	21 (2.2 %)	39 (2.5 %)	39 (2.5 %)
History: Sleep Apnoea	34 (5.8 %)	40 (6.8 %)	67 (6.9 %)	67 (7.0 %)	138 (8.8 %)	139 (8.8 %)
History: Myocardial Infarction	114 (19.5%)	120 (20.3%)	232 (23.8%)	224 (23.3%)	490 (31.2%)	459 (29.1%)
Prior HF Hospitalization Flag	226 (38.7%)	220 (37.2%)	403 (41.4%)	361 (37.6%)	639 (40.6%)	688 (43.6%)
Any Coronary Artery Disease	233 (39.9%)	229 (38.7%)	454 (46.6%)	428 (44.6%)	909 (57.8%)	910 (57.7%)
∧ny Atherosclerotic Cardiovascular Disease	274 (46.9%)	266 (45.0%)	522 (53.6%)	475 (49.5%)	1006 (64.0%)	1008 (63.9%)
Smoking Status						

Current	51 (8.7 %)	46 (7.8 %)	80 (8.2 %)	73 (7.6 %)	137 (8.7 %)	97 (6.1 %)
Former	193 (33.0%)	196 (33.2%)	336 (34.5%)	361 (37.6%)	578 (36.8%)	594 (37.6%)
Never	340 (58.2%)	349 (59.1%)	558 (57.3%)	526 (54.8%)	857 (54.5%)	887 (56.2%)
Baseline Body Mass Index	28.4 ± 5.7	28.3 ± 5.7	28.8 ± 5.9	29.1 ± 6.0	31.0 ± 6.1	30.8 ± 6.2
Body Mass Index Group (kg/m2)						
<18.5 (Underweight)	5 (0.9 %)	10 (1.7 %)	10 (1.0 %)	13 (1.4 %)	3 (0.2 %)	13 (0.8 %)
18.5-24.9 (Normal weight)	176 (30.1%)	175 (29.6%)	257 (26.5%)	235 (24.5%)	237 (15.1%)	263 (16.7%)
25.0-29.9 (Overweight)	193 (33.0%)	206 (34.9%)	341 (35.1%)	339 (35.3%)	513 (32.7%)	480 (30.4%)
30.0-34.9 (Class I obesity)	130 (22.3%)	134 (22.7%)	232 (23.9%)	214 (22.3%)	440 (28.0%)	423 (26.8%)
35.0-39.9 (Class II obesity)	61 (10.4%)	40 (6.8 %)	83 (8.5 %)	104 (10.8%)	241 (15.3%)	267 (16.9%)
>=40 (Class III obesity)	19 (3.3 %)	26 (4.4 %)	48 (4.9 %)	54 (5.6 %)	137 (8.7 %)	131 (8.3 %)
e from Diagnosis of HF to Baseline						
0 - 3 Months	58 (9.9 %)	50 (8.5 %)	92 (9.5 %)	95 (9.9 %)	134 (8.5 %)	139 (8.8 %)
>3 - 6 Months	61 (10.4%)	62 (10.5%)	88 (9.1 %)	80 (8.3 %)	153 (9.7 %)	148 (9.4 %)
>6 - 12 Months	92 (15.8%)	83 (14.1%)	135 (13.9%)	146 (15.2%)	200 (12.7%)	186 (11.8%)
>1 - 2 Years	80 (13.7%)	98 (16.6%)	162 (16.7%)	148 (15.4%)	246 (15.6%)	259 (16.4%)
>2 - 5 Years	136 (23.3%)	123 (20.9%)	272 (28.0%)	239 (24.9%)	391 (24.9%)	407 (25.8%)
>5 Years	157 (26.9%)	173 (29.4%)	223 (22.9%)	252 (26.3%)	448 (28.5%)	438 (27.8%)
NYHA Class at Baseline						
I	1 (0.2 %)	0 (0.0 %)				
II	469 (80.3%)	442 (74.8%)	762 (78.2%)	729 (75.9%)	1166 (74.2%)	1142 (72.4%)
III	113 (19.3%)	148 (25.0%)	210 (21.6%)	230 (24.0%)	401 (25.5%)	428 (27.1%)
IV	1 (0.2 %)	1 (0.2 %)	2 (0.2 %)	1 (0.1 %)	5 (0.3 %)	8 (0.5 %)
Baseline LVEF(%)	54.4 ± 9.0	54.2 ± 8.7	54.4 ± 8.9	54.3 ± 8.9	54.3 ± 8.9	53.7 ± 8.4
LVEF Group						
<= 40	0 (0.0 %)	2 (0.3 %)	0 (0.0 %)	1 (0.1 %)	1 (0.1 %)	0 (0.0 %)
>=41-49	194 (33.2%)	189 (32.0%)	326 (33.5%)	319 (33.2%)	527 (33.5%)	556 (35.2%)
50-59	211 (36.1%)	220 (37.2%)	343 (35.2%)	341 (35.5%)	568 (36.1%)	572 (36.2%)
>= 60	179 (30.7%)	180 (30.5%)	305 (31.3%)	299 (31.1%)	476 (30.3%)	450 (28.5%)
Baseline NT-proBNP (ng/L)	1029 [621, 1709]	996 [601, 1837]	1075 [649, 1855]	1122 [675, 1943]	952 [602, 1670]	951 [610, 1687]
NT-proBNP in AFF (ECG)	1381 [981, 2169]	1481 [987, 2104]	1448 [1005, 2281]	1505 [1037, 2329]	1349 [943, 2071]	1340 [897, 2297]
NT-proBNP when no AFF (ECG)	718 [464, 1402]	675 [467, 1238]	703 [464, 1200]	751 [487, 1333]	700 [469, 124]	732 [466, 1292]
line ECG Atrial Fibrillation/Flutter	233 (40.0%)	258 (43.7%)	466 (47.8%)	473 (49.3%)	616 (39.2%)	595 (37.7%)
e Systolic Blood Pressure (mmHg)	127.4 ± 15.9	127.1 ± 15.1	126.3 ± 14.8	127.2 ± 15.1	129.8 ± 15.2	129.3 ± 15.7
Diastolic Blood Pressure (mmHg)	74.2 ± 10.7	74.4 ± 10.1	73.9 ± 10.4	74.2 ± 10.0	73.9 ± 10.3	73.5 ± 10.5
Baseline HbA1c (%)	5.4 ± 0.2	5.4 ± 0.2	6.0 ± 0.2	6.0 ± 0.2	7.4 ± 1.5	7.4 ± 1.6
Baseline Pulse (beats/min)	70.9 ± 12.0	70.1 ± 11.2	70.7 ± 11.3	71.0 ± 11.8	72.2 ± 11.9	72.4 ± 11.9
Baseline Creatinine (umol/L)	97.2 ± 27.8	94.4 ± 28.4	100.4 ± 27.7	100.4 ± 28.8	106.1 ± 33.4	106.3 ± 33.0
Baseline eGFR (mL/min/1.73m2)	64.4 ± 18.5	66.5 ± 19.6	61.0 ± 18.5	60.7 ± 17.8	59.6 ± 19.8	59.4 ± 19.2
eGFR >=60	334 (57.3%)	373 (63.1%)	500 (51.3%)	496 (51.7%)	743 (47.3%)	745 (47.2%)
Loop diuretics	417 (71.5%)	429 (72.6%)	744 (76.4%)	736 (76.7%)	1245 (79.2%)	1236 (78.3%)
Ace inhibitor (ACEi)	199 (34.1%)	232 (39.3%)	376 (38.6%)	333 (34.7%)	575 (36.6%)	577 (36.6%)

ngiotensin receptor blocker (ARB)	197 (33.8%)	196 (33.2%)	315 (32.3%)	321 (33.5%)	627 (39.9%)	616 (39.0%)
Neprilysin inhibitor/ARB (ARNI)	31 (5.3 %)	37 (6.3 %)	52 (5.3 %)	42 (4.4 %)	53 (3.4 %)	86 (5.4 %)
Beta Blocker	462 (79.2%)	490 (82.9%)	811 (83.3%)	776 (80.9%)	1310 (83.3%)	1324 (83.9%)
neralocorticoid receptor antagonist (MRA)	260 (44.6%)	248 (42.0%)	451 (46.3%)	432 (45.0%)	616 (39.2%)	659 (41.8%)
Pacemaker	70 (12.0%)	65 (11.0%)	96 (9.9 %)	114 (11.9%)	171 (10.9%)	145 (9.2 %)
ICD	5 (0.9 %)	13 (2.2 %)	24 (2.5 %)	14 (1.5 %)	24 (1.5 %)	33 (2.1 %)

Table S2 - Primary and secondary outcomes by baseline glycaemic status (adjusted for age, sex and region)

	Normoglycaemia	Prediabetes	Type 2 diabetes
Outcome	N = 1175	N = 1934	N = 3150
Primary composite	172 events	305 events	644 events
	[6.9 / 100py]	[7.6 / 100py]	[10.1 / 100py]
	[REF]	HR=1.09 (0.90, 1.31)	HR=1.46 (1.24, 1.73)
Overall p<0.001		p = 0.38	p<0.001
Cardiovascular death	93 events	132 events	266 events
	[3.6 / 100py]	[3.1 / 100py]	[3.8 / 100py]
	[REF]	HR=0.85 (0.65, 1.11)	HR=1.07 (0.85, 1.36)
Overall p=0.10		p = 0.23	p = 0.56
Worsening heart failure event	118 events	229 events	475 events
	[4.7 / 100py]	[5.7 / 100py]	[7.5 / 100py]
	[REF]	HR=1.19 (0.95, 1.49)	HR=1.58 (1.30, 1.94)
Overall p<0.001		p = 0.13	p<0.001
Hospitalisation for heart failure	113 events	204 events	429 events
	[4.5 / 100py]	[5.0 / 100py]	[6.7 / 100py]
	[REF]	HR=1.10 (0.87, 1.38)	HR=1.49 (1.21, 1.83)
Overall p<0.001		p = 0.43	p<0.001
Urgent heart failure visit	11 events	41 events	86 events
	[0.4 / 100py]	[1.0 / 100py]	[1.3 / 100py]
	[REF]	HR=2.28 (1.17, 4.43)	HR=3.00 (1.60, 5.61)
Overall p=0.002		p = 0.016	p<0.001
Composite of CV death and all heart failure events (including recurrent)	284 events	502 events	1084 events
	[10.9 / 100py]	[11.8 / 100py]	[15.6 / 100py]
	[REF]	RR=1.06 (0.85, 1.33)	RR=1.45 (1.19, 1.76)
Overall p<0.001		p = 0.58	p<0.001
All-cause death	181 events	284 events	556 events
	[6.9 / 100py]	[6.6 / 100py]	[8.0 / 100py]
	[REF]	HR=0.93 (0.77, 1.12)	HR=1.17 (0.99, 1.38)
Overall p=0.005		p = 0.46	p = 0.07

Table S3. Key outcomes by treatment: Normoglycaemia subgroup (Full Analysis Set)

Outcome	Dapagliflozin		Placebo			
	n/N	Rate (per 100 pt-yrs)	n/N	Rate (per 100 pt-yrs)	HR (95% CI); p-value	ARR
Primary composite	76/591 (13%)	6.0	96/584 (16%)	7.8	0.77 (0.57, 1.04); p=0.09	1.8 per 100 pt-yrs
CV death	42/591 (7%)	3.2	51/584 (9%)	3.9	0.82 (0.54, 1.23); p=0.33	0.7 per 100 pt-yrs
HF Event	52/591 (9%)	4.1	66/584 (11%)	5.4	0.76 (0.53, 1.10); p=0.15	1.2 per 100 pt-yrs
HF Hospitalization	47/591 (8%)	3.7	66/584 (11%)	5.3	0.69 (0.47, 1.00); p=0.05	1.7 per 100 pt-yrs
Urgent HF Visit	7/591 (1%)	0.5	4/584 (1%)	0.3	1.73 (0.51, 5.91); p=0.38	-0.2 per 100 pt-yrs
All-cause death	81/591 (14%)	6.1	100/584 (17%)	7.7	0.80 (0.60, 1.07); p=0.14	1.5 per 100 pt-yrs

Table S4. Key outcomes by treatment: Prediabetes subgroup (Full Analysis Set)

Outcome	Dapagliflozin		Placebo			
	n/N	Rate (per 100 pt-yrs)	n/N	Rate (per 100 pt-yrs)	HR (95% CI); p-value	ARR
Primary composite	142/960 (15%)	7.1	163/974 (17%)	8.2	0.87 (0.69, 1.08); p=0.21	1.1 per 100 pt-yrs
CV death	66/960 (7%)	3.1	66/974 (7%)	3.1	1.02 (0.72, 1.43); p=0.91	-0.1 per 100 pt-yrs
HF Event	97/960 (10%)	4.8	132/974 (14%)	6.6	0.73 (0.56, 0.95); p=0.019	1.8 per 100 pt-yrs
HF Hospitalization	87/960 (9%)	4.3	117/974 (12%)	5.8	0.74 (0.56, 0.98); p=0.034	1.5 per 100 pt-yrs
Urgent HF Visit	15/960 (2%)	0.7	26/974 (3%)	1.2	0.59 (0.31, 1.11); p=0.10	0.5 per 100 pt-yrs
All-cause death	150/960 (16%)	7.1	134/974 (14%)	6.2	1.14 (0.90, 1.44); p=0.27	-0.9 per 100 pt-yrs

Table S5. Key outcomes by treatment: Type 2 diabetes subgroup (Full Analysis Set)

Outcome	Dapagliflozin		Placebo			
	n/N	Rate (per 100 pt-yrs)	n/N	Rate (per 100 pt-yrs)	HR (95% CI); p-value	ARR
Primary composite	294/1578 (19%)	9.0	350/1572 (22%)	11.2	0.81 (0.69, 0.95); p=0.008	2.2 per 100 pt-yrs
CV death	123/1578 (8%)	3.5	143/1572 (9%)	4.1	0.85 (0.67, 1.08); p=0.19	0.6 per 100 pt-yrs
HF Event	219/1578 (14%)	6.7	256/1572 (16%)	8.2	0.83 (0.69, 0.99); p=0.038	1.5 per 100 pt-yrs
HF Hospitalization	195/1578 (12%)	5.9	234/1572 (15%)	7.4	0.81 (0.67, 0.98); p=0.028	1.4 per 100 pt-yrs
Urgent HF Visit	38/1578 (2%)	1.1	48/1572 (3%)	1.4	0.78 (0.51, 1.19); p=0.25	0.3 per 100 pt-yrs
All-cause death	266/1578 (17%)	7.6	290/1572 (18%)	8.4	0.91 (0.77, 1.07); p=0.25	0.8 per 100 pt-yrs

Table S6: Safety outcomes: Adverse events by baseline glycaemic status (Safety Analysis Set)

	Normoglycaemia n=1175	Prediabetes n=1934	Type 2 diabetes n=3150
Any SAE	484 (41.2%)	806 (41.7%)	1492(47.5%)
Any AE with outcome = death	145 (12.3%)	227 (11.8%)	448 (14.3%)
Any AE leading to discontinuation of IP (DAE)	68 (5.8 %)	118 (6.1 %)	177 (5.6 %)
Any AE leading to interruption of IP	160 (13.6%)	255 (13.2%)	513 (16.3%)
Any amputation	3 (0.3 %)	5 (0.3 %)	36 (1.1 %)
Any potential risk factor AE for amputation affecting lower limbs	48 (4.1 %)	95 (4.9 %)	243 (7.7 %)
Any definite or probable diabetic ketoacidosis	0 (0.0 %)	0 (0.0 %)	2 (0.1 %)
Any major hypoglycemic event	0 (0.0 %)	0 (0.0 %)	13 (0.4 %)
Any SAE or DAE suggestive of volume depletion	9 (0.8 %)	32 (1.7 %)	32 (1.0 %)
Any renal SAE or DAE	22 (1.9 %)	38 (2.0 %)	91 (2.9 %)

Table S7: Adverse events by glycaemic subgroups (Safety Analysis Set)

Normoglycaemia subgroup

	Placebo n=584	Dapa n=591	Risk Difference (95% CI)
Any AE with outcome = death	80 (13.7%)	65 (11.0%)	-2.7% (-6.5%, +1.1%)
Any SAE (including outcome = death)	244 (41.8%)	240 (40.6%)	-1.2% (-6.8%, +4.5%)
Any AE leading to discontinuation of IP	34 (5.8 %)	34 (5.8 %)	-0.1% (-2.8%, +2.6%)
Any AE leading to interruption of IP	90 (15.4%)	70 (11.8%)	-3.6% (-7.5%, +0.4%)
Any AE possibly related to IP	49 (8.4 %)	46 (7.8 %)	-0.6% (-3.7%, +2.5%)
Any amputation	1 (0.2 %)	2 (0.3 %)	+0.2% (-0.6%, +0.9%)
Any potential risk factor AE for amputation affecting lower limbs	21 (3.6 %)	27 (4.6 %)	+1.0% (-1.3%, +3.3%)
Any definite or probable diabetic ketoacidosi	0 (0.0 %)	0 (0.0 %)	0.0% (-0.5%, +0.5%)
Any MI	15 (2.6 %)	10 (1.7 %)	-0.9% (-2.6%, +0.8%)
Any Stroke	13 (2.2 %)	20 (3.4 %)	+1.2% (-0.8%, +3.1%)
Any major hypoglycemic event	0 (0.0 %)	0 (0.0 %)	0.0% (-0.5%, +0.5%)
Any SAE or DAE suggestive of volume depletion	3 (0.5 %)	6 (1.0 %)	+0.5% (-0.6%, +1.6%)
Any renal SAE or DAE	10 (1.7 %)	12 (2.0 %)	+0.3% (-1.3%, +1.9%)

Prediabetes subgroup

	Placebo n=974	Dapa n=957	Risk Difference (95% CI)
Any AE with outcome = death	114 (11.7%)	113 (11.8%)	+0.1% (-2.8%, +3.0%)
Any SAE (including outcome = deat	408 (41.9%)	398 (41.6%)	-0.3% (-4.7%, +4.1%)
Any AE leading to discontinuation o	54 (5.5 %)	64 (6.7 %)	+1.1% (-1.0%, +3.3%)
Any AE leading to interruption of IP	135 (13.9%)	120 (12.5%)	-1.3% (-4.3%, +1.7%)
Any AE possibly related to IP	69 (7.1 %)	89 (9.3 %)	+2.2% (-0.2%, +4.7%)
Any amputation	3 (0.3 %)	2 (0.2 %)	-0.1% (-0.6%, +0.4%)
Any potential risk factor AE for amputation affecting lower limbs	53 (5.4 %)	42 (4.4 %)	-1.1% (-3.0%, +0.9%)

Any definite or probable diabetic ketoacidosis	0 (0.0 %)	0 (0.0 %)	0.0% (-0.3%, +0.3%)
Any MI	10 (1.0 %)	19 (2.0 %)	+1.0% (-0.2%, +2.1%)
Any Stroke	30 (3.1 %)	33 (3.4 %)	+0.4% (-1.2%, +2.0%)
Any major hypoglycemic event	0 (0.0 %)	0 (0.0 %)	0.0% (-0.3%, +0.3%)
Any SAE or DAE suggestive of volu depletion	16 (1.6 %)	16 (1.7 %)	0.0% (-1.1%, +1.2%)
Any renal SAE or DAE	23 (2.4 %)	15 (1.6 %)	-0.8% (-2.1%, +0.5%)

Type 2 diabetes subgroup

	Placebo n=1567	Dapa n=1576	Risk Difference (95% CI)
Any AE with outcome = death	225 (14.4%)	223 (14.1%)	-0.2% (-2.7%, +2.2%)
Any SAE (including outcome = death)	769 (49.1%)	723 (45.9%)	-3.2% (-6.7%, +0.03%)
Any AE leading to discontinuat of IP	93 (5.9 %)	84 (5.3 %)	-0.6% (-2.2%, +1.0%)
Any AE leading to interruption IP	267 (17.0%)	246 (15.6%)	-1.4% (-4.0%, +1.2%)
Any AE possibly related to IP	117 (7.5 %)	138 (8.8 %)	+1.3% (-0.6%, +3.2%)
Any amputation	21 (1.3 %)	15 (1.0 %)	-0.4% (-1.2%, +0.4%)
Any potential risk factor AE fo amputation affecting lower limb	124 (7.9 %)	119 (7.6 %)	-0.4% (-2.2%, +1.5%)
Any definite or probable diabet ketoacidosis	0 (0.0 %)	2 (0.1 %)	+0.1% (-0.1%, +0.4%)
Any MI	46 (2.9 %)	39 (2.5 %)	-0.5% (-1.6%, +0.7%)
Any Stroke	57 (3.6 %)	53 (3.4 %)	-0.3% (-1.6%, +1.0%)
Any major hypoglycemic event	7 (0.4 %)	6 (0.4 %)	-0.01% (-0.5%, +0.4%)
Any SAE or DAE suggestive o volume depletion	12 (0.8 %)	20 (1.3 %)	+0.5% (-0.2%, +1.2%)
Any renal SAE or DAE	45 (2.9 %)	46 (2.9 %)	0.0% (-1.1%, +1.2%)

Figure S1. CONSORT diagram (patient flow)

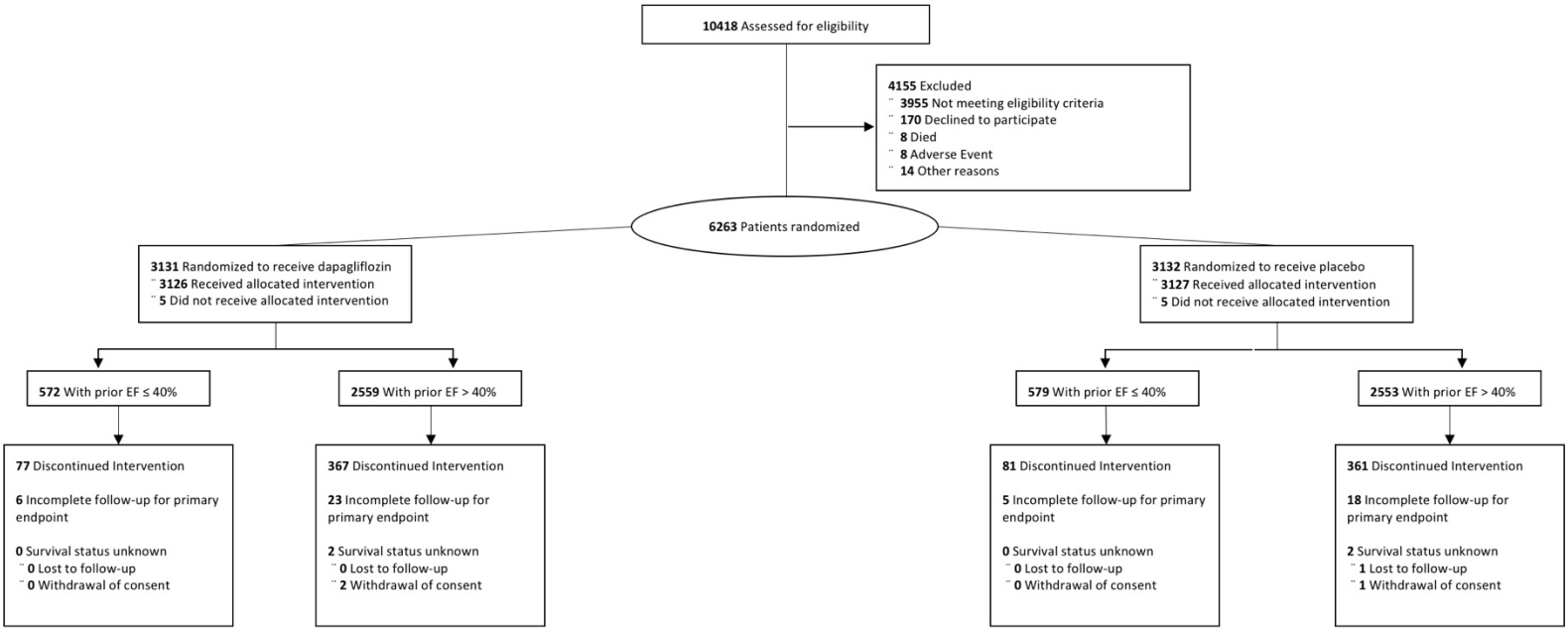
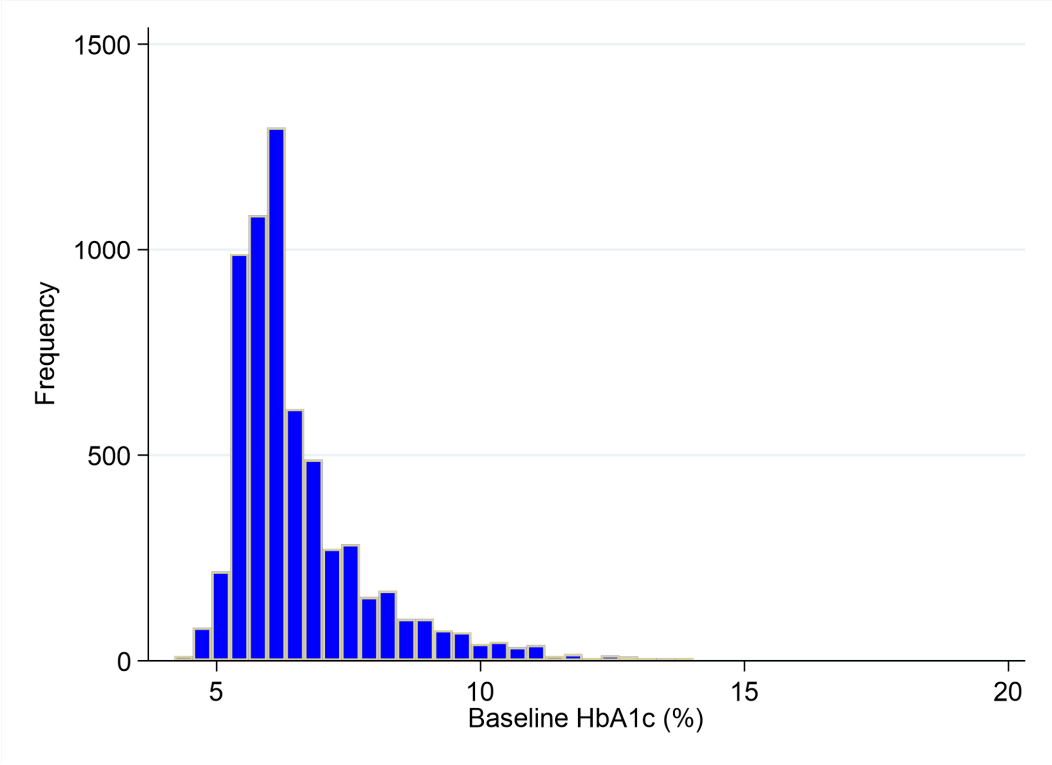


Figure S2. Histogram and summary statistics for baseline HbA1c (%)



Baseline HbA1c (%)	Total
N	6247
mean	6.59
SD	1.41
min	4.2
p25	5.7
p50	6.2
p75	7
max	17.2

Figure S3. Kaplan-Meier curves (panels A-C) and Forest plot (panel D), dapagliflozin versus placebo, for CV death by baseline glycaemic status

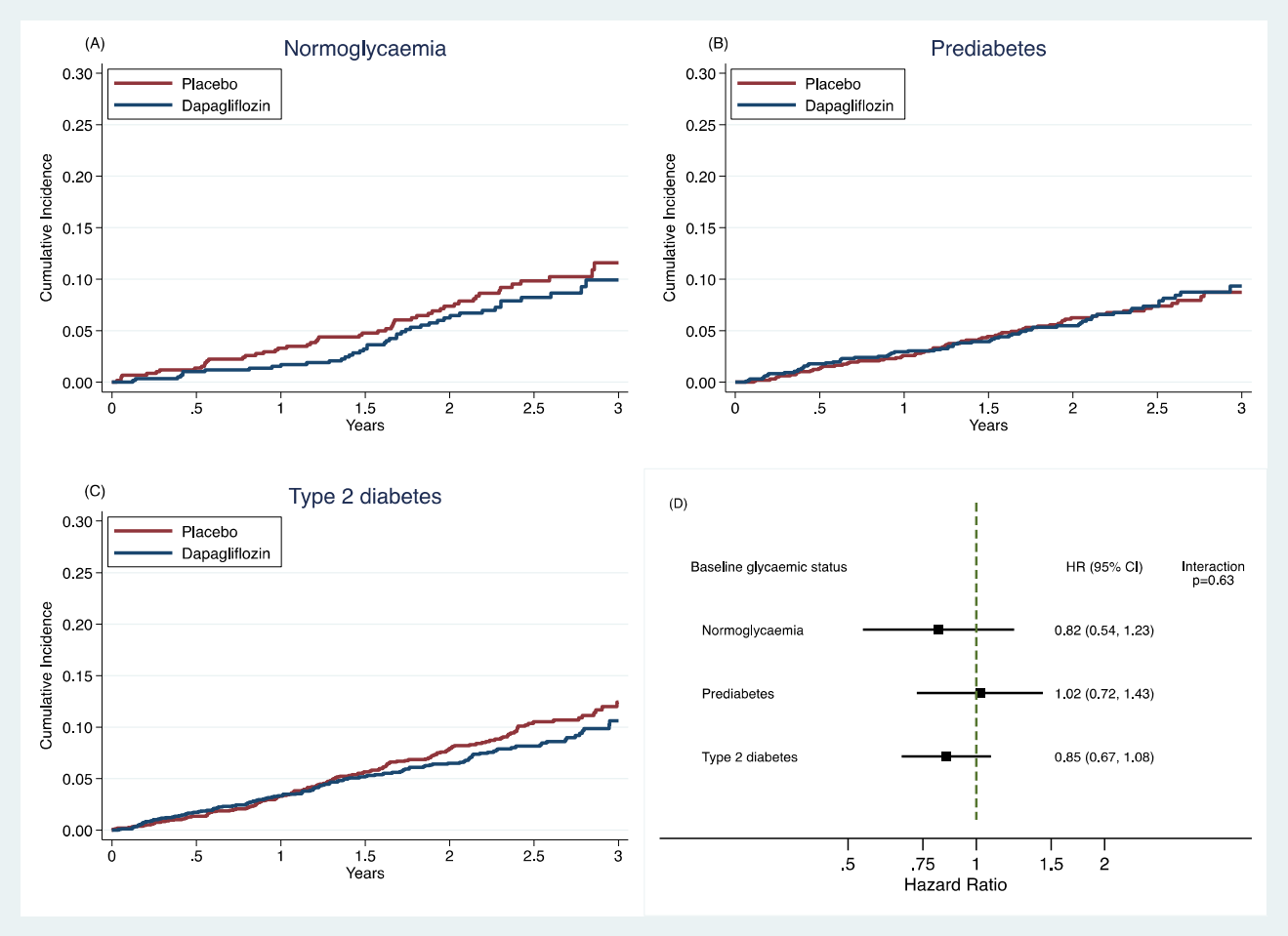


Figure S4. Kaplan-Meier curves (panels A-C) and Forest plot (panel D), dapagliflozin versus placebo, for heart failure events (time to first) by baseline glycaemic status

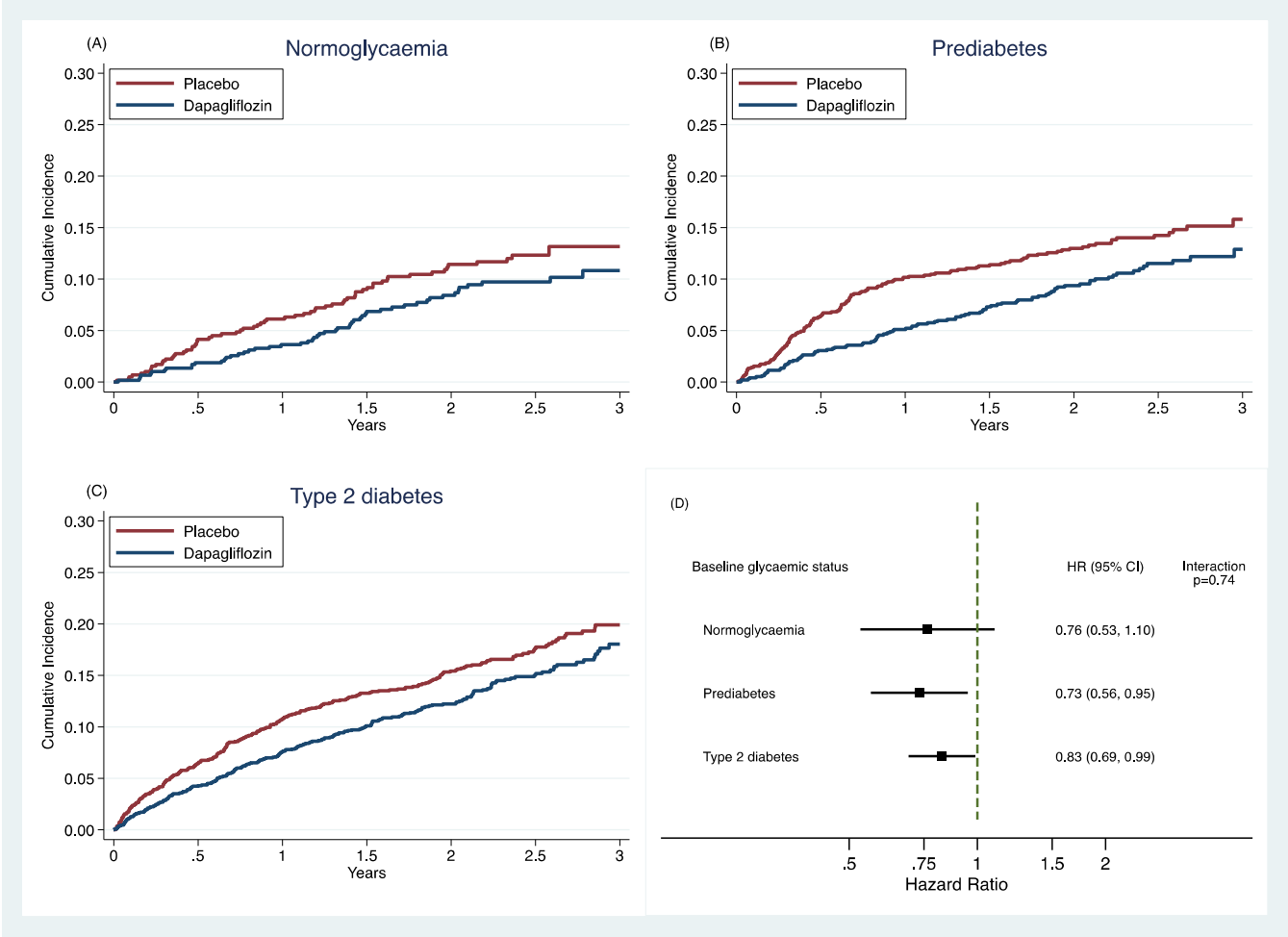


Figure S5. Kaplan-Meier curves (panels A-C) and Forest plot (panel D), dapagliflozin versus placebo, for heart failure hospitalization (time to first) by baseline glycaemic status

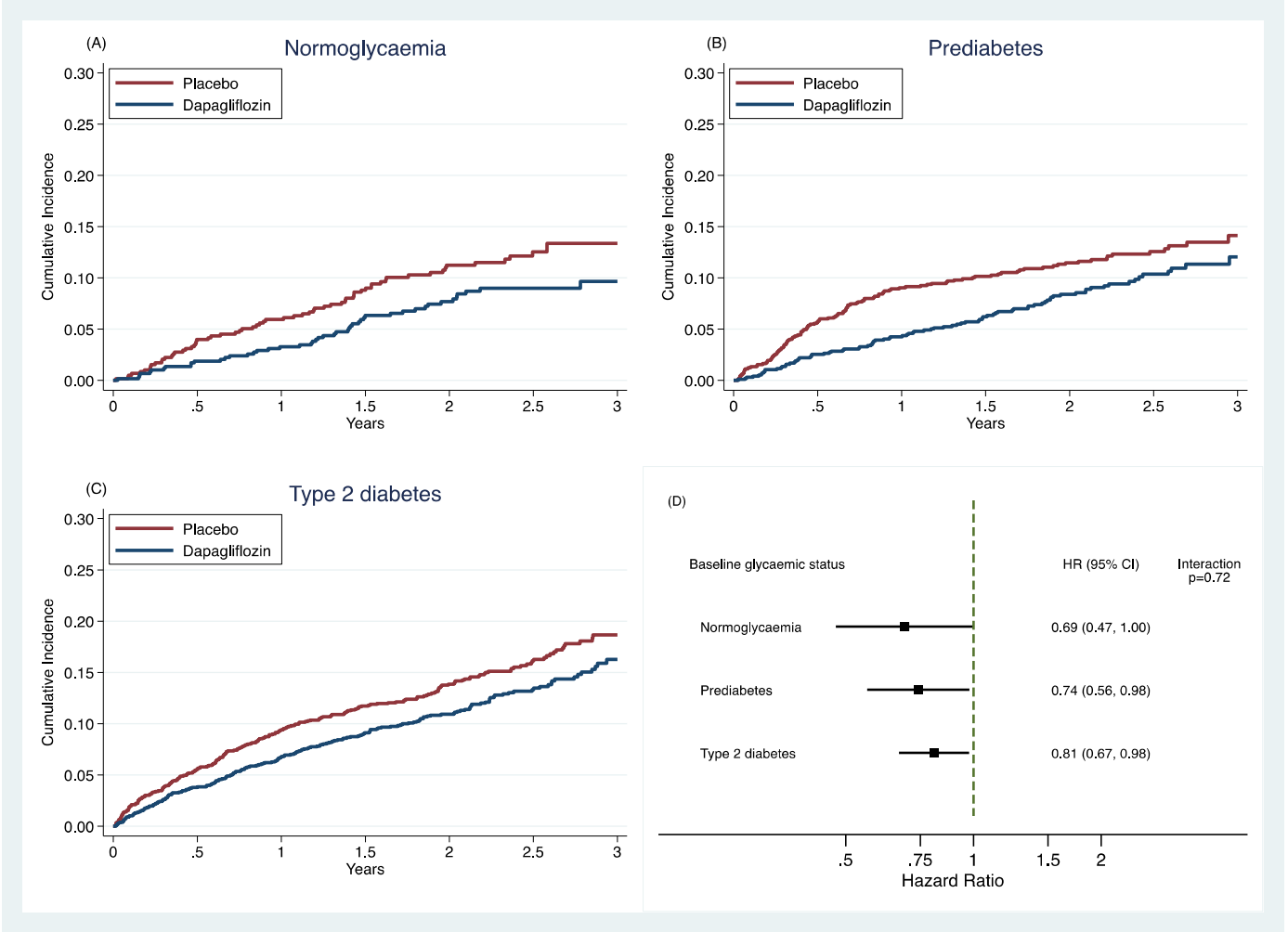


Figure S6. Forest plot of key diabetes variables in the type 2 diabetes subgroup. For most parameters there was no statistical interaction, with the exception of sulfonylurea use which appeared to predict a better effect of dapagliflozin.

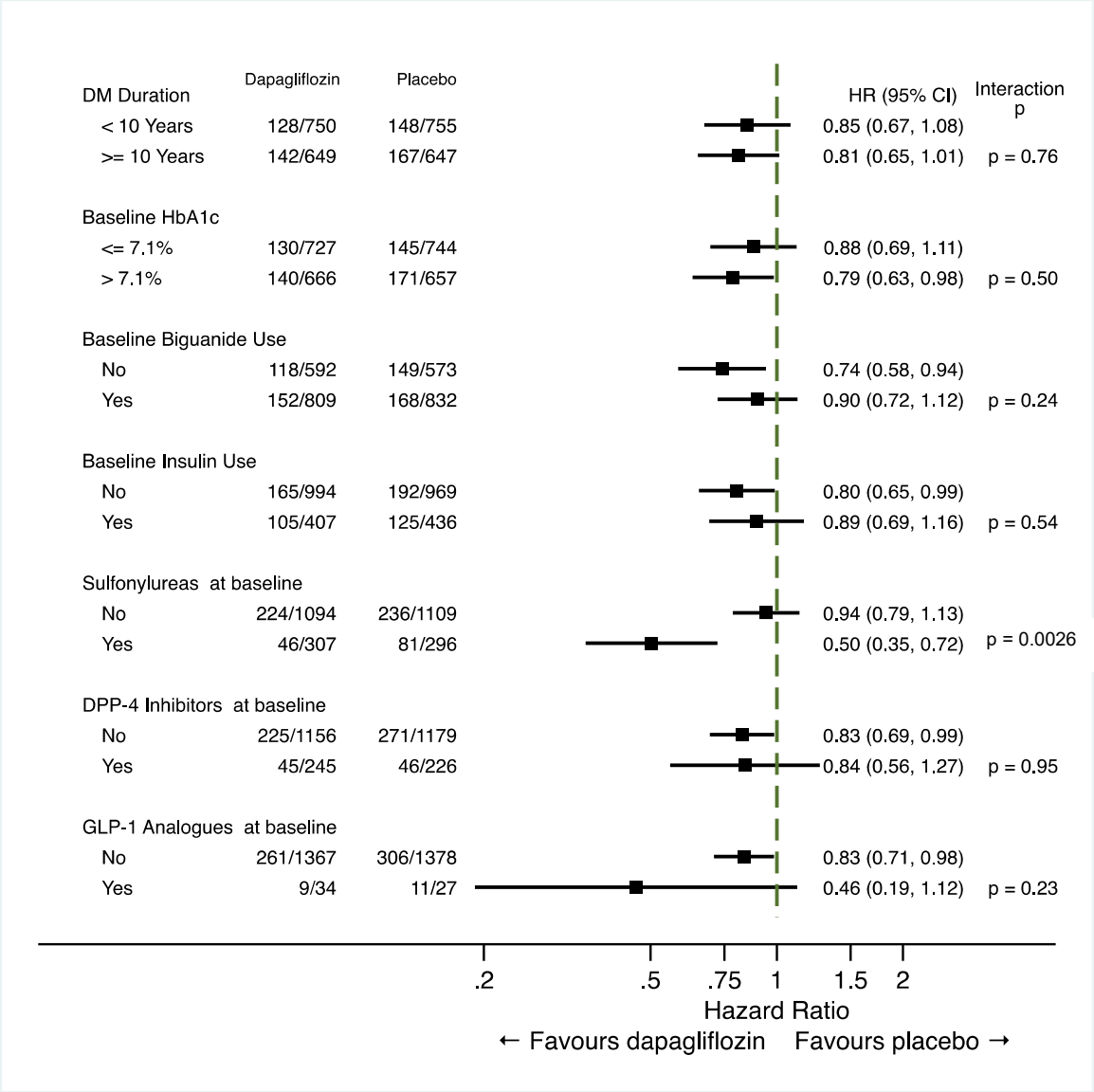


Figure S7. Treatment effect on the primary composite outcome of worsening heart failure and cardiovascular death (ratio, dapagliflozin versus placebo) by glycaemic subgroup and left ventricular ejection fraction (LVEF.) Restricted cubic spline analysis of the effect of dapagliflozin on the primary outcome in patients with normoglycaemia (green line), prediabetes (blue line) and type 2 diabetes (red line) across the range of LVEF. Solid lines represent continuous rate ratios and the dotted lines show the 95% confidence intervals around the rate ratio. The rate ratios are generally <1.0, indicating a treatment benefit in all subgroups, and the overlapping confidence intervals indicate no interaction between glycemic subgroup and LVEF. Confidence intervals widen at the extremes of LVEF due to relatively smaller numbers of patients.