RESPONSE TO COMMENT ON NEELAND ET AL.

The Impact of Empagliflozin on Obstructive Sleep Apnea and Cardiovascular and Renal Outcomes: An Exploratory Analysis of the EMPA-REG OUTCOME Trial. Diabetes Care 2020;43:3007–3015

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We acknowledge the thought-provoking hypothesis that Brikman and Dori (1) suggest to explain the lower incidence of new-onset obstructive sleep apnea (OSA) observed among participants treated with empagliflozin compared with placebo we recently reported. They suggest that sodium–glucose cotransporter 2 inhibition (SGLT2i) decreases endogenous carbon dioxide (CO_2) through a shift in metabolic substrate away from carbohydrates and toward utilization of lipids and proteins, leading to a lower concentration of CO_2 in the pulmonary circulation and lower likelihood of apneic events during sleep. While the mechanisms explaining our observations remain unknown and open to discussion, we disagree with the physiological description proposed and believe this hypothesis is unlikely to be correct.

First, alkalization of the blood through lower CO_2 production should decrease, not increase, ventilatory drive as the apneic threshold is approached. This might lead to actual induction of central sleep apnea and reduced upper airway muscle tone. In fact, several studies have investigated the use of acetazolamide, a carbonic anhydrase inhibitor that increases urinary bicarbonate excretion leading to acidification of the blood, to treat central sleep apnea by causing compensatory hyperventilation (the opposite of Brikman and Dori's proposed mechanism) (2). One might speculate that diminished respiratory drive and reduced upper airway muscle tone could actually lead to a higher incidence of new-onset OSA in the SGLT2i-treated group. Decreased ventilatory drive would increase both the severity and frequency of apneic events, leading to increased awakenings and less opportunity to achieve more restorative sleep. Patients with more apneic events would have poorer quality sleep and would likely be referred to sleep physicians, undergo more sleep studies, and have more diagnosed OSA. This effect would be magnified among patients with obesity hypoventilation syndrome because these patients have reduced CO_2 chemosensitivity at baseline.

Second, if endogenous CO_2 production is significantly decreased with SGLT2i, one would expect to see a commensurate decrease in bicarbonate to maintain normal blood pH. However, we did not observe any changes in bicarbonate or other electrolytes in a pooled empagliflozin safety analysis (3) or in the BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME).

Third, the substrate utilization switch is unlikely to be dramatic enough to cause a clinically significant decrease in endogenous CO_2, with only modest increases in free fatty acids and ketone bodies observed with treatment. Furthermore, SGLT2i therapy increases hepatic glucose production (4), blunting any need to burn alternative fuels, and may also induce a preference for carbohydrate ingestion, which might further offset a switch away from carbohydrates toward other substrates (5).

Although we believe their proposed mechanism is unlikely, we agree that there are likely several plausible mechanisms to explain our findings, including a decrease in the rostral-to-caudal fluid shifts in the recumbent sleep position (a known mechanism of OSA) as well as modulation of other nonanatomic physiologic traits of sleep apnea such as arousal threshold, loop gain, or muscle compensation, all of which deserve further study. We hope additional investigations will verify and elucidate our finding that SGLT2i may reduce new-

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onset OSA among adults with type 2 diabetes.

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