



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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In a recent issue of *Diabetes Care*, Ferrannini et al. (1) postulated a “thrifty substrate” hypothesis suggesting that the benefit in heart failure outcomes in patients treated with the sodium–glucose cotransporter 2 (SGLT2) inhibitor empagliflozin in the BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial is at least in part due to a switch in myocardial substrate metabolism away from fat and glucose oxidation toward an “energy-efficient super fuel like ketone bodies” (2). According to the authors, ketones improve myocardial work efficiency and function specifically in the failing heart (1,2). Indeed, evidence suggests that in heart failure, ketone use by the heart increases compared with other tissues. Ketones enhance mitochondrial function, and the failing heart switches substrate oxidation rates from fatty acids to ketone bodies, lowering oxygen demand. The authors speculate that this mechanism together with natriuresis and diuresis induced by inhibition of SGLT2, as well as the blood pressure lowering effect, may explain the preferential heart failure outcome in the EMPA-REG OUTCOME trial (1,2).

In response to a volume overload, the heart is not only in need of energy

but also secretes counterregulatory hormones, namely atrial natriuretic peptide (ANP) and brain natriuretic peptide. ANP acts by binding its cognate receptor A, a transmembrane guanylyl cyclase hydrolyzing cyclic guanosine monophosphate, on endothelial cells, kidney, heart, brain, and adipose tissue. It is well established that ANP induces natriuresis and diuresis, reducing blood pressure, similar to SGLT2 inhibitors (3). By this mechanism, ANP lowers cardiac preload and afterload and thus myocardial congestion and oxygen demand of the myocardium.

Besides these similarities to SGLT2 inhibition, we observed an intriguing metabolic link: our group showed previously that ANP also markedly increases ketone levels in human subjects (4). The ANP-induced increase in circulating ketones was secondary to fatty acid mobilization in adipose tissue (4), an effect termed lipolysis, which is also increased when patients are treated with SGLT2 inhibitors (1). Interestingly, we also observed that the lipolytic effect of ANP is preserved in adipose tissue when ANP is chronically increased in patients with heart failure with reduced ejection fraction, excluding the possibility that adipocytes desensitize to the lipolytic action of ANP (5). Since ANP is markedly increased in heart failure,

it is tempting to speculate that this mechanism serves as a rescue strategy of the heart to secure its energy demand (3).

Together with our previous work and in the light of the elegant thrifty substrate hypothesis by Ferrannini et al. (1), we hypothesize that the heart possesses an endocrine factor, ANP, to cope with increased energy demand as observed in heart failure (3). Accordingly, in conditions with cardiac congestion, the heart secretes ANP. ANP induces lipolysis in adipose tissue and ketogenesis in the liver (4). Ketones reach the heart via the circulation, supplying the heart with oxygen-efficient substrates. This may be a crucial mechanism for the failing heart, an “engine out of fuel” (2), to secure its energy supply. The natriuretic peptide system may be an ideal target for the treatment of cardiometabolic disease (3).

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

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