



# The Impact of Empagliflozin on Obstructive Sleep Apnea and Cardiovascular and Renal Outcomes: An Exploratory Analysis of the EMPA-REG OUTCOME Trial

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Ian J. Neeland,<sup>1</sup> Bjorn Eliasson,<sup>2</sup> Takatoshi Kasai,<sup>3</sup> Nikolaus Marx,<sup>4</sup> Bernard Zinman,<sup>5</sup> Silvio E. Inzucchi,<sup>6</sup> Christoph Wanner,<sup>7</sup> Isabella Zwiener,<sup>8</sup> Brian S. Wojcek,<sup>6</sup> Henry K. Yaggi,<sup>9</sup> and Odd Erik Johansen,<sup>10</sup> on behalf of the EMPA-REG OUTCOME Investigators

## OBJECTIVE

To explore the effects of empagliflozin on the incidence of obstructive sleep apnea (OSA) and its effects on metabolic, cardiovascular (CV), and renal outcomes among participants with or without OSA in the EMPA-REG OUTCOME trial.

## RESEARCH DESIGN AND METHODS

Participants with diabetes and CV disease were randomized to empagliflozin (10 and 25 mg) or placebo daily in addition to standard of care. OSA was assessed by investigator report using Medical Dictionary for Regulatory Activities version 18.0, and CV outcomes were independently adjudicated. Analyses were performed using multivariable-adjusted Cox regression models.

## RESULTS

OSA was reported in 391 of 7,020 (5.6%) participants at baseline. Those with OSA were more likely to be male (83% vs. 71%) and to have moderate to severe obesity (BMI  $\geq 35$  kg/m<sup>2</sup>; 55% vs. 18%). Over a median of 3.1 years, empagliflozin had similar placebo-adjusted reductions in HbA<sub>1c</sub>, waist circumference, and systolic blood pressure, regardless of OSA status, but a larger effect on weight (adjusted mean  $\pm$  SE difference at week 52: OSA vs. no OSA  $-2.9 \pm 0.5$  vs.  $-1.9 \pm 0.1$  kg). Incidence of 3-point major adverse CV events, CV death, heart failure hospitalization, and incident or worsening nephropathy in the placebo group was 1.2- to 2.0-fold higher for those with baseline OSA compared with those without. Empagliflozin significantly reduced the risk for outcomes regardless of OSA status (*P*-interaction all  $>0.05$ ). Fifty patients reported a new diagnosis of OSA through 7 days after medication discontinuation, and this occurred less often with empagliflozin treatment (hazard ratio 0.48 [95% CI 0.27, 0.83]).

## CONCLUSIONS

In EMPA-REG OUTCOME, participants with OSA had greater comorbidity and higher frequency of CV and renal events. Empagliflozin had favorable effects on risk factors and CV and renal outcomes regardless of preexisting OSA and may also reduce the risk for new-onset OSA.

<sup>1</sup>University Hospitals Harrington Heart and Vascular Institute and Case Western Reserve University School of Medicine, Cleveland, OH

<sup>2</sup>Department of Medicine, University of Gothenburg, Sahlgrenska University Hospital, Gothenburg, Sweden

<sup>3</sup>Department of Cardiovascular Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan

<sup>4</sup>Department of Internal Medicine I (Cardiology), RWTH University Hospital, Aachen, Germany

<sup>5</sup>Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada

<sup>6</sup>Section of Endocrinology, Yale School of Medicine, Yale University, New Haven, CT

<sup>7</sup>Department of Medicine, Wuerzburg University Clinic, Wuerzburg, Germany

<sup>8</sup>Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim am Rhein, Germany

<sup>9</sup>Section of Pulmonary, Critical Care, and Sleep Medicine, Yale School of Medicine, Yale University, New Haven, CT

<sup>10</sup>Boehringer Ingelheim Norway KS, Asker, Norway

Corresponding author: Ian J. Neeland, [ian.neeland@uhhospitals.org](mailto:ian.neeland@uhhospitals.org)

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H.K.Y. and O.E.J. contributed equally to this work.

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Obstructive sleep apnea (OSA) is a common clinical syndrome characterized by intermittent sleep state-dependent collapse of the upper airway, resulting in periodic cessations or reductions in airflow and subsequent hypoxia, hypercapnia, or frequent arousals from sleep (1). Its prevalence in adults is conservatively estimated to be ~3% in women and 10% in men, with higher prevalence with advancing age (e.g., at 50–70 years, 9% in women and 17% in men) (2). OSA is a multifaceted syndrome caused by conditions that reduce the size of the resting pharynx or increase airway collapsibility. Since increased adipose tissue within the soft tissues of the head and neck compromises upper-airway dimensions and makes the airway more prone to collapse during sleep, obesity is the most prevalent risk factor, with OSA reported in >40% of adults with BMI  $\geq 30$  kg/m<sup>2</sup>; other risk factors include male sex, metabolic syndrome, and type 2 diabetes (1). Certain medications, such as opioids, benzodiazepines, and testosterone, may also worsen or induce OSA (3).

OSA and type 2 diabetes frequently occur together, and both are associated with adverse metabolic consequences that increase the risk for cardiovascular disease (CVD) (4), including stroke, myocardial infarction, hospitalization for heart failure (HHF), cardiovascular (CV) death, and all-cause mortality (5,6), as well as the risk for chronic kidney disease (7). Furthermore, OSA may worsen glucose tolerance, impair diabetes management, and lead to poor glycemic control (8). There are no pharmacological therapies currently approved for the treatment of OSA (9), and therapies for OSA have historically been designed to reduce the frequency of sleep-disordered breathing events (e.g., with continuous positive airway pressure [CPAP] devices or surgical procedures) (1). An effective treatment measure, however, involves treatment of the underlying metabolic cause (e.g., obesity), and with guideline-recommended weight loss, OSA has been reported to resolve in >50% of patients (10). Unfortunately, effective and sustained weight loss in people with or at risk for type 2 diabetes using lifestyle approaches alone remains challenging (11).

Empagliflozin is a potent and selective sodium–glucose cotransporter 2 (SGLT2) inhibitor used for the treatment of type 2 diabetes that can significantly improve

multiple metabolic factors associated with OSA, such as glycosylated hemoglobin (HbA<sub>1c</sub>) (12,13), systolic blood pressure (SBP) (14), waist circumference, and body weight (15). In the BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME), a randomized placebo-controlled CV outcomes trial of individuals with type 2 diabetes and established CVD, empagliflozin reduced the risk of 3-point major adverse CV events (3P-MACE) by 14%, CV death by 38%, HHF by 35% (16), and incident or worsening nephropathy by 39% (17). There are currently no randomized controlled trial data of SGLT2 inhibitors reporting outcomes related to OSA. Therefore, we performed a post hoc analysis of the EMPA-REG OUTCOME trial, investigating the prevalence of OSA in the trial cohort; the effects of empagliflozin on metabolic, CV, and renal outcomes according to baseline OSA status; and the effect of empagliflozin on new-onset OSA during the course of the trial among participants without OSA at baseline.

## RESEARCH DESIGN AND METHODS

### Trial Population and Design

The design and conduct of the EMPA-REG OUTCOME study have been published previously (16). Briefly, participants with type 2 diabetes (HbA<sub>1c</sub> 7.0–9.0% [53–75 mmol/mol] for those who are medication naive and 7.0–10.0% [53–86 mmol/mol] for those on stable glucose-lowering therapy), established CVD, and estimated glomerular filtration rate (eGFR)  $\geq 30$  mL/min/1.73 m<sup>2</sup> were randomized to receive empagliflozin 10 mg, empagliflozin 25 mg, or placebo once daily in addition to standard of care and followed for a median of 3.1 years. Background glucose-lowering therapy remained unchanged for the first 12 weeks and was subsequently adjusted at the investigator's discretion to achieve glycemic control. Independent ethics committees or institutional review boards approved the clinical protocol, and participants provided written informed consent before study initiation.

### OSA

Data on the presence of OSA were collected at baseline and during follow-up on the basis of study investigator reports conforming to the Medical Dictionary for Regulatory Activities (MedDRA) version 18.0, a standardized and clinically

validated international medical terminology code. Reporting used the single preferred term sleep apnea syndrome (<https://bioportal.bioontology.org/ontologies/MEDDRA?p=classes&conceptid=10040979>), which included the following synonyms: hypopnea syndrome, obstructive sleep apnea syndrome, central sleep apnea syndrome, sleep apnea, obstructive sleep apnea hypopnea syndrome, hypopnea syndrome, apnea syndrome, sleep apnea, sleep apnea syndrome, obstructive sleep apnea syndrome, apnea syndrome, sleep apnea syndromes, central sleep apnea syndrome, and obstructive sleep apnea hypopnea syndrome, as previously applied by others (18).

### Primary Outcome and Further CVD and Renal End Points

All CVD outcome events, HHFs, and deaths were prospectively adjudicated by independent, blinded clinical events committees. The primary outcome of the main trial was the composite outcome 3P-MACE (death as a result of CV causes, nonfatal myocardial infarction, or nonfatal stroke), with secondary outcomes including HHF, all-cause death, and incident or worsening nephropathy. The latter was defined as progression to macroalbuminuria (urinary albumin-to-creatinine ratio [UACR] >300 mg albumin/g creatinine); a doubling of the serum creatinine level accompanied by an eGFR of  $\leq 45$  mL/min/1.73 m<sup>2</sup>, as calculated by the MDRD equation; the initiation of continuous renal replacement therapy; or death as a result of renal disease. Additional renal outcomes included progression to macroalbuminuria (in patients who did not have macroalbuminuria at baseline) and changes in UACR over time. Participants who prematurely discontinued study medication were followed for ascertainment of CV outcomes and vital status.

### Statistical Analysis

All analyses were performed in participants treated with one or more doses of study medication (modified intention-to-treat [mITT] approach), and all empagliflozin treatment analyses were performed using the pooled empagliflozin treatment groups (10 and 25 mg). Baseline characteristics of those with and without OSA at baseline are presented as mean  $\pm$  SD, and categorical variables are presented as numbers and proportions. Effects of empagliflozin versus

placebo on cardiometabolic risk factors (HbA<sub>1c</sub>, weight, waist circumference, SBP, and log[UACR]) by OSA status at baseline were performed using a mixed-effects repeated-measures model that included terms for the baseline parameter in question and baseline HbA<sub>1c</sub> as linear covariates and geographical region, BMI categories, number of weeks reachable with a post-randomization measurement of the parameter of interest, baseline eGFR 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, baseline HbA<sub>1c</sub>-by-visit interaction, and baseline parameter in question-by-visit interaction as fixed effects. Treatment effects on risks for CVD, HHF, mortality, and renal outcomes between treatment groups by OSA status at baseline were assessed using a Cox proportional hazards model that included terms for age, sex, baseline BMI category, baseline HbA<sub>1c</sub> category, baseline eGFR category, geographical region, treatment, OSA, and treatment-by-OSA interaction.

Kaplan-Meier estimates for time to first OSA event on treatment for participants without OSA at baseline were plotted on the basis of investigator-reported events until treatment end plus an additional 7 days, and a sensitivity analysis using all reported OSA events until study end was done (mITT analysis) to determine consistency of results. Hazard ratios (HRs) comparing time to first OSA were based on a Cox regression model with terms for age, sex, baseline BMI categories, baseline HbA<sub>1c</sub> categories, baseline eGFR categories, geographical region, and treatment.

Baseline characteristics in those who developed OSA versus those who did not were also evaluated, and an exploratory mediation analysis was performed to evaluate whether a treatment-related change in conventional OSA risk factors over time could explain the observed difference in new onset of OSA between empagliflozin and placebo, as previously conducted to analyze mediation effects of empagliflozin on CV deaths (19) (Supplementary Appendix, Section A). Comparisons were not adjusted for multiple testing, and  $P < 0.05$  was considered statistically significant. All statistical analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC).

## RESULTS

Of 7,020 patients with type 2 diabetes and CVD, OSA was reported at baseline in 391 (5.6% overall, placebo 5.4%, pooled empagliflozin doses 5.7%). Compared with participants without OSA at baseline, those with OSA were more likely to be male (82.9% vs. 70.8%), have moderate to severe obesity (BMI  $\geq 35$  kg/m<sup>2</sup>) (55.2% vs. 18.2%), and have greater prevalence of coronary artery disease (88.0% vs. 74.9%). Furthermore, those with OSA had longer diabetes duration, higher rates of insulin use (64.2% vs. 47.3%), and more prevalent use of antihypertensive therapies (98.5% vs. 94.8%) (Table 1).

Over a median 3.1 years, empagliflozin led to similar placebo-adjusted reductions in HbA<sub>1c</sub>, waist circumference, SBP, and UACR (Supplementary Appendix, Section B, and Supplementary Figs. B1–B4), regardless of OSA status at baseline. However, there was a trend for a larger effect of empagliflozin on weight reduction (adjusted for baseline weight) in patients with OSA compared with those without OSA (adjusted mean  $\pm$  SE difference vs. placebo from baseline at week 52,  $-2.9 \pm 0.5$  vs.  $-1.9 \pm 0.1$  kg, and at week 108,  $-3.1 \pm 0.6$  vs.  $-2.0 \pm 0.1$  kg, respectively) (Fig. 1).

During the course of the trial, individuals with baseline OSA in the placebo group experienced 1.2- to 2.0-fold higher incidence rates for 3P-MACE (OSA vs. no OSA 6.49 vs. 4.27/100 patient-years), CV death (2.57 vs. 1.99/100 patient-years), HHF (2.71 vs. 1.38/100 patient-years), all-cause mortality (4.29 vs. 2.78/100 patient-years), incident or worsening nephropathy (9.16 vs. 7.52/100 patient-years), and progression to macroalbuminuria (9.08 vs. 6.36/100 patient-years) (Supplementary Appendix, Section C, and Supplementary Fig. C1). Empagliflozin reduced the risk for CV, HHF, mortality, and renal outcomes regardless of presence of OSA at baseline, with no evidence for heterogeneity of effect ( $P$ -interaction for all  $>0.05$ ) (Fig. 2), except for the risk of progression to macroalbuminuria. Here, there was some indication for a larger magnitude of benefit among those with OSA at baseline (HR 0.32 [95% CI 0.17, 0.60]) versus no OSA at baseline (0.65 [0.56, 0.75];  $P$ -interaction = 0.0312).

Adverse events during trial follow-up among those with and without OSA at

baseline are reported in Supplementary Appendix, Section D, and Supplementary Table D1 and were consistent with observations reported previously (16), regardless of OSA status at baseline. Of note, the reported frequency of nocturia among those with OSA at baseline between those treated with empagliflozin and placebo appeared to be similar (1.9% with empagliflozin vs. 3.2% with placebo).

Fifty participants (representing 25 new cases among 4,421 [0.57%] without OSA at baseline in the empagliflozin group and 25 new cases among 2,208 [1.13%] without OSA at baseline in the placebo group) reported to develop new-onset OSA during the trial until 7 days after study drug discontinuation. Those treated with empagliflozin were 52% less likely to report new OSA (Fig. 3) compared with those treated with placebo (HR 0.48 [95% CI 0.27, 0.83]), with consistent effects also seen in the sensitivity mITT analysis (0.52 [0.30, 0.89]). Baseline characteristics of those who developed OSA (Supplementary Appendix, Section E, and Supplementary Table E1) suggested that these participants had a greater cardiometabolic burden than those who did not develop OSA. In an exploratory analysis for evaluating possible mediators of the treatment difference on new-onset OSA, the effects of empagliflozin on conventional OSA risk factors only partially explained the lower frequency for reporting of new OSA (Supplementary Appendix, Section F, and Supplementary Table F1). Weight reduction alone mediated 16.5%; HbA<sub>1c</sub> reduction alone, 12.2%; hematocrit increase alone, 9.4%; and SBP reduction alone, 8.9%. In a multivariable analysis, only 22.4% of the decreased-onset OSA in the empagliflozin arm was mediated by the treatment's effect on all four conventional risk factors combined.

## CONCLUSIONS

In the EMPA-REG OUTCOME randomized placebo-controlled CV outcomes trial involving participants with type 2 diabetes and established CVD, we found that ~6% of participants had OSA at baseline and that those with OSA experienced higher overall CV and renal event rates during the trial. We observed that empagliflozin improved multiple cardiometabolic risk markers, with a larger effect to reduce body weight among those with prevalent

**Table 1—Baseline characteristics of participants with and without reported prevalent OSA**

	Participants without OSA		Participants with OSA	
	Empagliflozin (n = 4,421)	Placebo (n = 2,208)	Empagliflozin (n = 266)	Placebo (n = 125)
Male sex	3,120 (70.6)	1,572 (71.2)	216 (81.2)	108 (86.4)
Age (years)	63.1 ± 8.6	63.2 ± 8.9	63.7 ± 7.7	63.7 ± 7.3
≥75	405 (9.2)	220 (10.0)	19 (7.1)	8 (6.4)
Region				
Europe	1,841 (41.6)	927 (42.0)	85 (32.0)	32 (25.6)
North America	766 (17.3)	381 (17.3)	166 (62.4)	81 (64.8)
Latin America	720 (16.3)	354 (16.0)	1 (0.4)	6 (4.8)
Africa	206 (4.7)	100 (4.5)	5 (1.9)	2 (1.6)
Asia	888 (20.1)	446 (20.2)	9 (3.4)	4 (3.2)
Diabetes duration (years)				
≤1	125 (2.8)	50 (2.3)	3 (1.1)	2 (1.6)
>1–5	682 (15.4)	360 (16.3)	30 (11.3)	11 (8.8)
>5–10	1,101 (24.9)	543 (24.6)	74 (27.8)	28 (22.4)
>10	2,513 (56.8)	1,255 (56.8)	159 (59.8)	84 (67.2)
HbA <sub>1c</sub> (%)	8.1 ± 0.9	8.1 ± 0.9	8.1 ± 0.9	8.1 ± 0.8
≥9.0 (≥75 mmol/mol)	760 (17.2)	358 (16.2)	52 (19.5)	24 (19.2)
Diabetes medications				
Metformin	3,271 (74.0)	1,653 (74.9)	188 (70.7)	81 (64.8)
Sulfonylurea	1,924 (43.5)	952 (43.1)	90 (33.8)	40 (32.0)
Insulin	2,084 (47.1)	1,052 (47.6)	168 (63.2)	83 (66.4)
TZD	186 (4.2)	97 (4.4)	12 (4.5)	4 (3.2)
DPP-4 inhibitors	493 (11.2)	252 (11.4)	36 (13.5)	15 (12.0)
GLP-1 receptor analogs	100 (2.3)	56 (2.5)	26 (9.8)	14 (11.2)
eGFR (MDRD) (mL/min/1.73 m <sup>2</sup> )	74.5 ± 21.6	74.1 ± 21.1	68.0 ± 20.2	68.4 ± 20.0
<60	1,115 (25.2)	557 (25.2)	97 (36.5)	50 (40.0)
UACR (mg/g), median (IQR)	17.7 (7.1, 70.7)	17.7 (7.1, 74.3)	16.8 (6.2, 80.4)	18.6 (6.2, 74.3)
UACR (mg/g)				
<30	2,638 (59.7)	1,310 (59.3)	151 (56.8)	72 (57.6)
30–300	1,263 (28.6)	635 (28.8)	75 (28.2)	40 (32.0)
>300	475 (10.7)	247 (11.2)	34 (12.8)	13 (10.4)
Missing	45 (1.0)	16 (0.7)	6 (2.3)	0 (0.0)
BMI (kg/m <sup>2</sup> )	30.3 ± 5.1	30.4 ± 5.1	35.5 ± 5.0	36.0 ± 4.9
≥35	808 (18.3)	401 (18.2)	143 (53.8)	73 (58.4)
Weight (kg)	85.1 ± 18.4	85.4 ± 18.4	104.6 ± 18.1	107.6 ± 18.0
Waist circumference (cm)	104.0 ± 13.4	104.2 ± 13.6	116.5 ± 12.6	119.3 ± 13.0
Coronary artery disease	3,315 (75.0)	1,649 (74.7)	230 (86.5)	114 (91.2)
Myocardial infarction	2,078 (47.0)	1,025 (46.4)	112 (42.1)	58 (46.4)
Stroke	1,032 (23.3)	535 (24.2)	52 (19.5)	18 (14.4)
Peripheral arterial disease	927 (21.0)	458 (20.7)	55 (20.7)	21 (16.8)
Heart failure	424 (9.6)	224 (10.1)	38 (14.3)	20 (16.0)
Current smoking	602 (13.6)	289 (13.1)	25 (9.4)	13 (10.4)
SBP (mmHg)	135.3 ± 16.9	135.9 ± 17.3	133.8 ± 17.9	133.1 ± 15.0
DBP (mmHg)	76.7 ± 9.7	76.9 ± 10.1	75.0 ± 9.5	75.2 ± 10.6
Any antihypertensives	4,184 (94.6)	2,098 (95.0)	262 (98.5)	123 (98.4)
ACEi/ARBs	3,571 (80.8)	1,759 (79.7)	227 (85.3)	109 (87.2)
β-Blockers	2,855 (64.6)	1,403 (63.5)	201 (75.6)	95 (76.0)
Diuretics	1,877 (42.5)	914 (41.4)	170 (63.9)	74 (59.2)
Antihypertensives (n)				
0	237 (5.4)	110 (5.0)	4 (1.5)	2 (1.6)
1	832 (18.8)	423 (19.2)	29 (10.9)	11 (8.8)
2	1,379 (31.2)	737 (33.4)	72 (27.1)	36 (28.8)
3	1,160 (26.2)	548 (24.8)	82 (30.8)	51 (40.8)
>3	813 (18.4)	390 (17.7)	79 (29.7)	25 (20.0)
Total cholesterol (mg/dL)	164.3 ± 44.4	162.6 ± 43.5	150.5 ± 38.3	149.6 ± 31.8
LDL cholesterol (mg/dL)	86.6 ± 36.1	85.4 ± 35.6	74.2 ± 30.7	74.5 ± 27.9
HDL cholesterol (mg/dL)	44.8 ± 11.9	44.3 ± 11.4	40.4 ± 11.3	40.0 ± 8.9
Triglycerides (mg/dL), median (IQR)	141.7 (102.7, 195.7)	139.9 (104.5, 200.2)	158.5 (116.0, 217.0)	160.3 (110.7, 217.0)

Continued on p. 3011

**Table 1—Continued**

	Participants without OSA		Participants with OSA	
	Empagliflozin (n = 4,421)	Placebo (n = 2,208)	Empagliflozin (n = 266)	Placebo (n = 125)
Any lipid-lowering medications	3,580 (81.0)	1,755 (79.5)	240 (90.2)	109 (87.2)
Statins	3,404 (77.0)	1,672 (75.7)	226 (85.0)	101 (80.8)
Fibrates	386 (8.7)	178 (8.1)	45 (16.9)	21 (16.8)
Ezetimibe	171 (3.9)	73 (3.3)	18 (6.8)	8 (6.4)
Aspirin	3,646 (82.5)	1,818 (82.3)	230 (86.5)	109 (87.2)
Vitamin K antagonists	242 (5.5)	146 (6.6)	24 (9.0)	10 (8.0)

Data are n (%) or mean ± SD unless otherwise indicated. ACEi, ACE inhibitor; ARB, angiotensin receptor blocker; DBP, diastolic blood pressure; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; IQR, interquartile range; TZD, thiazolidinedione.

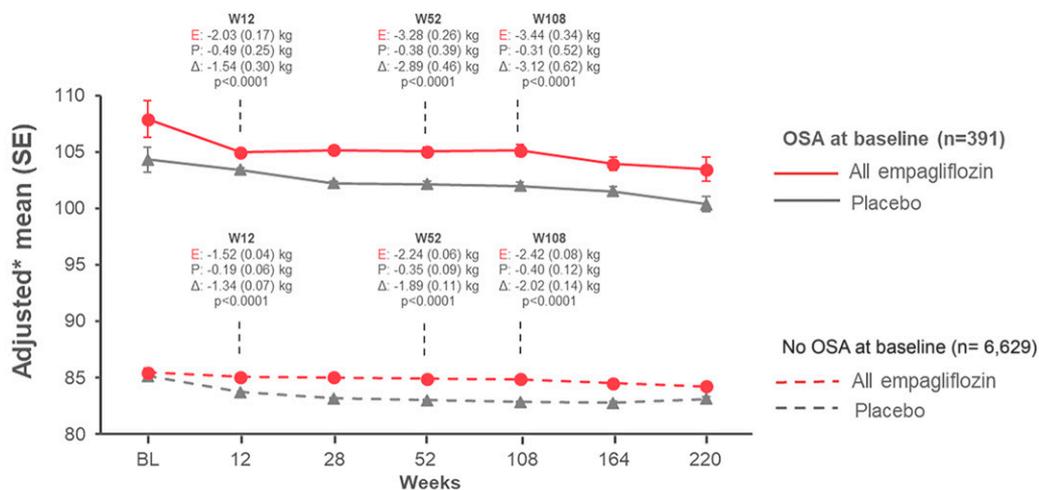
OSA. Furthermore, empagliflozin significantly reduced the risk for CV, HHF, mortality outcomes, and incident or worsening nephropathy, regardless of OSA status, consistent with the results in the overall study population. There was some evidence of a larger magnitude of effect on reducing the progression to macroalbuminuria. Furthermore, we found that empagliflozin may reduce the incidence of new-onset OSA among those without OSA at baseline and that this effect might be only partially attributable to its effects on conventional OSA risk factors. To our knowledge, this is the first report of outcomes related to OSA in a randomized controlled trial of SGLT2

inhibition. Given the increasing global burden of type 2 diabetes and obesity (20) and the lack of effective pharmacological treatments for OSA, these observations should prompt further study of SGLT2 inhibition as a therapeutic strategy for patients with type 2 diabetes and OSA.

The 6% prevalence of OSA in EMPA-REG OUTCOME is lower than expected on the basis of a study population with a mean age of 63 years and mean BMI of 30.6 kg/m<sup>2</sup> (21). This may be because OSA is systematically underdiagnosed since it is notoriously difficult to diagnose and classify (22) and often not prioritized during busy clinic visits (23–25), leading

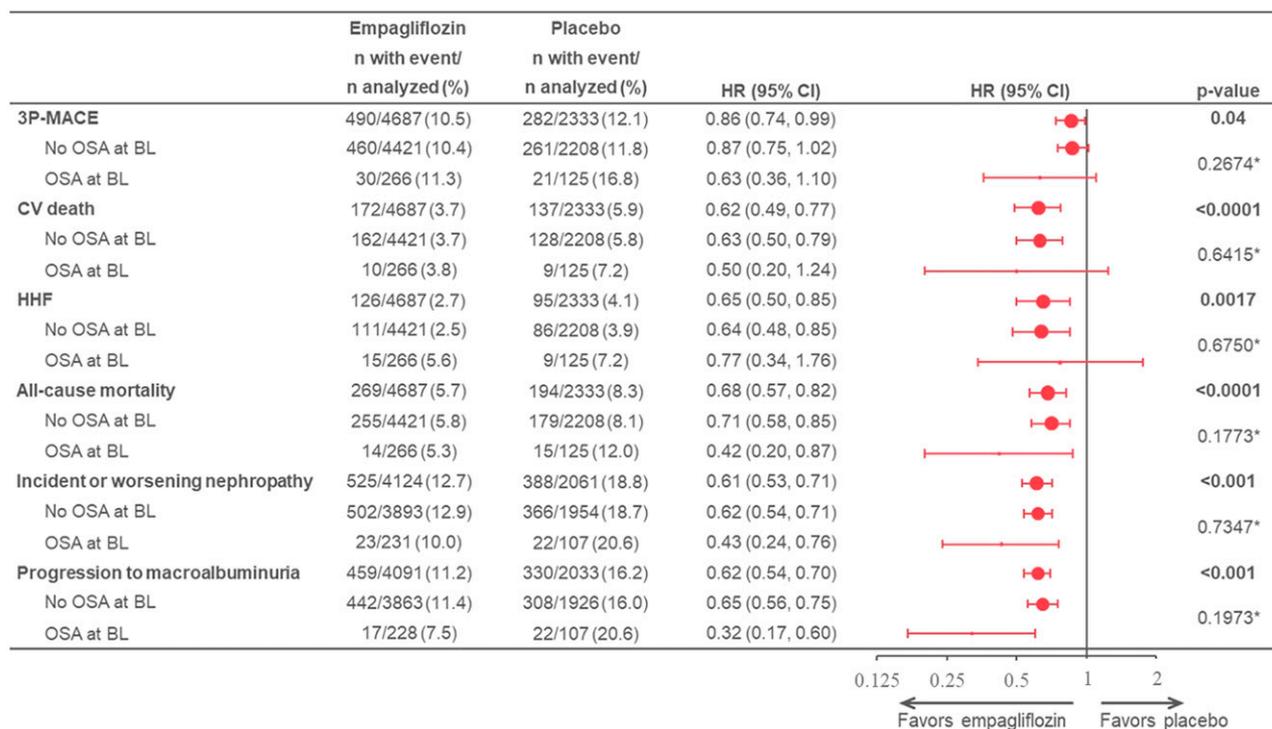
to low reporting in trials (26). Nevertheless, as reported by others (27), we found in individuals with type 2 diabetes a consistently higher cardiometabolic burden associated with baseline OSA (e.g., higher BMI, higher utilization of insulin and antihypertensive medication, more prevalent CVD, and higher event rates for CV and heart failure outcomes).

From a mechanistic perspective, OSA in type 2 diabetes is believed to contribute to both intermittent hypoxia during sleep and frequent fragmentation of sleep patterns, which in turn promote deleterious effects on metabolic health. Multiple mechanistic pathways have been implicated, including increased



OSA at baseline (n=391)	Empagliflozin	261	212	256	247	185	134	50
	Placebo	121	96	116	107	74	56	19
No OSA at baseline (n=6629)	Empagliflozin	4312	3572	4208	4105	3166	2499	922
	Placebo	2164	1819	2099	2031	1524	1183	406

**Figure 1**—Effects of empagliflozin treatment on body weight by OSA status at baseline. Model reflects a mixed-model repeated-measures analysis that included terms for baseline weight and baseline HbA<sub>1c</sub> as linear covariates and baseline eGFR category, geographical region, baseline BMI category, number of weeks reachable with a postrandomization weight measurement, treatment, visit, sleep apnea syndrome at baseline, treatment-by-visit interaction, visit-by-sleep apnea syndrome at baseline interaction, treatment-by-sleep apnea syndrome at baseline interaction, treatment-by-visit by sleep apnea syndrome at baseline interaction, baseline HbA<sub>1c</sub>-by-visit interaction, and baseline weight-by-visit interaction as fixed effects. P values indicated are for differences in change between empagliflozin and placebo at respective time points. \*Adjusted mean (SE) changes from baseline by OSA status at baseline. BL, baseline; E, empagliflozin; P, placebo; W, week.



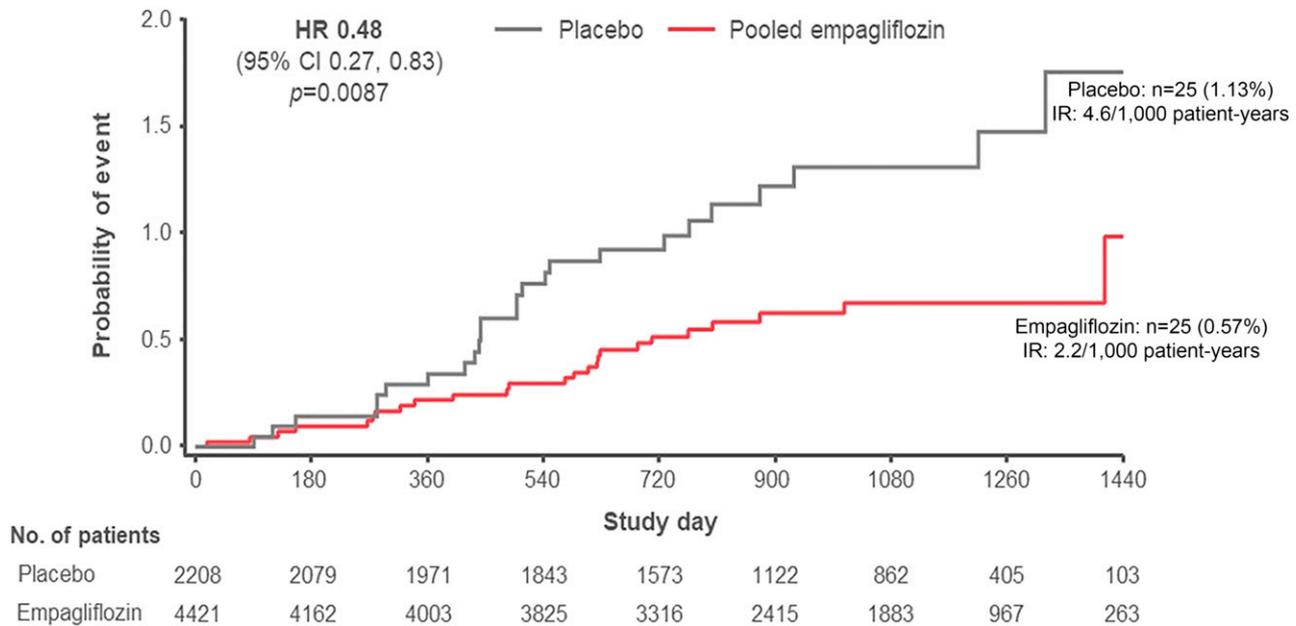
**Figure 2**—Effects of empagliflozin treatment on CV, HHF, mortality, and renal outcomes by OSA status at baseline (BL). Events and HRs (95% CIs) for empagliflozin treatment on 3P-MACE, CV death, HHF, all-cause mortality, incident and worsening nephropathy, and progression to macroalbuminuria both overall (indicated in bold) and by OSA status at BL. Cox model includes age, sex, region, BL eGFR, BL BMI, BL HbA<sub>1c</sub>, treatment, OSA at BL, and treatment-by-OSA at BL interaction. \*P-interaction.

sympathetic activation, oxidative stress, systemic inflammation, hypothalamic pituitary axis activation, and adipokine dysregulation (28), with each of these factors more highly prevalent in obese states (29). Indeed, a small, open-label, single-arm study in Japanese patients with moderate to severe OSA, obesity, and diabetes showed improved metabolic parameters and less oxygen desaturation events with low-dose dapagliflozin administered over 24 weeks (30). In the current trial, empagliflozin treatment improved several metabolic end points in participants with OSA, with a trend for a larger effect on weight loss among those with baseline OSA, and may also reduce new-onset OSA. Empagliflozin is known to improve body weight and several indices of visceral adiposity (15), with greater effects on weight loss among those with higher baseline weight, which may in part explain its effects on metabolic parameters and reduced risk for new-onset OSA. However, we adjusted for baseline BMI in our analysis and continued to observe a lower frequency of new-onset OSA, suggesting that the observed weight loss may have included changes in total body water in addition to adipose

tissue. Indeed, empagliflozin has modest diuretic and natriuretic effects and may improve OSA symptoms by reducing intrathoracic fluid retention (31) and rostral fluid shifts from the legs (32) and influence sodium handling by the kidneys (33). An alternative consideration is that a modest increase in urinary frequency with empagliflozin treatment, manifested nocturnally as nocturia, might have led to interrupted sleep cycles and decreasing the duration of rapid eye movement (REM) sleep. REM sleep is a higher risk period for OSA events (34), and a decrease in REM sleep would lead to fewer observed apneic events, leading to a potential ascertainment bias. However, since the frequency of nocturia in EMPA-REG OUTCOME was relatively balanced between treatment groups, we do not believe that this is a likely explanation for the results.

There are no pharmacological therapies currently approved for the treatment of OSA (9), and most investigations have focused on medications that can influence mechanisms like increasing the tone in the upper-airway dilator muscles, increasing ventilatory drive, reducing the proportion of REM sleep, increasing

cholinergic tone during sleep, increasing arousal threshold, reducing airway resistance, or reducing surface tension in the upper airway. Several medication classes that are known to have beneficial effects on body weight and/or glycemic control have been studied in randomized controlled trials with varying results (9). Extended-release phentermine/topiramate (approved for long-term weight reduction) was investigated in a single-center study of 45 patients with moderate to severe OSA not receiving CPAP therapy. After 28 weeks of therapy, extended-release phentermine/topiramate reduced weight by ~10% (placebo corrected ~6%) and improved change in the apnea-hypopnea index (AHI) by ~15 events (35). Liraglutide 3.0 mg (also approved for long-term weight reduction) was studied in 359 patients with moderate to severe OSA not receiving CPAP therapy; after 32 weeks of therapy, liraglutide reduced weight by ~4% (vs. placebo) and significantly reduced the AHI by approximately six events (36). Although post hoc and not directly comparable to these studies, in the EMPA-REG OUTCOME trial, empagliflozin reduced weight by ~2.5–3.0 kg in patients with baseline OSA (~2.5% from baseline), yet empagliflozin treatment was



**Figure 3**—Kaplan-Meier estimates for time to first OSA event on treatment for patients without OSA at baseline. OSA events are based on investigator-reported events (MedDRA version 18.0) until treatment end plus an additional 7 days. HRs are based on a Cox regression model with terms for age, sex, baseline BMI categories, HbA<sub>1c</sub> categories, eGFR categories, geographical region, and treatment. Empagliflozin estimates correspond to pooled treatment groups. IR, incidence rate.

associated with a 52% lower reported frequency of new-onset OSA.

With regard to mechanisms, when we performed a mediation analysis to further investigate what factors may have contributed to the lower hazard for OSA, we found that only ~22% of the lower risk was attributable to the combined change in conventional risk factors, with the majority being due to weight loss. Thus, the majority of the empagliflozin effect on lower incidence of OSA may be mediated directly or indirectly by empagliflozin through factors not assessed in the trial.

There are several strengths of this study over prior work that add to our understanding of OSA, type 2 diabetes, and CVD. To our knowledge, this is the first report of outcomes related to OSA in a randomized controlled trial of SGLT2 inhibition, albeit in a post hoc, exploratory analysis. Second, all CV outcomes were prospectively adjudicated by independent, blinded clinical events committees, ensuring accurate and complete event reporting. Third, use of a mediation analysis allowed us to explore potential explanatory factors contributing to our prospective findings of lower new-onset OSA frequency with empagliflozin. Several limitations also merit comment. First, since the diagnosis of OSA was

based on patient/investigator report rather than on systematic prospective polysomnography, the reported diagnosis is likely to be accurate/specific (i.e., low likelihood of false positives) but under-identified in patients without a prior sleep study. Thus, the prevalence of OSA in our population was lower than that expected in the general population, although under-reporting in patients without a prior formal sleep study should be independent of randomized treatment. As such, it should not introduce a bias in the measured relative risk reduction between the two treatment arms. Second, since AHI was not prospectively measured in EMPA-REG OUTCOME, we are unable to comment on OSA severity with empagliflozin treatment. Third, we are unable to report on how participants were treated (CPAP vs. other treatments) for OSA during the course of the trial and how adherent they were to OSA therapies. Consequently, we are unable to determine to what extent a lack of sleep apnea treatment may have hindered weight loss and associated cardiometabolic benefits, thereby influencing our results. Fourth, since there are no AHI data to verify sleep apnea type or severity, and the MedDRA identifier code does not differentiate between OSA and central sleep apnea (CSA), we are unable to report the differential effects of

empagliflozin on OSA versus CSA. However, since the prevalence of OSA is substantially higher than CSA in the general population, and both entities have adverse consequences, the overall findings remain pertinent. In summary, our findings are exploratory and should be understood to be hypothesis generating only; further prospective assessment of SGLT2 inhibition in OSA should be performed to confirm our results.

In conclusion, patients with type 2 diabetes, established CVD, and baseline OSA had greater cardiometabolic comorbidity and higher frequency of 3P-MACE, HHF, mortality, and renal outcomes in the EMPA-REG OUTCOME trial. Empagliflozin had favorable effects on cardiometabolic risk factors and consistently reduced risk for 3P-MACE, HHF, mortality, and renal outcomes in those with and without OSA at baseline. Furthermore, we found that empagliflozin could reduce the risk for new-onset OSA and that this additional potential benefit of empagliflozin could be partially independent of its effects on traditional OSA risk factors. Prospectively powered randomized controlled trials, including objective assessments of OSA using polysomnography (e.g., AHI, apnea severity, sleep efficiency, periodic limb movement, differentiation of OSA vs.

CSA) are needed to further inform the effectiveness and limitations of novel therapies such as SGLT2 inhibition for OSA to treat residual CV risk related to OSA in this high-risk patient population.

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Boehringer Ingelheim was involved in the design and conduct of the study; collection, analysis, and interpretation of data; and preparation of the manuscript.

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