Efpeglenatide and Clinical Outcomes with and without Concomitant Sodium-Glucose Co-Transporter-2 Inhibition Use in Type 2 Diabetes: Exploratory Analysis of the AMPLITUDE-O Trial

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ABSTRACT

Background

Sodium-glucose co-transporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) both reduce cardiovascular (CV) events among patients with type 2 diabetes. However, no CV outcome trial has evaluated the long-term effects of their combined use.

The AMPLITUDE-O trial reported that once weekly injections of the GLP-1 RA efpeglenatide (vs. placebo) reduced major adverse cardiovascular events (MACE); MACE, coronary revascularization or unstable angina hospitalization (expanded MACE); a renal composite outcome; and MACE or death in people with type 2 diabetes and CV and/or renal disease. The trial uniquely stratified randomization by baseline or anticipated use of SGLT2 inhibitors and included the highest prevalence at baseline (N=618, 15.2%) of SGLT2 inhibitor use among GLP-1 RA CV outcome trials to date. Its results were analyzed to estimate the combined effect of SGLT2 inhibitors and efpeglenatide on clinical outcomes.

Methods

Cardiovascular and renal outcomes were analyzed using Cox proportional hazards models adjusted for region, SGLT2 inhibitor randomization strata, and the SGLT2 inhibitor-by-treatment interaction. Continuous variables were analyzed using a mixed-effects models for repeated measures that also included an interaction term.

Results

The effect (hazard ratio [95% confidence interval]) of efpeglenatide versus placebo in the absence and presence of baseline SGLT2 inhibitors, respectively, on MACE (0.74 [0.58-

0.94] and 0.70 [0.37- 1.30]), expanded MACE (0.77 [0.62- 0.96] and 0.87 [0.51- 1.48]), renal composite (0.70 [0.59- 0.83] and 0.52 [0.33- 0.83]), and MACE or death (0.74 [0.59- 0.93] and 0.65 [0.36- 1.19]) did not differ by baseline SGLT2 inhibitor use (P for all interactions >0.2). Efpeglenatide's reduction of blood pressure, body weight, low density lipoprotein cholesterol and urinary albumin:creatinine ratio also appeared to be independent of concurrent SGLT2 inhibitor use (all interaction P ≥0.08). Finally, adverse events did not differ by baseline SGLT2 inhibitor use.

Conclusions

The efficacy and safety of efpeglenatide appear independent of concurrent SGLT2 inhibitor use. These data support combined SGLT2 inhibitor and GLP-1 RA therapy in type 2 diabetes.

Clinical Trial Registration

ClinicalTrials.gov number, NCT03496298

Key Words: Diabetes, Glucagon-like peptide-1 receptor agonists, Sodium-glucose co-transporter-2 inhibitors

Non-standard Abbreviations and Acronyms

SGLT2: sodium-glucose co-transporter-2

GLP-1 RA: glucagon-like peptide-1 receptor agonist

MACE: major adverse cardiovascular events

UACR: urinary albumin-to-creatinine ratio

eGFR: estimated glomerular filtration rate

CLINICAL PERSPECTIVE

What is new?

- In this exploratory analysis of the AMPLITUDE-O trial, the salutary effects of the glucagon-like peptide-1 receptor agonist (GLP-1 RA) efpeglenatide on major adverse cardiovascular events (MACE), expanded MACE, renal composite outcome, MACE or death, and heart failure hospitalizations as well as adverse events appeared independent of concurrent sodium-glucose co-transporter-2 (SGLT2) inhibitor use, as judged by point estimates in those receiving vs. not receiving baseline SGLT2 inhibitor and lack of any formal interactions.

What are the clinical implications?

- These data support combined SGLT2 inhibitor and GLP-1 RA therapy in type 2 diabetes.
- Combined treatment with SGLT2 inhibitors and GLP-1 RAs has the potential to yield substantial benefits across a wide range of CV outcomes among patients with type 2 diabetes based on this analysis of a small subgroup in the AMPLITUDE-O trial.
- However, more data are needed to confirm both the efficacy and tolerability of this combination of treatments.

INTRODUCTION

Two commonly used classes of glucose lowering drugs, the sodium-glucose co-transporter-2 (SGLT2) inhibitors, and the glucagon-like peptide-1 receptor agonists (GLP-1 RAs), have individually been shown to reduce cardiovascular (CV) and kidney outcomes among patients with type 2 diabetes.[1–7] The mechanisms by which SGLT2 inhibitor and GLP-1RA exert their CV benefit appear to be mostly independent of glucose lowering and complementary to each other, based on the different molecular mechanisms of action of the drugs and different types of CV harm prevented by each drug class. From large outcomes trials of individuals agents, GLP-1RAs reduce the risk of atherosclerotic ischemic events (stroke benefits being greater) and have a modest effect on kidney function and perhaps heart failure,[8,9] whereas SGLT2 inhibitors more impressively reduce the risk of heart failure, kidney function decline and kidney outcomes, with a modest effect on myocardial infarction and no effect on stroke.[10] It is therefore tantalizing to consider using these 2 drug classes in combination to achieve greater benefits for patients than either drug class alone.

Several short-term trials of combination SGLT2 inhibitor and GLP-1RA therapy showed potential benefits on metabolic parameters but did not include clinical outcome data.[11]However, no CV outcome trial has evaluated the long-term effects of the combined use of the 2 drugs classes in patients with type 2 diabetes. The AMPLITUDE-O trial showed that a once weekly injection of the exendin-based GLP-1RA efpeglenatide (vs. placebo) reduced CV and renal outcomes in people with type 2 diabetes and either CV or renal disease.[12] The trial was uniquely designed to stratify randomization by baseline or anticipated use of SGLT2 inhibitors, and included the highest prevalence (15.2%) of SGLT2 inhibitor use among GLP-1RA CV outcome trials to date, which subsequently increased to 21.2% vs. 17.5% in the placebo and efpeglenatide groups, respectively (P= 0.004). We therefore evaluated the effect

of concomitant SGLT2 inhibitor use on these clinical outcomes as well as heart failure and adverse events in the AMPLITUDE-O trial.

METHODS

The design, overall baseline characteristics and main outcomes of AMPLITUDE-O have been previously published.[12,13] In brief, AMPLITUDE-O was an international trial randomizing individuals with type 2 diabetes at high risk for CV events 1:1:1 to 4 mg efpeglenatide or 6 mg efpeglenatide or placebo. Randomization was stratified by SGLT2 inhibitor use (Current use, Potential future use, Neither current nor potential future use), and study medication was added to pre-randomization therapy. Post-randomization visits were at 12 weeks, 24 weeks, and then every 24 weeks with intervening phone visits. The pre-specified primary analysis pooled the two efpeglenatide dose groups (4/6 mg) for comparison with placebo. The study was approved by an institutional review committee and that the participants gave informed consent

Outcomes

The AMPLITUDE-O primary and secondary outcomes that were significantly reduced by efpeglenatide included major adverse cardiovascular events (MACE), defined as a non-fatal myocardial infarction, a non-fatal stroke, or death from CV or undetermined causes; an expanded MACE (MACE, coronary revascularization or hospitalization for unstable angina); a renal composite outcome (incident macroalbuminuria defined as a urinary albumin-to-creatinine ratio [UACR] > 300 mg/g or 33.9 mg/mmol, ≥ 30% rise of UACR from baseline, decrease in estimated glomerular filtration rate [eGFR] by ≥ 40% for ≥ 30 days, renal replacement therapy, or eGFR < 15 ml/min/1.73 m^2 for ≥ 30 days); and the composite of MACE or non-CV death. These outcomes, as well as heart failure hospitalizations, were analyzed.

Statistical Analysis

Continuous variables were summarized with either means and standard deviations or medians and interquartile ranges, and categorical variables were summarized as counts and percentages. Kaplan Meier curves were used to display cumulative risks. Cox proportional hazards models adjusted for region and the three-level SGLT2 inhibitor randomization strata, were used to estimate hazard ratios and 95% confidence intervals overall and within subgroups defined by baseline SGLT2 inhibitor use. SGLT2 inhibitor-by-treatment interaction terms were added to the model to test for interactions. These models were additionally adjusted for heart rate as a time-varying covariate in sensitivity analyses.

Three exploratory analyses were conducted to address previously reported differences in post-randomization use of SGLT2 inhibitor (21.2% vs. 17.5% in the placebo and efpeglenatide groups, P= 0.004) use during the trial.[12] First, two novel sub-groups were defined as anyone ever exposed to SGLT2 inhibitors from the baseline to the final visit versus everyone never exposed, and the above analyses were repeated. Second, anyone starting an SGLT2 inhibitor after randomization was censored at the time of drug initiation and the above analyses were repeated.[14] Third, Cox proportional hazards models were run that included an SGLT2 inhibitor-by-treatment interaction term and that were adjusted for region, three-level SGLT2 inhibitor randomization strata, and an additional "weighting" term that accounted for the likelihood of adding an SGLT2 inhibitor based on the participants' baseline characteristics. This weighting term was estimated from a Cox model that assessed the probability of adding an SGLT2 inhibitor after randomization after adjusting for age, sex, SGLT2 inhibitor randomization strata, region, diabetes duration, and the mean post-randomization values for eGFR, HbA1c, systolic blood pressure, weight, and log-transformed UACR. The inverse of the probability estimate for each patient was calculated[15] and this weighting term was used in a weighted Cox regression model that reflects the hazard of the outcomes with efpeglenatide versus placebo (after "stabilization" to account for spuriously

large weights)[16] after accounting for drop-in use of SGLT2 inhibitors. The resulting hazard ratios reflect the hazard of efpeglenatide for the outcomes had both groups been similar with respect to their likelihood of getting an SGLT2 inhibitor after randomization.

Changes in continuous variables were analyzed using a mixed-effects model for repeated measures using restricted maximum likelihood, with the baseline value as the covariate, the participant as a random effect, and fixed effects for region (North America, Latin America, Europe, other), the three SGLT2 inhibitor randomization strata, assigned treatment, visit, treatment-by-visit interaction and the SGLT2 inhibitor-by-treatment interaction term.

In all analyses, a p value < 0.05 was used to assess statistically significant differences, with no adjustment for multiplicity.

RESULTS

Baseline characteristics of patients receiving and not receiving concomitant SGLT2 inhibitors at enrollment

The 4076 participants in AMPLITUDE-O included 1344 (33%) women, were of mean (SD) age 64.5 (8.2) years, and 618 (15.2%) who reported SGLT2 inhibitor use at baseline (Table 1). Compared to patients not receiving SGLT2 inhibitors at enrollment, those receiving SGLT2 inhibitors were similar with respect to age, race/ ethnicity, body mass index, heart rate, prior CV, renal and retinal disease, drug use (except for statins), and eGFR. Notably, those on SGLT2 inhibitors included fewer females and more Canadians, Americans or Europeans, and had a longer duration of diabetes, lower systolic blood pressure, HbA1c, cholesterol, albumin-creatinine-ratio, and prevalence of prior heart failure and albuminuria. The majority of patients in both groups had background therapy with metformin, angiotensin converting enzyme inhibitors/angiotensin receptor blockers, beta-blockers, acetylsalicylic acid and statins. Randomized treatment arms (efpeglenatide vs placebo) were well-balanced among patients receiving and not receiving SGLT2 inhibitors at baseline (Supplemental Table 1).

Benefit of efpeglenatide in patients receiving and not receiving concomitant SGLT2 inhibitors at enrollment

As previously reported,[12] during a median follow-up of 1.81 years in the entire trial cohort, efpeglenatide reduced MACE by 27% (HR 0.73; 95% CI, 0.58–0.92), expanded MACE by 21% (0.79; 0.65–0.96), the renal composite outcome by 32% (0.68; 0.57–0.79), MACE or non-CV death by 27% (0.73; 0.59–0.91) and heart failure hospitalization by 39% (0.61; 0.38–0.98). Corresponding effect estimates among patients receiving and not receiving SGLT2 inhibitors at baseline are shown in Figure 1 with details in Supplemental Table 2.

While Kaplan Meier curves suggested a smaller efpeglenatide effect on the MACE outcomes, and a larger effect for the renal composite outcome and heart failure among patients receiving SGLT2 inhibitors at baseline (Figure 1), there was no statistical evidence of a difference in the effect of efpeglenatide on these outcomes in the presence or absence of baseline SGLT2 inhibitors (all interaction P >0.20). The absence of any interaction persisted after accounting for heart rate as a time-varying covariate (Supplemental Table 3).

Similar findings were noted after assessing the effect of post-randomization drop-in of SGLT2 inhibitors in sensitivity analyses (Supplemental Table 4). At the final trial visit, 475 (17.5%) of patient in the efpeglenatide groups (pooled doses) vs 288 (21.2%) patients in the placebo group were receiving concomitant SGLT2 inhibitor therapy.(12) In subgroup analyses including all patients ever exposed to SGLT2 inhibitors from baseline to final visit in the SGLT2 inhibitor group, the benefit of efpeglenatide vs placebo on the primary (MACE) and secondary outcomes (expanded MACE, renal composite outcome, MACE or non-CV death, heart failure hospitalizations) remained unchanged and did not differ by SGLT2 inhibitor use (all interaction P >0.30). Similar results were obtained following right-censoring at SGLT2 inhibitor drop-in (all interaction P >0.2). Accounting for the differential drop-in of SGLT2 inhibitor use by inverse probability for treatment weighting, the benefit of efpeglenatide on MACE, expanded MACE, MACE or non-CV death and heart failure hospitalizations remained unchanged; however the benefit on the renal composite endpoint appeared greater in those exposed to SGLT2 inhibitor during the course of the trial (n=618) when compared with those not exposed to SGLT2 inhibitor (n=3458) during the course of the trial (HR efpeglenatide vs placebo 0.52, 95% CI 0.32- 0.84 versus 0.91, 95% CI 0.77- 1.07, respectively; interaction P =0.021) (Supplemental Table 4).

Effect on Clinical and Biochemical Variables

Baseline SGLT2 inhibitor use did not modify the effects of efpeglenatide on blood pressure, heart rate, body weight, low density lipoprotein cholesterol, eGFR, and UACR over time (all interaction P ≥0.08) (Table 2). The reduction in HbA1c over time with efpeglenatide (vs placebo) appeared greater in patients not receiving (vs receiving) SGLT2 inhibitors at baseline (interaction P =0.014). (Table 2).

Adverse events in patients receiving and not receiving concomitant SGLT2 inhibitors at enrollment

The frequency of discontinuation due to adverse events, severe gastrointestinal events, and acute renal failure were similarly low in patients receiving and not receiving SGLT2 inhibitors at baseline (Table 3). While patients treated with efpeglenatide had a higher rate of severe gastrointestinal events compared to those treated with placebo, the frequency of these events were not influenced by baseline SGLT2 inhibitor use (Table 3).

DISCUSSION

In this exploratory analysis of AMPLITUDE-O we found that efpeglenatide's salutary effects on MACE, expanded MACE, renal composite outcome, MACE or non-CV death, and heart failure hospitalizations as well as adverse events appeared independent of concurrent SGLT2 inhibitor use, as judged by point estimates in those receiving vs. not receiving baseline SGLT2 inhibitor and lack of any formal interactions. Similarly, efpeglenatide's reduction of blood pressure, body weight, low density lipoprotein cholesterol and UACR appeared to be independent of concurrent SGLT2 inhibitor use.

Several lines of evidence provide a strong basis for the combined use of GLP-1 RAs and SGLT2 inhibitors in the treatment of type 2 diabetes and potential additive effect on glucose-lowering and prevention of cardiorenal events. The two drug classes have distinct mechanisms of action and complementary CV benefits from clinical trials in diabetes,[8–10] thus raising the possibility that combined therapy may produce more comprehensive beneficial effects than when either drug class is given alone. Indeed, guidelines and societies recommend the addition of SGLT2 inhibitors after a GLP-1 RA or vice versa for patients with diabetes, with or at high risk of atherosclerotic CV disease or chronic kidney disease.[17–20] Although logical, clinical trial evidence to support a recommendation for simultaneous use of both therapies is lacking. Among prior CV outcome trials, the combined use of both drug classes was rare -- in GLP-1 RA CV outcomes trials the prevalence of baseline SGLT2 inhibitor use ranged from 0% to 5.3%; similarly in SGLT2 inhibitor CV outcome trials the prevalence of baseline GLP-1RA use ranged from 2.5% to 4.4%.[1–7] A recent systematic review and meta-analysis revealed only seven trials including a total of 1913 adults with type 2 diabetes that compared the combination of a GLP-1 RA and an SGLT2 inhibitor with placebo or an active control.[11] Six out of the seven trials only reported short-term (up to 30

weeks) outcomes mainly limited to surrogate measures such as glycated hemoglobin, body weight, blood pressure and eGFR. There were too few events of death, myocardial infarction and stroke to allow meaningful conclusions, and no trial that reported data for heart failure hospitalizations. Importantly, the meta-analysis showed that combined therapy did not increase the odds of severe hypoglycaemia compared with either GLP-1 RA or SGLT2 inhibitor alone.[11] Our study therefore extends the prior data in showing reduction in clinical events – including MACE as well as renal outcomes and heart failure hospitalizations – in patients receiving SGLT2 inhibitors at baseline who were randomized to also receive the GLP-1 RA efpeglenatide in the setting of the AMPLITUDE-O trial.

Our results are complementary to the analyses from the Dapagliflozin Effect on Cardiovascular Events (DECLARE)-TIMI 58 trial[21] where 750 patients (4.4% of the trial population) were receiving GLP-1RAs at baseline. Randomization to dapagliflozin vs. placebo was not stratified by GLP-1RA use at baseline. While the benefits of dapagliflozin on major adverse CV events were generally consistent regardless of baseline GLP-1RA use, there appeared to be greater benefit on heart failure hospitalization in the subgroup of patients with baseline GLP-1 RA use (HR 0.20, 95% CI 0.07-0.60 vs. 0.77, 95% CI 0.64-0.92 in GLP-1RA non-users, P for interaction = 0.014). As for renal outcomes, DECLARE-TIMI 58 also showed that the benefit of dapagliflozin was consistent in baseline GLP-1RA users vs. non-users (HR 0.36, 95% CI 0.11-1.15 vs, 0.54, 95% CI 0.43-0.67 respectively, P for interaction 0.49). We found remarkably similar results for the estimated benefit of combined therapy (baseline SGLT2 inhibitor users randomized to efpeglenatide treatment vs. placebo), with HR 0.23, 95% CI 0.05- 0.97 for heart failure hospitalizations and HR 0.52, 95% CI 0.33- 0.83 for the renal composite outcome respectively. While we did not demonstrate statistically significant effect modification for either outcomes, our limited number of events within the subgroup of baseline SGLT2 inhibitor users (particularly for heart failure

hospitalizations) may have precluded detection of modest interactions. This is reflected in the wide confidence intervals within the SGLT2 inhibitor subgroup. Further adequately powered clinical studies on this combination therapy are warranted based on these data.

More recently, a real world observational study using insurance claims databases in the United States showed that, among people with type 2 diabetes who were already taking GLP-1 RAs, the addition of SGLT2 inhibitors to GLP-1RA therapy was associated with lower MACE and heart failure hospitalization compared with initiation of sulfonylureas.[22] Despite inherent limitations of observational data and potential for residual confounding, the study provided support for adding SGLT2 inhibitor to existing GLP-1 RA therapy to reduce CV events in patients with diabetes. Our data showing that the effect of efpeglenatide on clinically important outcomes may be independent of the concomitant use of SGLT2 inhibitors provide further support for adding GLP-1 RA to existing SGLT2 inhibitor therapy in patients with diabetes.

Mechanistically, additive or synergistic effects on renal events may be explained by the effect of both drug types in reducing urinary protein excretion, slowing the rate of decline in glomerular filtration rate,[23,24] exerting natriuretic actions by inhibiting the sodium-hydrogen exchanger-3 in the proximal renal tubule,[25]and improving nitric oxide–dependent endothelial function.[26] Additive or synergistic effects on heart failure hospitalization may be explained by a reduction in ischemic heart failure by GLP-1 RAs coupled with beneficial diuretic, myocardial and anti-inflammatory effects of SGLT2 inhibitors on heart failure regardless of ejection fraction. The underlying mechanism for attenuated decline in HbA1c with combined therapy is unclear and unlikely related to lower baseline HbA1c among patients receiving SGLT2 inhibitors at enrollment (since analyses adjusted for baseline values). As many interaction P values were computed without adjustment for multiple testing,

the likeliest explanation was chance alone. Indeed, the threshold P value for significance based on the 10 tests reported in Table 2 would have been 0.05/10 =0.005 which is well above the observed P value of 0.014. Other possibilities include the higher drop-in of SGLT2 inhibitors in the placebo group or physiological reasons. Our study does not provide mechanistic details, is limited by small numbers of events in subgroup analyses and low power to detect small or modest interactions, and does not extend to GLP-1 RAs other than efpeglenatide. Furthermore, exploratory analyses relating to drop-in SGLT2 inhibitor use are limited by non-random drop-in and survivor bias associated with starting a new medication. Yet, our findings are consistent with growing evidence in support of the efficacy and safety of combined therapy in patients with type 2 diabetes. Of course, a prospective, randomized, controlled study testing the combination of a GLP-1 RA with a SGLT2 inhibitor vs. each individual component will provide definitive evidence, but that would be a huge undertaking that perhaps can only be accomplished with a pragmatic study design.

In conclusion, our exploratory analyses of AMPLITUDE-O showed that the efficacy and safety of efpeglenatide appeared to be independent of concurrent SGLT2 inhibitor use. Combined treatment with SGLT2 inhibitors and GLP-1 RAs may be expected to be well-tolerated and to yield substantial benefits across a wide range of CV outcomes among patients with type 2 diabetes.

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SUPPLEMENTAL MATERIALS

Supplemental Tables 1-4

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Table 1. Baseline characteristics of patients taking and not taking SGLT2 inhibitors at recruitment

	No Baseline SGLT2 inhibitors	Baseline SGLT2 inhibitors	P value
	[N (%) or Mean ±(SD)]	[N (%) or Mean ±(SD)]	
Randomized	3458	618	
Age (years)	64.63± 8.27	64.04± 8.05	0.103
Females	1170 (33.83)	174 (28.16)	0.005
Region: Canada/US	831 (24.03)	248 (40.13)	<0.001
Mexico/South America	879 (25.42)	45 (7.28)	
Europe	1024 (29.61)	261 (42.23)	
Other	724 (20.94)	64 (10.36)	
White Ancestry	3010 (87.04)	524 (84.79)	0.128
Diabetes Duration	15.27± 8.84	16.19± 8.49	0.004
Current tobacco Use	541 (15.64)	92 (14.89)	0.631
Prior cardiovascular disease	3101 (89.68)	549 (88.83)	0.529
eGFR <60 ml/min/1.73m^2	1101 (31.86)	186 (30.10)	0.385
Prior CVD & eGFR <60 ml/min/1.73m^2	764 (22.11)	124 (20.06)	0.257
Prior heart failure	652 (18.85)	85 (13.75)	0.002
Prior hypertension	3168 (91.61)	554 (89.64)	0.109
Prior diabetic retinopathy*	1138 (32.91)	204 (33.01)	0.960
Body Mass Index (kg/m^2)	32.68± 6.14	32.79± 6.20	0.762
Heart Rate (beats/min)	72.78±10.53	72.82±11.12	0.931
Systolic BP	135.4±15.54	131.8±15.06	<0.001
Diastolic BP	76.92± 9.69	75.56± 9.92	0.001
HbA1c (%)	8.97± 1.51	8.57± 1.23	<0.001
eGFR (ml/min/1.73m^2)	72.19±22.62	73.64±21.03	0.173

	No Baseline SGLT2 inhibitors	Baseline SGLT2 inhibitors	P value
	[N (%) or Mean ±(SD)]	[N (%) or Mean ±(SD)]	
Albuminuria (%)†	1718 (49.71)	259 (41.91)	<0.001
UACR (mg/mmol)‡	3.28 (1.13-14.01)	2.49 (1.02-7.68)	<0.001
Cholesterol (mmol/L)	4.23± 1.23	4.10± 1.26	<0.001
LDL cholesterol (mmol/L)	2.11± 0.97	1.85± 0.97	<0.001
HDL cholesterol (mmol/L)	1.11± 0.30	1.10± 0.32	0.298
Median triglycerides (mmol/L)	1.89 (1.36-2.69)	2.12 (1.44-3.22)	<0.001
Any Insulin	2181 (63.07)	379 (61.33)	0.408
Metformin	2466 (71.31)	519 (83.98)	<0.001
Any Sulfonylurea	882 (25.51)	154 (24.92)	0.757
No glucose-lowering drug	85 (2.46)	0 (0.00)	---
ACE-I or ARB or ARNi	2752 (79.58)	510 (82.52)	0.092
Beta Blocker	2260 (65.36)	410 (66.34)	0.634
Statin	2766 (79.99)	528 (85.44)	0.001
Fibrate	291 (8.42)	59 (9.55)	0.355
Acetylsalicylic acid	2345 (67.81)	423 (68.45)	0.756
Other antiplatelet drugs	896 (25.91)	153 (24.76)	0.545

*Diabetic Retinopathy definition includes Reported Diabetic Retinopathy, Vitrectomy, Diabetic laser therapy, or Anti-vascular Endothelial Growth Factor Injections

†Urine albumin:creatinine ratio > = 3.39 g/mol

‡Urine albumin:creatinine ratio, expressed as median (25^{th} – 75^{th} percentile)

P values refer to the difference between patients treated or not treated with a SGLT2 inhibitor at baseline, combining patients in the two randomized treatment groups.

eGFR, estimated glomerular filtration rate; CVD, cardiovascular disease; UACR, urinary albumin:creatinine ratio; LDL, low density lipoprotein cholesterol; HDL, high density lipoprotein cholesterol; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor neprilysin inhibitor.

For continuous variables used two-sample test for normally distributed (age, heart rate, systolic and diastolic blood pressure, eGFR), Wilcoxen for non-normally distributed (diabetes duration, cholesterol, LDL, HDL,triglycerides) and used chi-square test of homogeneity for categorical variables.

Table 2. Changes of clinical and biochemical variables from baseline with Efpeglenatide (4/6 mg) in patients taking and not taking SGLT2 inhibitors at baseline

	No Baseline SGLT2 inhibitors			Baseline SGLT2 inhibitors			
	Efpeglenatide	**Placebo**	**Adjusted LSM Differences (95%CI)**	**Efpeglenatide**	**Placebo**	**Adjusted LSM Differences (95%CI)**	**Interaction P-value**
Variable	**LS Mean (SE)**	**LS Mean (SE)**		**LS Mean (SE)**	**LS Mean (SE)**		
HbA1c(%)	-1.43 (0.07)	-0.16 (0.07)	-1.27 (-1.36- -1.19)	-1.29 (0.07)	-0.23 (0.09)	-1.06 (-1.21- -0.91)	0.014
SBP(mmHg)	-2.39 (0.68)	-0.80 (0.73)	-1.59 (-2.37- -0.82)	-2.42 (0.90)	-1.51 (1.09)	-0.91 (-2.75-0.92)	0.212
DBP(mmHg)	0.36 (0.41)	-0.14 (0.44)	0.50 (0.03-0.97)	0.98 (0.53)	0.08 (0.63)	0.90 (-0.16-1.96)	0.257
Change in SBP(mmHg)-DBP(mmHg) from Baseline	-2.74 (0.58)	-0.64 (0.62)	-2.10 (-2.76- -1.44)	-3.30 (0.74)	-1.43 (0.90)	-1.87 (-3.37- -0.37)	0.546
Change in Heart Rate(beats/min) from Baseline	4.69 (0.45)	0.75 (0.49)	3.94 (3.43-4.45)	5.05 (0.59)	1.43 (0.70)	3.62 (2.46-4.78)	0.854
Change in BMI(kg/m) from Baseline	-1.24 (0.09)	-0.32 (0.10)	-0.92 (-1.04- -0.80)	-1.08 (0.10)	-0.16 (0.12)	-0.92 (-1.15- -0.68)	0.578
Change in Weight(kg) from Baseline	-3.45 (0.27)	-0.86 (0.29)	-2.59 (-2.93- -2.25)	-3.06 (0.28)	-0.42 (0.36)	-2.64 (-3.32- -1.97)	0.641
Change in LDL(mmol/L) from Baseline	-0.05 (0.04)	0.03 (0.05)	-0.07 (-0.12- -0.02)	-0.12 (0.06)	-0.04 (0.07)	-0.09 (-0.21-0.03)	0.600
Change in eGFR (mL/min/1.73 m) from Baseline	-3.65 (0.58)	-4.43 (0.62)	0.78 (0.12-1.45)	-0.40 (0.79)	-1.91 (0.95)	1.52 (-0.14-3.17)	0.768
Change in Ln(UACR)(g/mol) from Baseline	0.65 (1.09)	0.84 (1.10)	0.78 (0.70-0.86)	0.69 (1.12)	0.78 (1.13)	0.89 (0.71-1.10)	0.080

Fixed effects in the model are: treatment, region, stratification factors and baseline score. LS = least squares. LSM = least squares mean. SE = standard error.

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; LDL, low density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; UACR, urinary albumin:creatinine ratio.

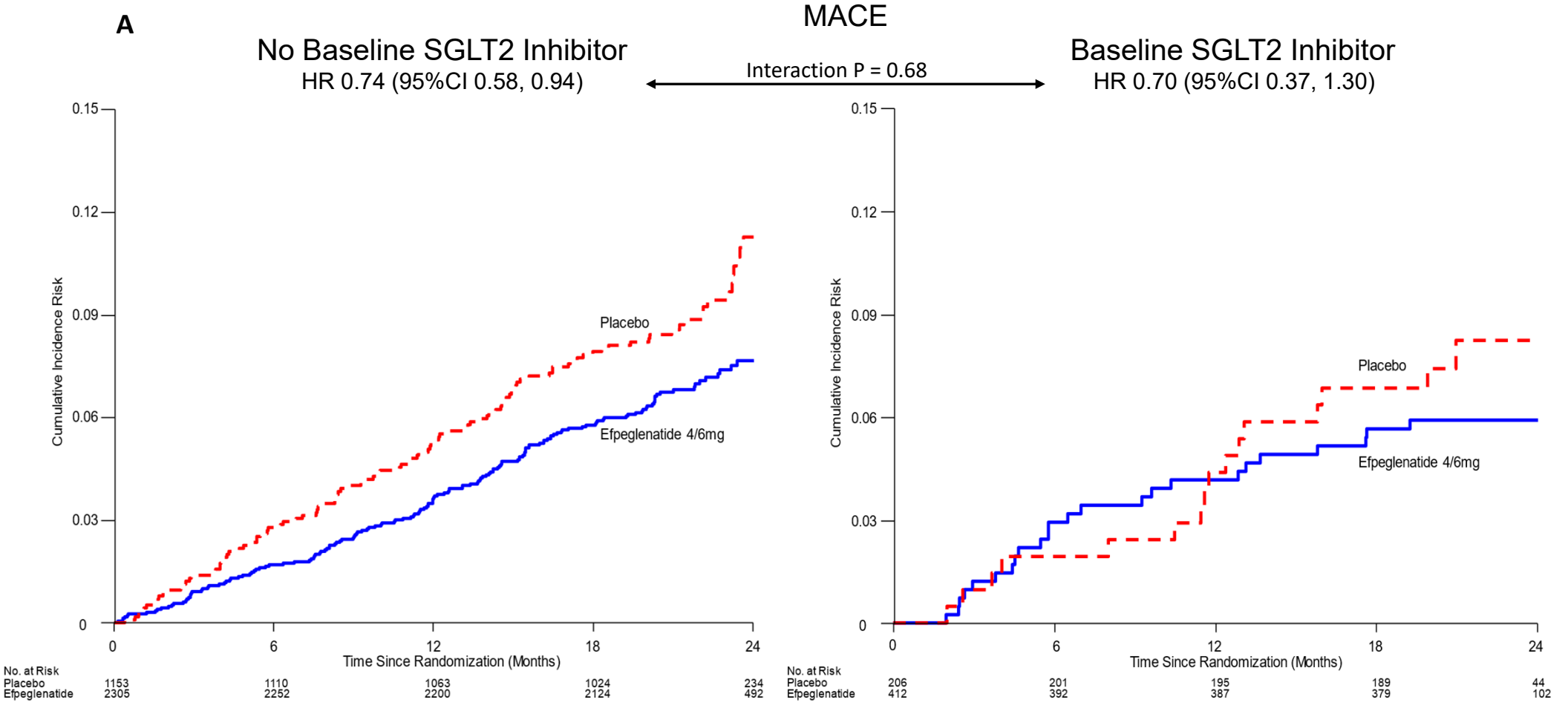
Table 3. Frequency of selected adverse events in placebo and efpeglenatide-treated patients, according to baseline SGLT2 inhibitor use

	No Baseline SGLT2 inhibitors [N (%)]		Baseline SGLT2 inhibitors [N (%)]	
	Efpeglenatide 4/6mg	**Placebo**	**Efpeglenatide 4/6mg**	**Placebo**
Randomized	2305	1153	412	206
Discontinuation for adverse events	131 (5.68)	35 (3.04)	16 (3.88)	14 (6.80)
Severe Gastrointestinal Event	75 (3.25)	19 (1.65)	15 (3.64)	6 (2.91)
Constipation, Diarrhea, Nausea, or Bloating	24 (1.04)	3 (0.26)	4 (0.97)	1 (0.49)
Vomiting	4 (0.17)	1 (0.09)	0 (0.00)	1 (0.49)
Other Severe Gastrointestinal Event	48 (2.08)	15 (1.30)	11 (2.67)	4 (1.94)
Acute Renal Failure	82 (3.56)	28 (2.43)	6 (1.46)	11 (5.34)

LEGENDS

Figure 1. Hazards plots showing the cumulative risk of (A) major adverse cardiovascular events (MACE), (B) expanded MACE, (C) renal composite outcome of incident macroalbuminuria, a decline in eGFR by ≥ 40% for ≥ 30 days, renal replacement therapy for ≥ 90 days, or an eGFR < 15 ml/min/1.73 m² for ≥ 30 days, (D) MACE or non-cardiovascular death, and (E) heart failure hospitalizations; in patients taking and not taking SGLT2 inhibitors at baseline

A


MACE
No Baseline SGLT2 Inhibitor
HR 0.74 (95%CI 0.58, 0.94)
Interaction P = 0.68
Baseline SGLT2 Inhibitor
HR 0.70 (95%CI 0.37, 1.30)
Cumulative Incidence Risk
0.15
0.12
0.09
0.06
0.03
0
Placebo
Efpeglenatide 4/6mg
0
6
12
18
24
Time Since Randomization (Months)
No. at Risk
Placebo 1153 1110 1063 1024 234
Efpeglenatide 2305 2252 2200 2124 492
Cumulative Incidence Risk
0.15
0.12
0.09
0.06
0.03
0
Placebo
Efpeglenatide 4/6mg
0
6
12
18
24
Time Since Randomization (Months)
No. at Risk
Placebo 206 201 195 189 44
Efpeglenatide 412 392 387 379 102

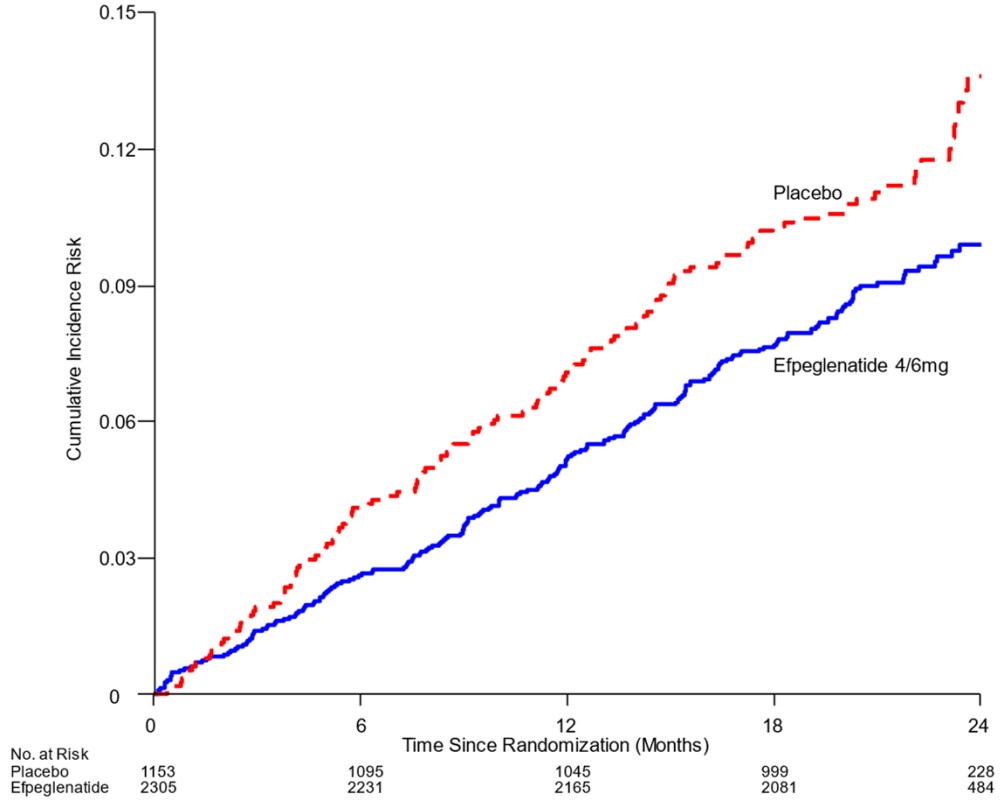
B

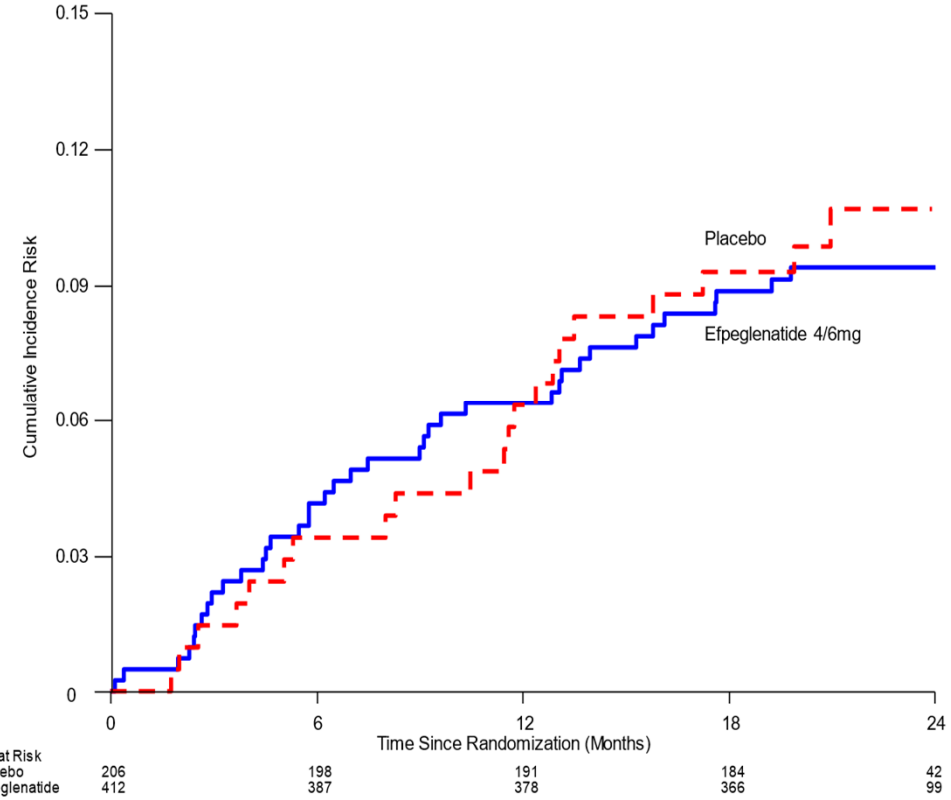
Expanded MACE

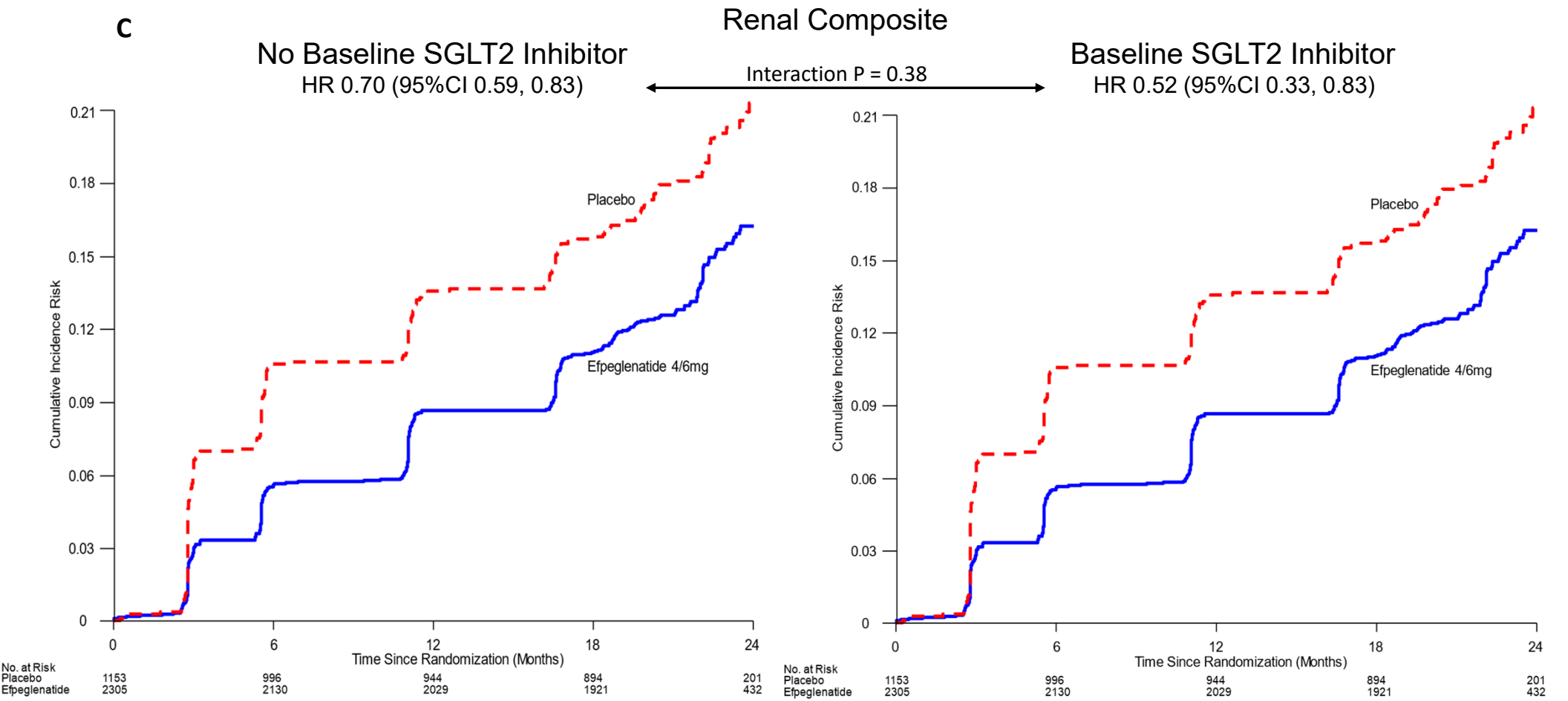
No Baseline SGLT2 Inhibitor
HR 0.77 (95%CI 0.62, 0.96)

Interaction P = 0.23

Baseline SGLT2 Inhibitor
HR 0.87 (95%CI 0.51, 1.48)






c
Renal Composite
No Baseline SGLT2 Inhibitor
HR 0.70 (95%CI 0.59, 0.83)
Interaction P = 0.38
Baseline SGLT2 Inhibitor
HR 0.52 (95%CI 0.33, 0.83)
Cumulative Incidence Risk
0.21
0.18
0.15
0.12
0.09
0.06
0.03
0
Placebo
Efpeglenatide 4/6mg
0
6
12
18
24
Time Since Randomization (Months)
No. at Risk
Placebo 1153 996 944 894 201
Efpeglenatide 2305 2130 2029 1921 432

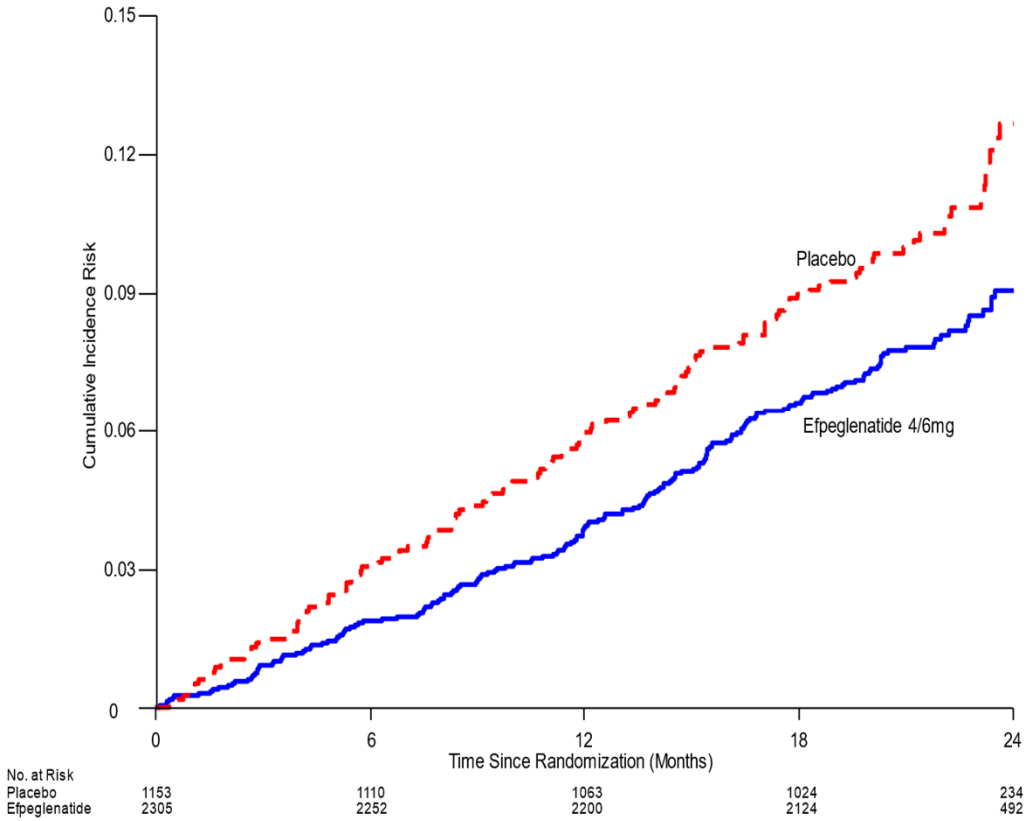
D

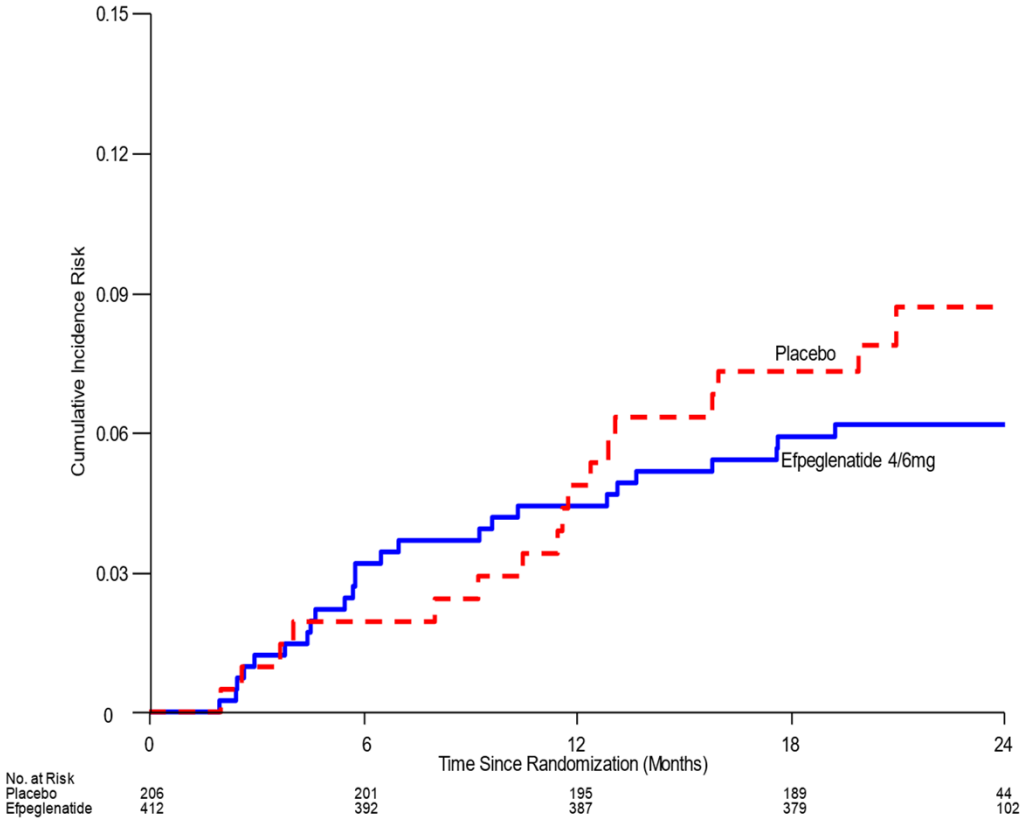
MACE or non-CV Death

No Baseline SGLT2 Inhibitor
HR 0.74 (95%CI 0.59, 0.93)

Interaction P = 0.75

Baseline SGLT2 Inhibitor
HR 0.65 (95%CI 0.36, 1.19)





E

Heart Failure Hospitalization

No Baseline SGLT2 Inhibitor
HR 0.70 (95%CI 0.42, 1.17)

Interaction P = 0.35

Baseline SGLT2 Inhibitor
HR 0.23 (95%CI 0.05, 0.97)