



Response to Comment on Ferrannini et al. Diabetes Care 2016;39:1108–1114. Comment on Mudaliar et al. Diabetes Care 2016;39:1115–1122

Diabetes Care 2016;39:e196–e197 | DOI: 10.2337/dci16-0027

Ele Ferrannini,¹ Michael Mark,² and
Eric Mayoux²

Ceriello et al. (1) argue that the cardiovascular benefit documented in the BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) study may be due to direct actions of glucagon on myocardial function. We regard this hypothesis as unlikely. Because of the widespread tissue distribution of its receptors, glucagon has been credited with exerting cardiovascular and renal actions in addition to its classical effects on liver and brain. In early studies of heart–lung preparations, glucagon increased heart rate and contractility in a dose-dependent manner. In intact animals, glucagon increased splanchnic and renal blood flow and glomerular filtration rate; reduced peripheral vascular resistance and enhanced natriuresis and kaliuresis were the main physiological consequences (2). However, careful analysis of the literature reveals that these effects 1) show large species differences (in some species, glucagon only activates auricular but not ventricular muscle), 2) have generally been documented using supraphysiological hormone levels (in the 10^{-6} to 10^{-8} mol/L range), and 3) resemble those of a β -adrenergic agonist (2). Studies in humans (reviewed in ref. 2) have concluded that the doses of glucagon required to produce hemodynamic effects produced plasma glucagon concentrations that would not be observed under either normal or pathological conditions. Likewise,

Sherwin et al. (reviewed in ref. 2) were unable to demonstrate a significant change in renal electrolyte and water excretion when plasma glucagon levels were raised within the physiological limits. With empagliflozin, the natriuretic effect is transient (typically, less than 1 month) (3). Furthermore, by increasing heart rate and cardiac oxygen consumption, glucagon might actually have deleterious effects under conditions of coronary ischemia (4). In patients with heart failure, the use of positive inotropic agents for heart failure is controversial: despite improving hemodynamic parameters, positive inotropic agents have not demonstrated improved outcomes (5). Clinically, the use of large intravenous doses of glucagon is probably limited to overdose of β -blockers and calcium channel blockers.

In overnight fasted humans, plasma glucagon concentrations are in the 10^{-12} mol/L range (6). Following administration of sodium–glucose cotransporter 2 inhibitors, plasma glucagon levels rise $\sim 25\%$; this change is consistent but appears to attenuate with chronic treatment (6). Thus, it is unlikely that any detectable cardiovascular effects could be attributed to such hormone concentrations. Even if this were the case, the best established effects of pharmacological doses of glucagon (increase in heart rate and glomerular filtration rate) are the opposite of the

changes documented with long-term empagliflozin treatment in EMPA-REG OUTCOME (where heart rate was stable despite a fall in arterial blood pressure and glomerular filtration rate was slightly but consistently decreased). In our hypothesis (6), we posit that the empagliflozin-induced modest rise in plasma glucagon coupled with a concomitant decrease in plasma insulin is sufficient to drive lipolysis and ketogenesis, thereby leading to the emergence of a metabolic signal (raised circulating β -hydroxybutyrate concentrations) postulated to be cardioprotective.

In conclusion, the hypothesis that glucagon may be responsible for the cardiovascular outcome of EMPA-REG OUTCOME through its direct actions on the heart and vasculature is not supported by glucagon pharmacology nor does it fit with the physiological changes detected in the trial.

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

References

1. Ceriello A, Genovese S, Mannucci E, Gronda E. Comment on Ferrannini et al. Diabetes Care 2016;39:1108–1114. Comment on Mudaliar et al. Diabetes Care 2016;39:1115–1122 (Letter). Diabetes Care 2016;39:e195. DOI: 10.2337/dci16-1332
2. Farah AE. Glucagon and the circulation. Pharmacol Rev 1983;35:181–217
3. Scheen AJ. Reappraisal of the diuretic effect of empagliflozin in the EMPA-REG OUTCOME

¹CNR Institute of Clinical Physiology, Pisa, Italy

²Cardiometabolic Disease Research, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany

Corresponding author: Ele Ferrannini, ferranni@ifc.cnr.it.

© 2016 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at <http://www.diabetesjournals.org/content/license>.

trial: comparison with classic diuretics. *Diabetes Metab* 2016;42:224–233

4. Maroko PR, Kjekshus JK, Sobel BE, et al. Factors influencing infarct size following experimental coronary artery occlusions. *Circulation* 1971;43:67–82

5. Yancy CW, Jessup M, Bozkurt B, et al.; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart

Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;62:e147–e239

6. Ferrannini E, Mark M, Mayoux E. CV protection in the EMPA-REG OUTCOME trial: a “thrifty substrate” hypothesis. *Diabetes Care* 2016;39:1108–1114