Supplementary Online Content

Neeland IJ, Eliasson B, Kasai T, Marx N, Zinman B, Inzucchi SE, Wanner C, Zwiener I, Wojeck BS, Yaggi HK and Johansen OE. Obstructive Sleep Apnea and Cardiovascular, Heart Failure, Mortality, and Renal Outcomes with Empagliflozin: An Exploratory Analysis from EMPA-REG OUTCOME®

A. Empagliflozin mediation analysis methodology for evaluation of covariates involved in developing OSA

The methodology followed the principles employed to analyze mediation effects of different parameters on the effect of empagliflozin on CV deaths, as previously published (1). This followed principles originally proposed by Baron and Kenny (2), taking the time-dynamic evolvement of both the potential mediators and the outcome new-onset OSA into account. A variable must satisfy several conditions to be a mediator of the treatment effect. Treatment must have an effect on the variable over time, and the change in the variable over time must have an effect on the outcome. As a further condition, in an analysis where the variable is included as a time-dependent covariate over time, the effect of treatment on the outcome (represented as the hazard ratio) must be reduced as compared to the treatment effect in an unadjusted analysis.

We considered that empagliflozin could have a direct effect on the risk of OSA or could affect OSA indirectly through its effects on one or more of potential mediators (weight, systolic blood pressure, HbA1c, hematocrit). Each variable was analyzed as a time-dependent covariate in Cox regression models with the outcome time to OSA.

Percentage mediation for each covariate was calculated as:

$$Mediation\,\% = 100 \times \frac{lnHR - lnHR_C}{lnHR}$$

where HR is the HR for the comparison of the treatment groups in the model with treatment group alone (in addition to age, sex, region, baseline estimated glomerular filtration rate [eGFR], baseline HbA1c, baseline body mass index [BMI]), and HR_c is the hazard ratio for the comparison of the treatment groups in the model adjusting for the baseline and on-study time-dependent covariate values (change from baseline).

References

1. Inzucchi SE, Zinman B, Fitchett D, Wanner C, Ferrannini E, Schumacher M, Schmoor C, Ohneberg K, Johansen OE, George JT, Hantel S, Bluhmki E, Lachin JM. How Does Empagliflozin Reduce Cardiovascular Mortality? Insights From a Mediation Analysis of the EMPA-REG OUTCOME Trial. Diabetes Care. 2018;41:356-363

2. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. J Pers Soc Psychol 1986;51:1173-1182

B. Effects on HbA1c, waist circumference and systolic blood pressure

Effects of empagliflozin treatment on cardiometabolic risk factors by obstructive sleep apnea status at baseline. Adjusted mean (standard error [SE] or geometric mean [95% confidence interval]) changes from baseline in (B1) glycosylated hemoglobin (HbA1c), (B2) waist circumference, (B3) systolic blood pressure, and (B4) urine albumin-to-creatinine ratio (UACR), in participants by OSA status at baseline. Model reflects a mixed model repeated measures analysis including terms for baseline parameter in question (log-value for UACR) and baseline HbA1c as linear covariate(s) and geographical region, body mass index categories, week reachable parameter in question, baseline estimated glomerular filtration rate categories, treatment, visit, OSA at baseline, treatment by visit interaction, visit by OSA at baseline interaction, treatment by OSA at baseline interaction, treatment by visit by OSA at baseline interaction, and baseline covariate in question by visit interaction as fixed effect(s).

Figure B1. Effects on HbA1c (%) by baseline obstructive sleep apnea (OSA).

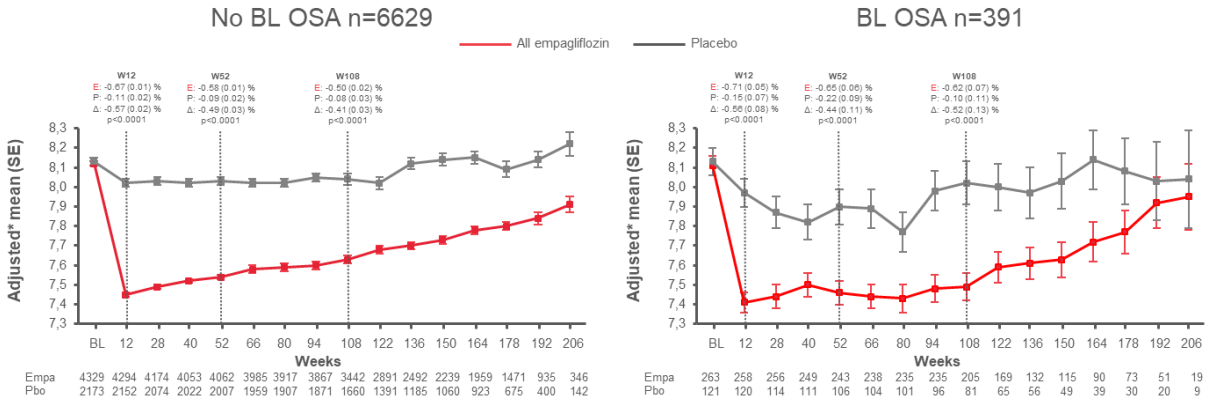


Figure B2. Effects on waist circumference (cm) by baseline obstructive sleep apnea (OSA).

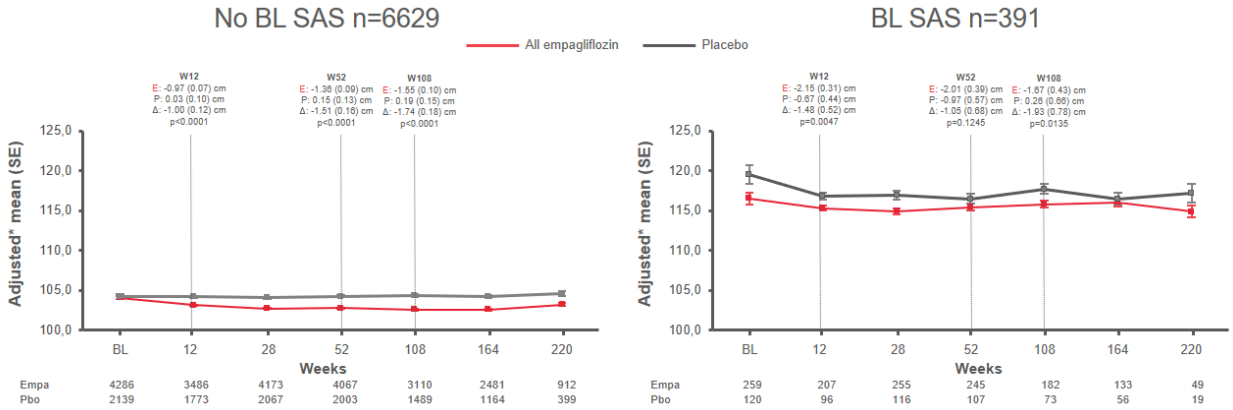


Figure B3. Effects on systolic blood pressure (mmHg) by baseline obstructive sleep apnea (OSA).

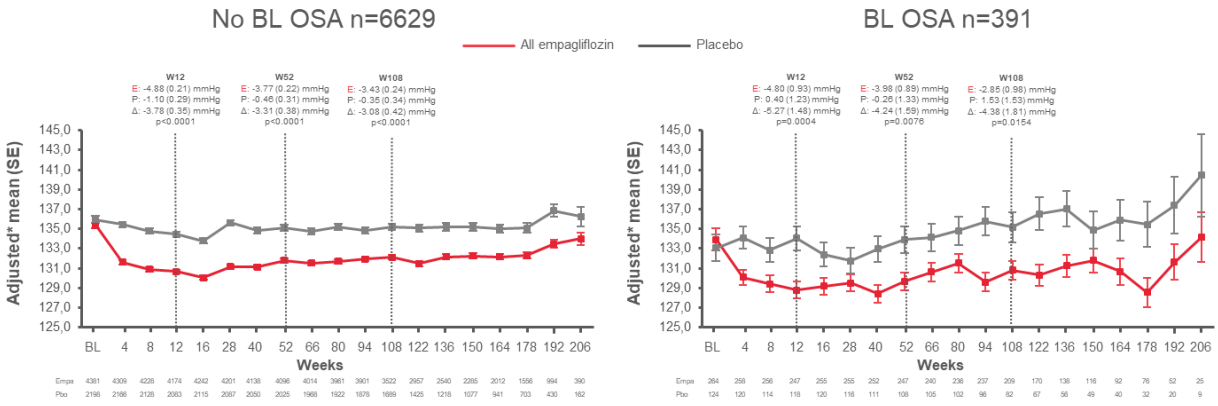
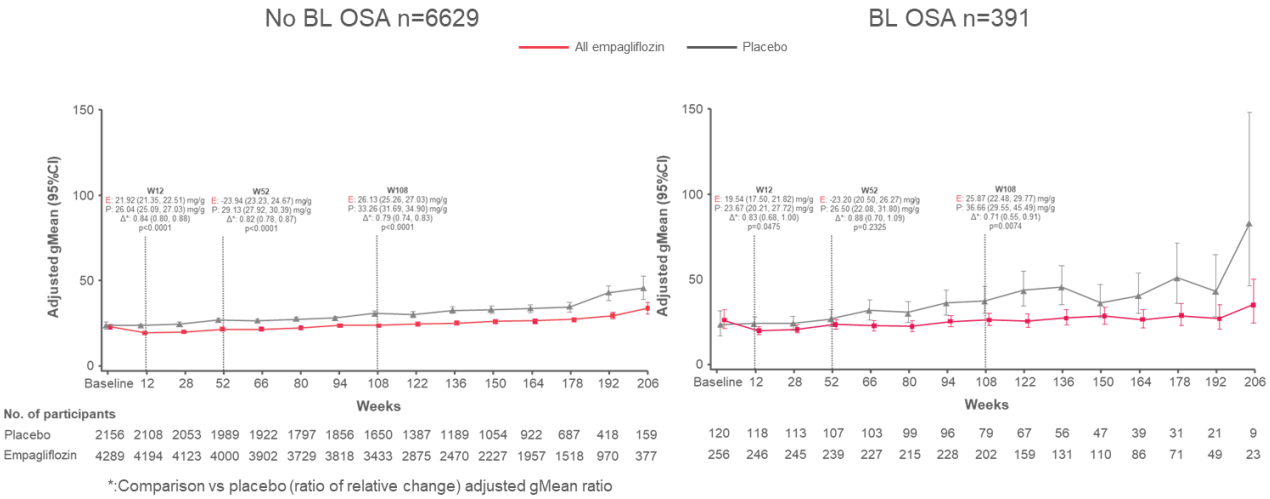
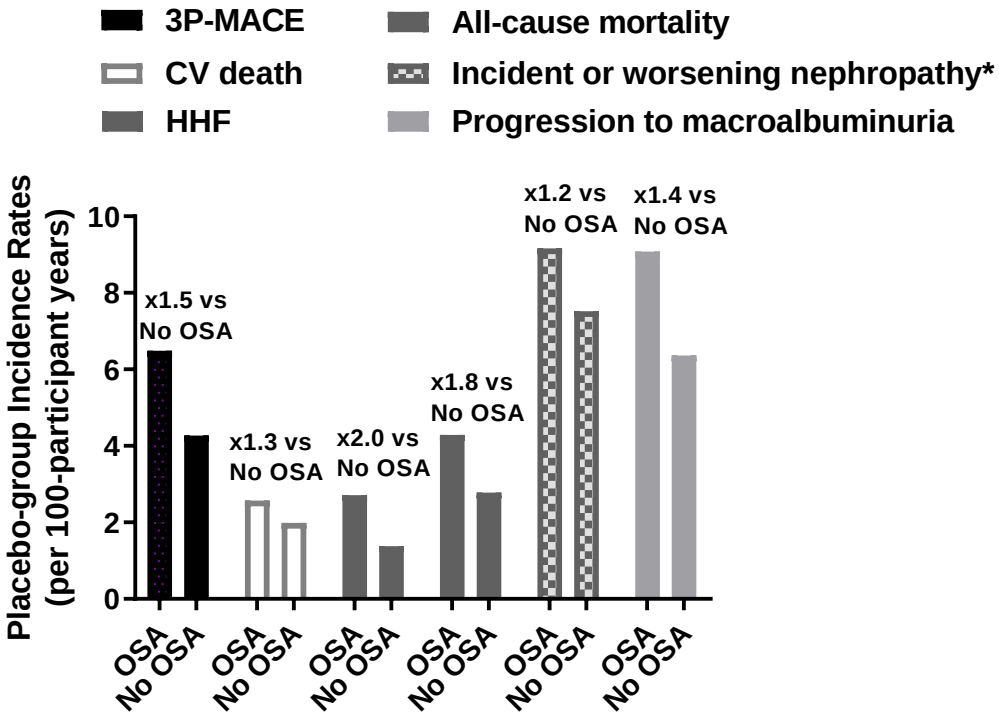


Figure B4. Effects on urine albumin-to-creatinine ratio (mg/g) by baseline obstructive sleep apnea (OSA).



*:Comparison vs placebo (ratio of relative change) adjusted gMean ratio

C. Placebo-group incidence rates for CV, HF and renal outcomes by prevalent obstructive sleep apnea (OSA) at baseline



OSA – obstructive sleep apnea, CV – cardiovascular, HHF – hospitalized heart failure. * progression to macroalbuminuria [urinary albumin to-creatinine ratio, >300 mg of albumin per gram of creatinine]; a doubling of the serum creatinine level, accompanied by an eGFR of ≤45 ml per minute per 1.73 m^2, as calculated by the MDRD formula; the initiation of renal-replacement therapy; or death from renal disease

D. Adverse events (n, %) occurring until 7 days after treatment discontinuation, in participants by treatment group and by obstructive sleep apnea (OSA) at baseline

	Without OSA at baseline		With OSA at baseline	
	Empagliflozin (N = 4421)	**Placebo (N = 2208)**	**Empagliflozin (N = 260)**	**Placebo (N = 125)**
Any adverse events	3977 (90.0)	2019 (91.4)	253 (95.1)	120 (96.0)
Serious adverse events	1652 (37.4)	926 (41.9)	137 (51.5)	62 (49.6)
Adverse events leading to discontinuation	751 (17.0)	417 (18.9)	62 (23.3)	36 (28.8)
Confirmed hypoglycemic adverse event[1]	1207 (27.3)	595 (26.9)	96 (36.1)	55 (44.0)
Aggregated system organ class or single preferred terms within category “Any adverse events”				
Infections and infestations[2]	2323 (52.5)	1236 (56.0)	184 (69.2)	75 (60.0)
Renal- and urinary disorders[2]	839 (19.0)	453 (20.5)	73 (27.4)	39 (31.2)
Increased urination	183 (4.1)	54 (2.4)	22 (8.3)	10 (8.0)
Nocturia	37 (0.8)	15 (0.7)	5 (1.9)	4 (3.2)
Polyuria	55 (1.2)	12 (0.5)	6 (2.3)	1 (0.8)
Pollakiuria	103 (2.3)	29 (1.3)	15 (2.3)	5 (4.0)

OSA – obstructive sleep apnea.1: plasma glucose level of less than 70 mg per deciliter (3.9 mmol per liter) or an event requiring assistance. 2: based on totality of events within the system organ class (SOC)

E. Baseline characteristics by treatment groups (excluding n=391 with prevalent obstructive sleep apnea [OSA] at baseline) in those developing vs not-developing new onset OSA

Table E1. Select baseline characteristics in those developing vs not-developing new onset obstructive sleep apnea (OSA)

	Participants without OSA at baseline who did not develop OSA		***Participants without OSA at baseline who developed OSA***	
	Empagliflozin (n=4396)	**Placebo (n=2183)**	**Empagliflozin (n=25)**	**Placebo (n=25)**
Male	3096 (70.4)	1552 (71.1)	24 (96.0)	20 (80.0)
Age, years	63.1 ± 8.6	63.2 ± 8.9	61.8 ± 8.6	62.1 ± 7.7
Diabetes duration, years				
≤ 1	124 (2.8)	50 (2.3)	1 (4.0)	0 (0)
>1 to 5	680 (15.5)	356 (16.3)	2 (8.0)	4 (16.0)
> 5 to 10	1095 (24.9)	540 (24.7)	6 (24.0)	3 (12.0)
> 10	2497 (56.8)	1237 (56.7)	16 (64.0)	18 (72.0)
HbA1c, %	8.1 ± 0.9	8.1 ± 0.9	8.3 ± 0.9	8.1 ± 0.8
Any insulin	2066 (47.0)	1032 (47.3)	18 (72.0)	20 (80.0)
eGFR (MDRD), ml/min/1.73 m^2	74.6 ± 21.6	74.2 ± 21.1	70.1 ± 19.1	70.6 ± 21.1
UACR, median (IQR)	17.7 (7.1, 70.7)	17.7 (7.1, 72.3)	16.8 (5.3, 99.9)	56.6 (8.8, 218.4)
Body mass index, kg/m^2	30.3 ± 5.1	30.3 ± 5.1	32.4 ± 3.4	33.2 ± 5.0
Weight, kg	85.0 ± 18.4	85.3 ± 18.4	97.9 ± 14.6	98.7 ± 14.3
Waist circumference, cm	104.0 ± 13.4	104.0 ± 13.5	112.3 ± 11.4	114.0 ± 13.8
Coronary artery disease	3293 (74.9)	1629 (74.6)	22 (88.0)	20 (80.0)
Systolic BP, mmHg	135.3 ± 16.8	135.9 ± 17.3	137.5 ± 23.1	138.5 ± 23.3
Any antihypertensives	4159 (94.6)	2073 (95.0)	25 (100.0)	25 (100.0)

OSA – obstructive sleep apnea, eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease formula; UACR, urine albumin:creatinine ratio, BP – blood pressure.

F. Results of mediation analysis for treatment effects on new onset obstructive sleep apnea

Table F1. Univariable mediation analysis of risk of OSA with empagliflozin vs placebo (ITT approach). Time-dependent covariate analysis adjusting for the change from baseline in each variable. Complete mediation would be indicated by an HR of 1.0 in the model adjusted for the covariate.

	HR for OSA with empagliflozin vs placebo	**95% confidence interval**	**Percentage mediation**
Unadjusted*:	0.52	0.30, 0.89	
Additional adjustment for changes over time in:			
HbA_{1c}	0.56	0.32, 0.97	12.2
SBP	0.55	0.32, 0.95	8.9
Weight	0.58	0.33, 1.01	16.5
Hematocrit	0.49	0.27, 0.88	-9.35
All 4 individual parameters above	0.60	0.32, 1.12	22.4
SBP + weight	0.61	0.35, 1.06	23.9

‘Cox regression analysis with adjustment on age, sex, baseline BMI, baseline eGFR, baseline HbA1c, region and treatment in patients treated with ≥1 dose of study drug; OSA – obstructive sleep apnea, SBP - systolic blood pressure.