



RESPONSE TO COMMENT ON FERRANNINI ET AL.

CV Protection in the EMPA-REG OUTCOME Trial: A “Thrifty Substrate” Hypothesis. *Diabetes Care* 2016;39:1108–1114

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Jordan et al. (1) propose a further loop to the β -hydroxybutyrate hypothesis by recalling that atrial natriuretic peptide (ANP) induces an increase in lipid oxidation and a ketone response by virtue of its intrinsic lipolytic properties. Elegant work in healthy subjects has found that graded infusions of ANP, raising circulating ANP levels up to 10-fold, are associated with enhanced lipolysis and lipid oxidation rates with no change in energy expenditure (2). The highest intravenous dose of ANP also lowered blood pressure (3)—to a similar extent as do sodium–glucose cotransporter 2 (SGLT2) inhibitors—through increased diuresis and natriuresis. We do not know whether the findings from these acute experiments translate into chronic, physiologically significant effects in patients with diabetes, in whom substrate utilization is already shifted in favor of lipid. Presumably, however, the segment of the BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial population with prevalent or incident heart failure would have had markedly elevated plasma ANP levels, which have been shown to retain the ability to induce the sequence lipolysis–ketogenesis–thrifty substrate supply to the heart (cited

in ref. 1). This part of the argument by Jordan et al. (1) therefore is pertinent and plausible. However, the question remains whether and how SGLT2 inhibition might interfere with the ANP system (natriuretic peptides were not measured in the EMPA-REG OUTCOME trial or any other preclinical or clinical study of SGLT2 inhibitors that we could find). Do SGLT2 inhibitors change ANP levels (or brain natriuretic peptide levels or both) and, if so, in what time course? Is this mechanism operative in heart failure with preserved or reduced ejection fraction? Are there differences in this putative effect between heart failure and other categories of cardiovascular risk? In the acute ANP infusion studies (3), the decrease in blood pressure was accompanied by a proportionate rise in heart rate, which typically is not seen with SGLT2 inhibition. Also, plasma aldosterone concentrations fell by ~40% in response to ANP infusion (4), whereas they were found to be increased by ~30% in patients with type 1 diabetes after 8 weeks of empagliflozin treatment (5).

Clearly, multiple pieces of the complete ANP hypothesis by Jordan et al. (1) are still missing and will undoubtedly be written in by ongoing or future

mechanistic studies. Definitely one merit of the EMPA-REG OUTCOME trial is that it raises old and new questions, all relevant to the prospect of improving the cardiovascular and renal prognosis of high-risk patients with diabetes.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

References

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