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

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





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 ~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.

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