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1 **Impact of Empagliflozin on Insulin Needs in patients with Heart Failure and Diabetes:**
2 **an EMPEROR-Pooled analysis**

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1 **ABSTRACT** (247/250 words)

2 Aims: To assess the effect of empagliflozin on patients with comorbid heart failure (HF) and
3 diabetes with or without baseline insulin, and to study the impact of empagliflozin on insulin
4 requirements over time.

5 Materials and Methods: We performed a post-hoc analysis of pooled patient-level data from
6 two cardiovascular outcomes trials of empagliflozin in HF (EMPEROR-Reduced and
7 EMPEROR-Preserved trials. We undertook a subgroup analysis by baseline insulin use
8 including all patients with diabetes. Studied endpoints included the primary composite
9 endpoint of first hospitalization for HF or cardiovascular death, rate of decline of estimated
10 glomerular filtration rate (eGFR), composite renal outcome, and rates of sustained insulin
11 initiation.

12 Results: Among 4,794 patients with diabetes, 1,333 (658 in empagliflozin, 675 in placebo)
13 were using insulin at baseline. The treatment effect of empagliflozin on the primary endpoint
14 was consistent irrespective of insulin use (no insulin, HR 0.74, 95% CI 0.63–0.86; using
15 insulin HR 0.81, 95%CI 0.66–1.00, p-interaction 0.49), as was the effect on the rate of
16 decline of eGFR (p-interaction=0.75). There was no effect of empagliflozin on the composite
17 renal outcome in patients using or not using insulin (p-interaction=0.30). Among patients not
18 using insulin at baseline, those randomized to empagliflozin initiated insulin less frequently
19 throughout the follow-up compared to those receiving placebo (2.6% vs 3.8%, odds ratio
20 0.66, 95%CI 0.50–0.88).

21 Conclusions: Empagliflozin exerts a consistent benefit on cardiovascular outcomes and renal
22 function decline irrespective of baseline insulin use and reduces the need for sustained
23 insulin initiation in patients with HF and diabetes.

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25 **1**

1 **INTRODUCTION**

2 Contemporary estimates suggest that the prevalence of type 2 diabetes (T2D) is
3 approximately 30% to 50% in patients with heart failure (HF) and is shown to increase
4 mortality by up to 50% compared to patients without diabetes. Individuals with T2D have a
5 two-to-four-fold higher prevalence of HF,¹⁻³ and approximately 30% of patients with HF and
6 diabetes are managed with insulin.⁴ T2D is characterized by sustained hyperinsulinemia
7 which has been suggested to worsen HF probably related to insulin-induced sodium
8 retention, epicardial adipose tissue proliferation, vascular smooth muscle hyperplasia, and
9 potentiation of endogenous vasoconstrictors.⁵⁻⁷

10 The EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic
11 Heart Failure and a Reduced Ejection Fraction) and EMPEROR-Preserved (Empagliflozin
12 Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction) trials
13 found that empagliflozin, a sodium-glucose cotransporter 2 inhibitor (SGLT2i), significantly
14 reduced the risk of a composite primary outcome of cardiovascular (CV) death or
15 hospitalization for HF^{8,9} irrespective of diabetes status or baseline hemoglobin A1c (HbA1c)
16 levels.^{10,11} In the EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event
17 Trial in Type 2 Diabetes Mellitus Patients) trial, treatment with empagliflozin significantly
18 delayed insulin initiation and reduced daily insulin requirement in patients with diabetes at
19 high cardiovascular risk.^{12,13} In a post-hoc analysis of the DAPA-HF (Dapagliflozin and
20 Prevention of Adverse Outcomes in Heart Failure) and DELIVER (Dapagliflozin Evaluation to
21 Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure) trials, SGLT2i
22 reduced the rate of new insulin initiation and prevented dose increments of ongoing insulin
23 therapy; however, the study did not evaluate the impact of baseline use on the treatment
24 effect of dapagliflozin.¹⁴ These data are important as a substantial number of patients with
25 HF have T2D treated with insulin which is considered a surrogate marker of T2D severity
26 and risk of adverse CV events.¹⁵⁻¹⁷ It is unknown if empagliflozin has a similar insulin-sparing
27 effect in patients with HF and if baseline use of insulin influences its treatment effect in HF.

1 Herein, we leveraged the individual patient-level data pooled from the EMPEROR-
2 Reduced and EMPEROR-Preserved trials to examine the influence of baseline use of insulin
3 on outcomes in patients with diabetes and HF and evaluate its impact on the treatment effect
4 of empagliflozin.

6 **MATERIALS AND METHODS**

7 The study design and main results of EMPEROR-Preserved and EMPEROR-Reduced trials,
8 and the pooled individual patient-level data from the EMPEROR-Pooled have been
9 described elsewhere.^{8,9,18} In brief, the two trials were phase III, double-blinded, parallel-
10 group, placebo-controlled trials. EMPEROR-Preserved enrolled 5,988 patients with
11 symptomatic HF, an ejection fraction above 40%, elevated natriuretic peptide levels and
12 evidence of structural cardiac disease or documented prior hospitalization for HF. Patients
13 were randomized to empagliflozin 10 mg daily or placebo and followed for a median of 26.2
14 months. EMPEROR-Reduced enrolled 3,730 patients with symptomatic HF, an ejection
15 fraction of 40% or less, and elevated natriuretic peptide levels. Patients were randomized to
16 empagliflozin 10 mg daily or placebo and followed for a median of 16 months. There were a
17 total of 4,794 participants with diabetes in the trials (2,938 in EMPEROR-Preserved and
18 1,856 in EMPEROR-Reduced). The trials were approved by the institutional ethics
19 committee at each site and all patients gave written informed consent.

20 **Endpoints**

21 We assessed the primary endpoint (time to first hospitalization for HF or CV death) and key
22 secondary endpoints of first and recurrent hospitalizations for HF, and the rate of decline in
23 estimated glomerular filtration rate (eGFR) after 4 weeks of double-blind treatment [chronic
24 eGFR slope], as well as time to CV death and first hospitalization for HF. In addition, we
25 assessed the pre-specified renal composite endpoint defined as the need for chronic dialysis
26 or renal transplant or a $\geq 40\%$ decrease in eGFR or a sustained eGFR < 15 mL/min/1.73 m²

1 (if the baseline eGFR was ≥ 30 mL/min/1.73 m²) or < 10 mL/min/1.73 m² (if the baseline
2 eGFR was < 30 mL/min/1.73 m²). We analyzed these endpoints in patients with diabetes
3 stratified by baseline use of insulin. In addition, we analyzed time to sustained insulin
4 initiation in patients with diabetes or pre-diabetes not using insulin at baseline, with
5 sustained use defined as insulin use over a period of at least two consecutive study visits. In
6 addition, we analyzed the change in HbA1c, body weight and eGFR over time. Any adverse
7 events (AEs), AEs that led to study drug discontinuation, serious AEs, and AEs of special
8 interest: hypotension, volume depletion, acute renal failure, lower limb amputation, genital
9 infections, urinary tract infections, confirmed hypoglycemia, and ketoacidosis were
10 consistently captured, and rates calculated.

11 **Statistical analyses**

12 Baseline characteristics for patients with diabetes using and not using insulin at baseline
13 were reported using descriptive statistics. The two groups were compared using the t- and
14 the chi-square test. For time-to-first-event analyses, differences between the placebo and
15 empagliflozin groups were assessed using a Cox proportional hazards model, with
16 prespecified covariates of study, gender, geographical region, left ventricular ejection
17 fraction (LVEF), age, eGFR at baseline and baseline use of insulin and baseline use of
18 insulin treatment interaction. Total (first and repeated) HHF were assessed using a joint
19 frailty model, with CV death as a competing risk. In addition, time to new insulin initiation was
20 analyzed using a logistic regression model among patients with baseline diabetes or pre-
21 diabetes not using insulin at baseline adjusting for study, gender, geographical region,
22 LVEF, age and eGFR at baseline.

23 The change in HbA1c, body weight and eGFR over time was analyzed using mixed
24 model of repeated measures (MMRM). The MMRM and the joint frailty model included the
25 same covariates as the Cox model. Between-group difference in the slope of change in
26 eGFR was analyzed using a random intercept random slope model including baseline
27 eGFR, baseline left ventricular ejection fraction and age as linear covariate and study, sex,

1 region, and baseline eGFR-by-time, treatment-by-insulin use group, and treatment-by-time-
2 by-insulin use group as fixed effects; the model allows for randomly varying slope and
3 intercept between patients. eGFR slope was analyzed using on-treatment data.

4 To account for differences in baseline characteristics between insulin users and
5 nonusers, the primary endpoint was analyzed within placebo patients besides the model
6 described above with a Cox model with further adjustment on baseline body mass index,
7 systolic blood pressure, HbA1c, time since diagnosis of diabetes, log (N-terminal pro-B
8 natriuretic peptide [NT pro-BNP]), etiology of HF (ischemic/non-ischemic), history of atrial
9 fibrillation, and urine albumin-to-creatinine ratio (UACR) were performed; these variables
10 were retained in a stepwise backward selection model in case of P values <0.05.

11 Analyses for safety were performed including all patients with diabetes who had
12 received at least one dose of empagliflozin or placebo. All analyses were performed using
13 SAS, version 9.4 (SAS Institute). All p-values reported are 2-sided, and p<0.05 was
14 considered as statistically significant. No adjustments for multiple testing were made.

15 **RESULTS**

16 Among the 4,794 patients with diabetes, 1,333 (27.8%; 658 in empagliflozin, 675 in placebo)
17 were using insulin at baseline. Compared with those not using insulin, patients on insulin had
18 a longer mean diabetes duration (16.7±10.0 vs. 9.2±8.1 years), lower mean eGFR
19 (55.4±22.1 vs. 62.2±20.7 ml/min/1.73 m²) and were more likely to have macroalbuminuria
20 (26.4 vs. 11.5%) and coronary artery disease (50.9 vs. 42.2%). Other baseline
21 characteristics of patients on insulin and those not using insulin is described in **Table 1**.

22 **HF outcomes by baseline insulin use**

23 In the placebo group, the primary endpoint of first hospitalization for HF or CV death
24 occurred more frequently in patients using insulin compared with those not using insulin
25 (28.7% vs. 21.0%; HR 1.47, 95% CI 1.22, 1.76). Similarly, in the placebo group, the
26 secondary endpoint of first and recurrent HHF (20.4% vs 13.6%; HR 1.67, 95% CI 1.31,

1 2.14), first hospitalization for HF (21.3% vs 15.8%; HR 1.44, 95% CI 1.16, 1.77), and CV
2 death (13.6% vs 8.3%; HR 1.77, 95% CI 1.35, 2.32) occurred more frequently in patients
3 using insulin compared with those not using insulin. The higher risk of the primary endpoint
4 for patients on insulin persisted following adjustment for the additional known risk factors
5 **(Supplemental Table 1)** including baseline BMI, SBP, log (NT pro-BNP) and baseline
6 UACR.

7 There were no differences in the treatment effect of empagliflozin in the primary
8 endpoint of first hospitalization for HF or CV death between patients not using insulin (HR
9 0.74, 95% CI 0.63, 0.86) and those using insulin (HR 0.81, 95% CI 0.66, 1.00; p-
10 interaction=0.49). Similar observations were made for the secondary cardiovascular
11 endpoints as demonstrated in **Figure 1**.

12 **Rate of Decline in Kidney Function and Composite Renal Outcome**

13 In the placebo arm, there was no difference in the rate of decline in kidney function (chronic
14 eGFR slope) in using insulin compared with those not using insulin (-3.0 mL/min/ 1.73 m² per
15 year in both). Compared to placebo, empagliflozin significantly slowed the rate of decline in
16 eGFR across all patients with T2D with no difference in treatment effect in patients using
17 insulin compared with those not using insulin (1.79 mL/min/ 1.73 m² /per year 95% CI 1.00,
18 2.58 vs 1.94 mL/min/ 1.73 m² /per year 95% CI 1.46, 2.42, p-interaction 0.75) **(Figure 2A**
19 **and B)**. There was also no difference on the effect of empagliflozin on the composite renal
20 outcome in patients using insulin compared with those not using insulin (p-interaction 0.31)
21 **(Figure 1)**.

22 **Effects on HbA1c and body weight by baseline insulin use**

23 A significant reduction in HbA1c was observed with empagliflozin in both patients using
24 insulin and not using insulin **(Figure 2C and D)**. Patients not using insulin had a lower
25 baseline HbA1c, but the reduction in HbA1c was consistent across both groups. Similarly, a

1 consistent reduction in body weight with empagliflozin spanning from 0.8 to 1.9 kg was
2 observed throughout the study period irrespective of baseline insulin use (**Figure 2E and F**).

3 **Sustained Insulin Initiation**

4 Among patients with diabetes or pre-diabetes not using insulin at baseline, a lower number
5 of patients receiving empagliflozin initiated insulin during the study compared to those
6 receiving placebo (86/3367 [2.6%] vs. 126/3340 [3.8%], odds ratio 0.66, 95% CI 0.50, 0.88).
7 in **Figure 3**.

8 **Safety**

9 The frequency of AEs in the two treatment groups and by baseline insulin use are given in
10 **Table 2**. Overall, patients using insulin reported more AEs than patients not using insulin,
11 particularly for acute renal failure and confirmed hypoglycaemic episodes. Notably, the
12 incidence of individual AEs including diabetic ketoacidosis were numerically similar in the
13 placebo and empagliflozin groups for both the insulin and no insulin subgroups, except for
14 AEs consistent with the known side effect of genital tract infections that were more frequent
15 in the empagliflozin treated group.

16 **DISCUSSION**

17 This study reports several key findings about the role of empagliflozin and baseline insulin
18 use in patients with HF and diabetes. First, the treatment effect of empagliflozin in reducing
19 CV events and its effect on rate of decline in eGFR and the composite renal outcome was
20 consistent in patients with diabetes irrespective of baseline insulin use. Second,
21 empagliflozin use in HF was associated with a significant 34% relative risk reduction in first
22 sustained initiation of insulin for diabetes management compared to placebo in patients with
23 prediabetes or diabetes not taking insulin at baseline. Third, there was no substantial
24 difference in the incidence of AEs with empagliflozin compared to placebo amongst patients
25 with diabetes using or not using insulin.

1 SGLT2i have been previously shown to provide glycemic benefit in diabetes patients
2 with and without baseline insulin use.¹⁹ They also aid with weight loss, modestly lower blood
3 pressure, and reduce adverse cardiovascular and renal events in patients with diabetes and
4 HF.^{20,21} However, the impact of baseline insulin use on these endpoints has not been
5 previously studied. In the EMPEROR-Preserved and EMPEROR-Reduced trials,
6 empagliflozin was found to reduce HbA1c levels and body weight in patients with HF and
7 diabetes status.¹⁰ In the current analysis, baseline HbA1c levels (6.95% vs 8.24%) and body
8 mass index (29.56 kg/m² vs 31.61 kg/m²) were lower in patients with diabetes not on
9 baseline insulin and the reduction in these parameters with empagliflozin in patients on
10 insulin was similar to that in patients not on insulin over most of the study period. Notably,
11 empagliflozin incurred an absolute reduction in the first initiation of insulin by 1.2% in
12 patients with prediabetes or T2DM and HF compared to placebo. These estimates are
13 consistent with a similar analysis of the DAPA-HF and DELIVER trials where the rate of
14 insulin initiation was significantly lower in the dapagliflozin group versus in the placebo group
15 (1.8 per 100 patient-years vs 2.5 per 100 patient-years; HR 0.68 [95% CI 0.50, 0.94]).¹⁴
16 Insulin-sparing observations were made in a retrospective analysis in Italy that reported a
17 significant reduction in the defined-daily dose of insulin in HF patients on concomitant
18 SGLT2i therapy over 3 years⁴. Our findings corroborate the EMPA-REG OUTCOME trial
19 report of a significant reduction in insulin initiation by 60% and a 20% daily-dose reduction in
20 insulin by 58% in patients with diabetes at high cardiovascular risk.^{12,13} A meta-analysis of
21 3069 T2D patients evaluating use of SGLT2i in combination with insulin, revealed a
22 statistically significant reduction in daily insulin dosage of ~5 units per day without an
23 increased risk of hypoglycemia²². These findings can be attributed to the glucosuric effect of
24 empagliflozin leading to lower blood glucose levels, but SGLT2i are also postulated to
25 improve pancreatic beta-cell function and reduce peripheral insulin resistance by reducing
26 body weight, adiposity, and tissue inflammation, which improves glycemic control.²³

1 The event rate for the cardiovascular endpoints was significantly higher in patients
2 with diabetes on insulin at baseline, even after adjustment for risk factors that differed
3 between the insulin and non-insulin users (**Supplemental Table 2**). The reason for this is
4 two-fold. First, patients on insulin generally have poorer glycaemic control and more
5 advanced micro- and macro-vascular disease; hence insulin use is a surrogate indicator of
6 severity of diabetes¹⁵ and is associated with worse cardiovascular outcomes in HF.^{16,17}
7 Second, insulin mediates several biochemical pathways that may promote adverse cardiac
8 remodelling and potentially increases epicardial adipose proliferation in hyperinsulinemic
9 states that could negatively affect myocardial function.^{6,7,24} Insulin also has a strong anti-
10 natriuretic action, causes vascular smooth muscle hyperplasia, and augments
11 vasoconstrictor signalling that can worsen the HF state.^{5,6,25,26} In a pooled analysis of the
12 CHARM-Preserved (Candesartan in Heart failure: Assessment of Reduction in Mortality and
13 morbidity – Preserved), I-PRESERVE (Irbesartan in Heart Failure with Preserved Ejection
14 Fraction), and TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an
15 Aldosterone Antagonist) trials,²⁷ patients with diabetes and HF with preserved ejection
16 fraction using insulin were found to have an increased risk of congestive symptoms, higher
17 natriuretic peptide levels, worse quality of life, and a two-fold risk of hospitalization for HF
18 and cardiovascular deaths. Moreover, insulin use was associated with an increased risk of
19 all-cause and sudden death, although a causal relationship between poor outcomes in HF
20 and insulin use is not known. However, in the current analyses, despite the difference in CV
21 risk, empagliflozin caused a consistent reduction in the primary and secondary
22 cardiovascular endpoints irrespective of baseline insulin use in HF.

23 Patients using insulin had a significantly higher risk of the composite renal outcome
24 compared to those not on insulin. Empagliflozin did not significantly affect the composite
25 renal endpoint overall, with no significant difference in treatment effect in patients using
26 insulin compared to those not using insulin (interaction p-value 0.31, **Figure 1**). These
27 observations are similar to what has been reported in major trials of SGLT2i in HF that did

1 not show a consistent reduction in the occurrence of renal outcomes.^{28,29} This is in contrast
2 to the marked improvement in renal outcomes with SGLT2i in patients with T2DM and
3 chronic kidney disease.²⁹⁻³¹ Packer et al. discuss that the attenuation of the beneficial effects
4 of empagliflozin in HF patients may be explained by the competing risk of the more frequent
5 HF hospitalizations and CV death in patients with HF, short duration of trials resulting in
6 lower number of renal adverse events, and pathophysiological differences in kidney damage
7 incurred in patients with HF compared with those in T2DM.²⁸ The current analysis does show
8 that empagliflozin significantly reduced the rate of decline of eGFR overall, with the effect
9 similar in patients using insulin compared with those not using insulin.

10 Although, there was no difference overall in AEs between empagliflozin and placebo
11 groups in patients with or without baseline insulin use, those on insulin had higher rates of
12 AEs than those not using insulin in both the empagliflozin and placebo groups. There was an
13 increased risk of uncomplicated genital infections, which are known side effects of SGLT2i
14 therapy. SGLT2i have been shown to increase the risk of ketoacidosis due to suppression of
15 insulin secretion and increased ketogenesis.²⁹ However, the risk of DKA in both treatments
16 groups was low and not different in patients with or without baseline insulin use which is an
17 important observation not precluding the use of empagliflozin in this vulnerable population on
18 insulin.

19 **LIMITATIONS**

20 This is an exploratory patient-level analysis of the EMPEROR-Preserved and EMPEROR-
21 Reduced trials; hence the findings of this study are considered hypothesis generating.
22 Moreover, diabetes patients included in this trial may not be representative of the general
23 diabetes population as only patients with diabetes and HF were included.

24 **CONCLUSIONS**

25 Baseline use of insulin in patients with diabetes and HF does not impact the treatment effect
26 of empagliflozin. Moreover, empagliflozin use was associated with a reduced risk of

1 sustained insulin initiation in patients with diabetes and HF. These findings are potentially
2 related to several mechanistic effects of empagliflozin including glucosuria, anti-natriuresis,
3 reduction in peripheral insulin resistance, reduction in epicardial adipose tissue deposition,
4 and induction of autophagy and nutrient deprivation signalling^{6,32,33}. These findings reinforce
5 the metabolic, cardiovascular, and renal benefits of empagliflozin across patients with HF
6 and abnormal glucose metabolism.

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3 **DATA AVAILABILITY**

4 To ensure independent interpretation of clinical study results and enable authors to fulfil their
5 role and obligations under the ICMJE criteria, Boehringer Ingelheim grants all external
6 authors access to relevant clinical study data. In adherence with the Boehringer Ingelheim
7 Policy on Transparency and Publication of Clinical Study Data, scientific and medical
8 researchers can request access to clinical study data, typically, one year after the approval
9 has been granted by major Regulatory Authorities or after termination of the development
10 program. Researchers should use the <https://vivli.org/> link to request access to study data
11 and visit <https://www.mystudywindow.com/msw/datasharing> for further information.

1 REFERENCES

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1 **Table 1:** Baseline characteristics in patients in pooled EMPEROR Trials with
 2 diabetes at baseline, by baseline use of insulin

	Without insulin (n=3461)	With insulin (n=1333)	P value
Trial			
EMPEROR-Reduced	1384 (40.0)	472 (35.4)	
EMPEROR-Preserved	2077 (60.0)	861 (64.6)	
Age, years	69.7 ± 9.8	68.4 ± 9.4	<0.0001
Female, n (%)	1177 (34.0)	507 (38.0)	0.0089
Race, n (%)[†]			<0.0001
White	2448 (70.7)	1045 (78.4)	
Black/African American	187 (5.4)	74 (5.6)	
Asian	640 (18.5)	111 (8.3)	
Other, including mixed race	168 (4.9)	95 (7.1)	
Missing	18 (0.5)	8 (0.6)	
Geographic region, n (%)			<0.0001
North America	389 (11.2)	198 (14.9)	
Latin America	1001 (28.9)	438 (32.9)	
Europe	1363 (39.4)	556 (41.7)	
Asia	474 (13.7)	73 (5.5)	
Other	234 (6.8)	68 (5.1)	
NYHA class, n (%)			<0.0001
I/II	2697 (77.9)	962 (72.2)	
III/IV	764 (22.1)	371 (27.8)	
Body mass index, kg/m²	29.56 ± 5.75	31.61 ± 5.77	<0.0001
Systolic blood pressure, mmHg	128.4 ± 16.6	131.8 ± 16.8	<0.0001
Diastolic blood pressure,	75.2 ± 10.7	73.6 ± 10.4	<0.0001

mmHg			
HbA1c, %	6.95 ± 1.26	8.24 ± 1.76	<0.0001
Diabetes duration, years[‡]	9.2 ± 8.1	16.7 ± 10.0	<0.0001
LVEF			
Mean, %	43.2 ± 15.1	44.9 ± 15.2	0.0003
<50, n (%)	2149 (62.1)	732 (54.9)	<0.0001
50–<60, n (%)	684 (19.8)	323 (24.2)	
≥60, n (%)	628 (18.1)	278 (20.9)	
NT-proBNP, pg/mL (IQR)	1283 (673, 2374)	1120 (583, 2186)	0.0008 [#]
Principal cause of HF, n (%)			<0.0001
Ischemic	1557 (45.0)	727 (54.5)	
Non-ischemic	1903 (55.0)	606 (45.5)	
Missing	1 (<0.1)	0	
Medical history, n (%)			
Hospitalization for HF in last 12 months[§]	956 (27.6)	418 (31.4)	0.0104
AF[¶]	1527 (44.1)	448 (33.6)	<0.0001
Hypertension	2985 (86.2)	1234 (92.6)	<0.0001
Coronary artery disease	1460 (42.2)	679 (50.9)	<0.0001
eGFR, mL/min/1.73 m²			
Mean	62.2 ± 20.7	55.4 ± 22.1	<0.0001
<60, n (%)	1639 (47.4)	810 (60.8)	<0.0001
UACR, mg/g			<0.0001
Normal (<30)	1841 (53.2)	465 (34.9)	
Microalbuminuria (30–300)	1206 (34.8)	508 (38.1)	
Macroalbuminuria (>300)	398 (11.5)	352 (26.4)	
Missing	16 (0.5)	8 (0.6)	
HF medication, n (%)			
ACE inhibitor	1451 (41.9)	556 (41.7)	0.8930
ARB^{††}	1206 (34.8)	485 (36.4)	0.3178
ARNi	315 (9.1)	104 (7.8)	0.1535
Diuretic other than MRA	2925 (84.5)	1186 (89.0)	<0.0001
MRA	1825 (52.7)	623 (46.7)	0.0002
Beta blocker	3118 (90.1)	1222 (91.7)	0.0934
Cardiovascular medication, n			

(%)			
Lipid lowering	2600 (75.1)	1139 (85.4)	<0.0001
Aspirin	1623 (46.9)	780 (58.5)	<0.0001
Anticoagulants	1485 (42.9)	453 (34.0)	<0.0001
Glucose-lowering therapy, n (%)			
Any glucose lowering therapy	2373 (68.6)	1333 (100.0)	<0.0001
Biguanide	1872 (54.1)	567 (42.5)	<0.0001
Insulin	0	1333 (100.0)	NA
Sulfonylurea	871 (25.2)	159 (11.9)	<0.0001
DPP-4 inhibitors	481 (13.9)	165 (12.4)	0.1674
GLP-1 receptor analogues	32 (0.9)	46 (3.5)	<0.0001
Other	149 (4.3)	52 (3.9)	0.5316

1 Data are mean (SD) or n (%) except for NT-proBNP and UACR, which are median
2 (IQR). ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin
3 receptor blocker; ARNi, angiotensin receptor neprilysin inhibitor; DPP-4, dipeptidyl
4 peptidase-4; GFR, glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1c,
5 hemoglobin A1c; HF, heart failure; HF_rEF, heart failure with reduced ejection
6 fraction; HF_pEF, heart failure with preserved ejection fraction; IQR, interquartile
7 range; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor
8 antagonist; NT-proBNP, N-terminal prohormone B-type natriuretic peptide; NYHA,
9 New York Heart Association; SD, standard deviation; UACR, urinary-albumin
10 creatinine ratio.

11 †Race was reported by the patient.

12 ‡Only reported for patients with investigator reported medical history of diabetes.

13 §Reported either on heart failure history and diagnosis or Health Care Resource
14 Utilization form.

15 ¶AF reported in any ECG before treatment intake or history of AF reported as
16 medical history.

17 ††Excluding valsartan when taken with sacubitril, as sacubitril/valsartan is shown as
18 an ARNi.

19 #Based on log-transformed results.

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1 **Table 2.** Pooled EMPEROR trials: adverse events in patients with diabetes by
 2 baseline use of insulin

	Baseline use of insulin			
	No		Yes	
	Empagliflozin (N=1735)	Placebo (N=1724)	Empagliflozin (N= 657)	Placebo (N= 673)
	n (%) – IR per 100 pt-yrs	n (%) – IR per 100 pt-yrs	n (%) – IR per 100 pt-yrs	n (%) – IR per 100 pt-yrs
Patients with any AE	1414 (81.5) - 140.0	1435 (83.2) - 155.5	574 (87.4) - 169.6	589 (87.5) – 188.6
Patients with AE leading to discontinuation	302 (17.4) - 10.9	293 (17.0) - 10.5	163 (24.8) – 15.1	171 (25.4) - 16.1
Patients with SAE	753 (43.4) - 35.3	854 (49.5) - 42.9	376 (57.2) - 51.1	401 (59.6) - 60.1
Hypotension	158 (9.1) - 6.0	135 (7.8) - 5.1	70 (10.7) – 6.9	59 (8.8) – 5.8
Volume depletion	182 (10.5) - 6.9	152 (8.8) – 5.7	82 (12.5) – 8.1	69 (10.3) – 6.9
Acute renal failure	199 (11.5) - 7.6	206 (11.9) - 7.8	129 (19.6) – 13.2	114 (16.9) – 11.6
Lower limb amputation	11 (0.6) – 0.3	9 (0.5) – 0.3	19 (2.8) – 1.5	18 (2.7) – 1.5
Genital tract infections	37 (2.1) - 1.3	8 (0.5) - 0.3	18 (2.7) – 1.7	10 (1.5) – 0.9
Urinary tract infections	122 (7.0) - 4.6	111 (6.4) - 4.1	78 (11.9) – 7.7	69 (10.3) – 6.9
Confirmed hypoglycemia[†]	20 (1.2) - 0.7	35 (2.0) – 1.3	63 (9.6) – 6.2	53 (7.9) – 5.3
Ketoacidosis[‡]	2 (0.1) – 0.07	2 (0.1) – 0.07	2 (0.3) – 0.2	3 (0.4) – 0.3

3 AEs are shown up to 7 days after discontinuation of study medication, but lower limb
 4 amputations are shown for the total study period. The search for specified AEs of
 5 interest was based on the predefined list of preferred terms.

6 AE, adverse event; IR, incident rate; SAE, serious adverse event.

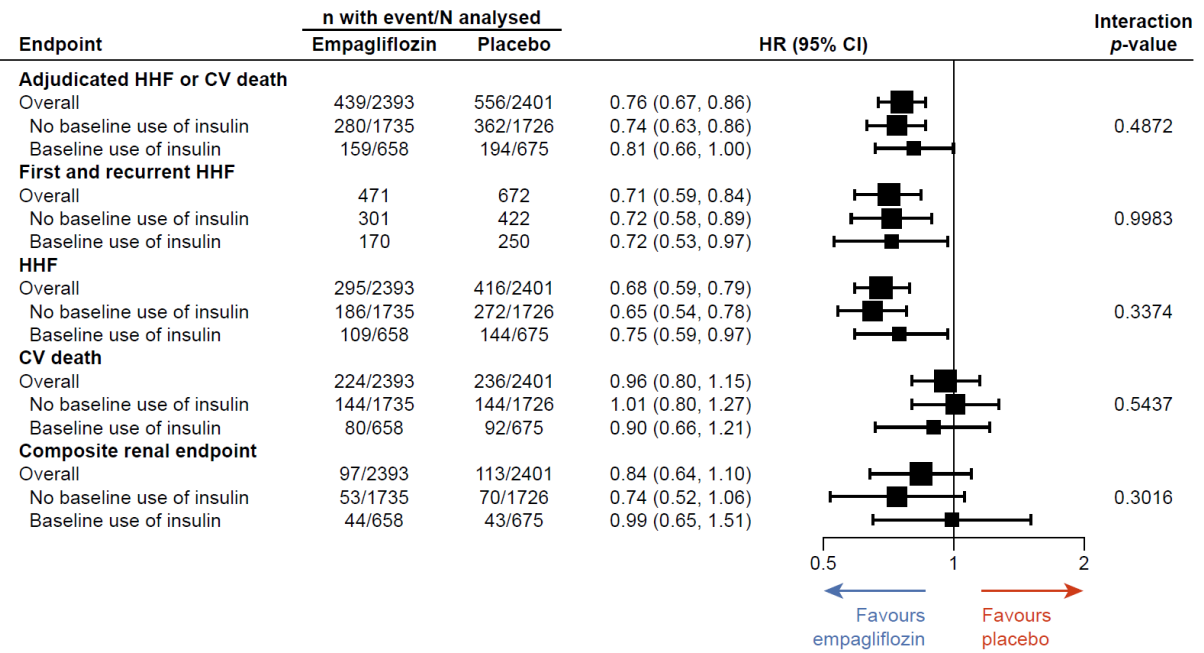
1 †Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse
2 events that had a glucose concentration ≤ 70 mg/dL (3.9 mmol/L) or required
3 assistance.

4 ‡Preferred terms: Includes the preferred terms Diabetic ketoacidosis and
5 Ketoacidosis.

6

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1 **Figure 1: Effect of empagliflozin on clinical outcomes and mortality stratified by**
 2 **insulin use at baseline.**

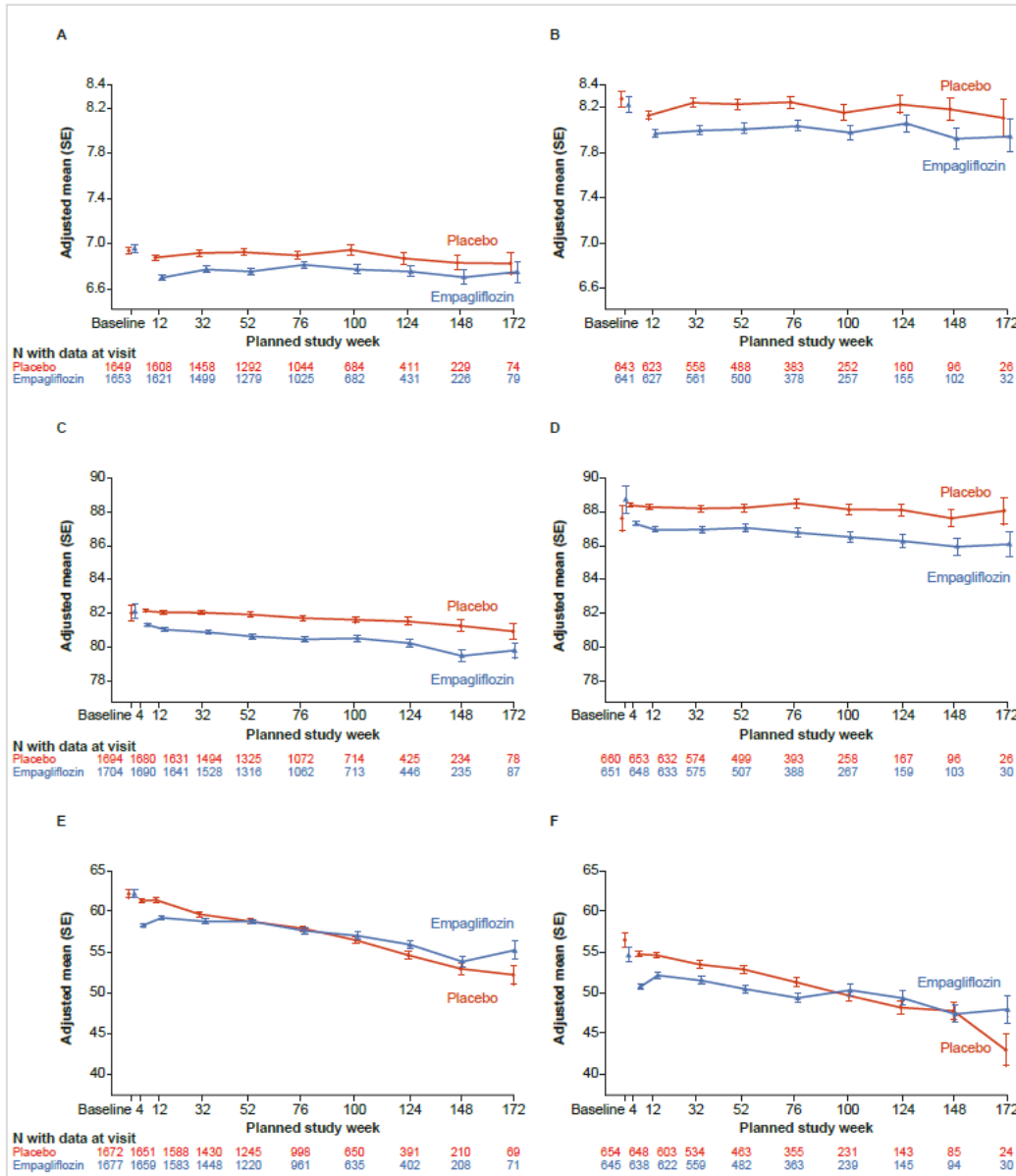


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 4 CI, confidence interval; CV, cardiovascular; HHF, hospitalization for heart failure;

5 HR, hazard ratio.

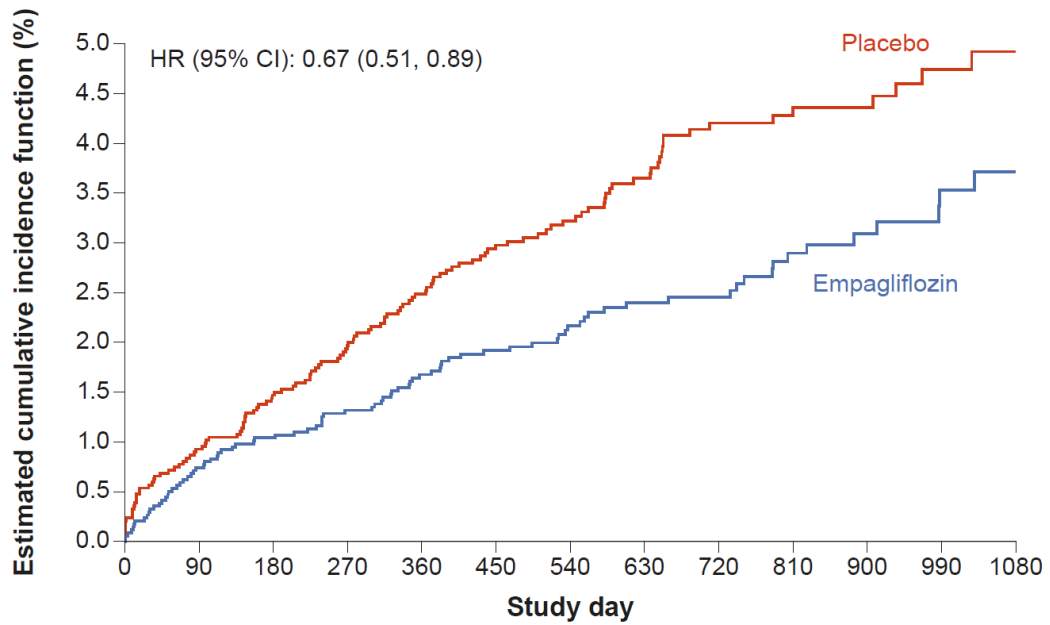
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- 1 **Figure 2:** Effect of empagliflozin on estimated glomerular filtration slope (A, B),
- 2 mean hemoglobin A1c levels (C, D), and mean weight (E, F) in patients with
- 3 diabetes by no insulin use at baseline (A, C, E), and insulin use at baseline (B, D, F).



- 4
- 5 SE, standard error.
- 6
- 7

- 1 **Figure 3:** Incidence of first insulin initiation in the empagliflozin and placebo groups
- 2 in patients with diabetes or pre-DM



Patients at risk

Placebo	3341	3246	3165	2956	2736	2416	1969	1640	1292	1014	718	494	300
Empagliflozin	3368	3288	3215	3010	2790	2444	2004	1665	1296	1007	712	496	292

- 3
- 4 CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio.
- 5

1 **SUPPLEMENTARY APPENDIX**

2

3 **Supplemental Table 1**

4 Prognostic effect of baseline use of insulin on clinical outcomes and mortality within
5 placebo patients

	Without insulin (N=1726) n (%)	With insulin (N=675) n (%)	HR (95% CI)
Time to first event of HHF or CV death	362 (21.0)	194 (28.7)	1.47 (1.22,1.76)
Recurrent HHF[†]	422	250	1.67 (1.31, 2.14)
Time to first HHF	272 (15.8)	144 (21.3)	1.44 (1.16,1.77)
Time to CV Death	144 (8.3)	92 (13.6)	1.77 (1.35, 2.32)
Composite Renal Endpoint	70 (4.1)	43 (6.4)	1.43 (0.97, 1.12)

6 Cox regression model adjusted for age, baseline eGFR (CKD-EPI), baseline LVEF,
7 region, sex, study and baseline use of insulin.

8 [†]Joint Frailty model accounting for CV death adjusted for the same factors.

9 CI, confidence interval; CKD-EPI, chronic kidney disease Epidemiology

10 Collaboration; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HHF,
11 hospitalization for heart failure; HR, hazard ratio; LVEF, left ventricular ejection
12 fraction.

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1 **Supplemental Table 2**

2

3 Prognostic Analysis for time to first event of adjudicated HHF or CV death within
 4 placebo patients (Backward Selection)

	Without insulin (N=1726)	With insulin (N=675)	HR (95% CI)
	n (%)	n (%)	
	362 (21.0)	194 (28.7)	
Standard Model			1.47 (1.22,1.76)
Full model			1.48 (1.20,1.83)
Final model			1.45 (1.21,1.75)

5 Standard model: Cox regression model adjusted for age, baseline eGFR (CKD-EPI),
 6 baseline LVEF, region, sex, study and baseline use of insulin.

7 Full model: standard model additionally adjusted for baseline BMI, baseline systolic
 8 BP, baseline HbA1c, time since diagnosis of diabetes, baseline log(NT pro-BNP),
 9 cause of HF (ischemic/non-ischemic), history of AF (yes/no). baseline UACR (3 cat.)

10 Final model: standard model additionally adjusted for baseline BMI, baseline SBP,
 11 baseline log (NT pro-BNP) and baseline UACR (3 cat.).

12 CI, confidence interval; CKD-EPI, chronic kidney disease Epidemiology
 13 Collaboration; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HHF,
 14 hospitalization for heart failure; HR, hazard ratio; LVEF, left ventricular ejection
 15 fraction.

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