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EDITORIAL COMMENT

The Enigmata of Cardioprotection With SGLT2 Inhibition

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The inhibition of sodium-glucose cotransporter 2 (SGLT2) provides clinical cardiovascular outcome benefits not only in diabetic patients but also in patients with cardiovascular disease and no diabetes. These benefits include decreased all-cause mortality and decreased hospitalization for heart failure. The clinical benefits for patients with acute myocardial infarction are not clear or consistent so far. In EMMY (Impact of Empagliflozin in Cardiac Function and Biomarkers of Heart Failure in Patients With Acute Myocardial Infarction), left ventricular function was improved. In DAPA-MI (Dapagliflozin Effects on Cardiometabolic Outcomes in Patients With Acute Heart Attack), no benefit on mortality or heart failure hospitalization was seen. In EMPACT-MI (Study to Evaluate the Effect of Empagliflozin on Hospitalization for Heart Failure and Mortality in Patients With Acute Myocardial Infarction), no benefit on a composite of mortality and heart failure hospitalization was reported; however, empagliflozin reduced the risk for first and total heart failure hospitalization. In preclinical studies, infarct size was the major endpoint, and with SGLT2 inhibition by canagliflozin, dapagliflozin, and empagliflozin, it was reduced in mice, rats, and pigs without and with diabetes. Surprisingly, the infarct size reduction required chronic oral pretreatment with SGLT2 inhibition but was not seen with acute pretreatment.[1] Even more surprisingly, the infarct size reduction by chronic oral empagliflozin was also evident in transgenic mice lacking the SGLT2 receptor.[2]

The mechanisms underlying these off-target effects of SGLT2 inhibition in cardioprotection are still mysterious. A number of previously identified and established cardioprotective signal transduction steps were suggested, mostly by investigators who have previously worked on such cardioprotective signaling—that is, sodium-proton exchange inhibition,[3] attenuation of oxidative stress,[4] more favorable metabolism involving ketones[4] and mitochondrial respiration,[5] signal transducer and activator of transcription 3 (STAT3) activation,[5,6] inhibition of the inflammasome, and autosis.[7]

The study by Nikolaou et al[8] in this issue of *JACC: Basic to Translational Science* adds to these mechanisms by focusing on the role of endothelial cells in cardioprotection and rightfully extending the endpoint of cardioprotection from infarct size to coronary microvascular injury. More specifically, the study revealed the following: 1) there was major deregulation of transcriptomics in endothelial cells, fibroblasts, and cardiomyocytes by reperfused myocardial infarction, and empagliflozin mainly restored these alterations in endothelial cells—the identified RNA expression changes related to growth factors, adhesion molecules, and matrix metalloproteinases; 2) not only pre- but surprisingly also posttreatment of empagliflozin in mice reduced infarct size and no-reflow and preserved left ventricular function—also, inflammatory infiltration and capillary destruction were attenuated; and 3) patients with empagliflozin rather than insulin had improved flow-mediated brachial artery vasodilation, reduced sublingual glycocalyx thickness at 4 months, reduced global longitudinal strain at 4 and 12 months, and reduced thrombomodulin at 4 months and intercellular adhesion molecule at 4- and 6-month follow-ups.

This is a composite data set of data from mice and diabetic patients that all, however, support a cardioprotective role of empagliflozin in myocardial

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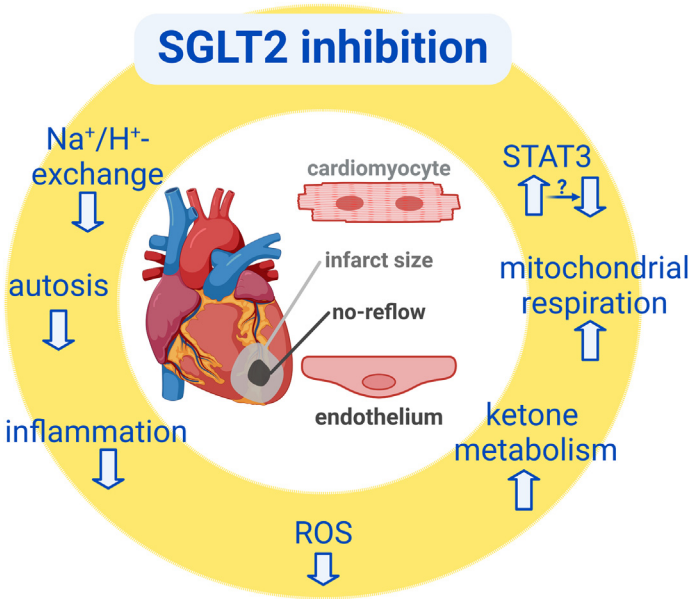
ischemia/reperfusion with a preferential effect on endothelium and coronary microvascular integrity. The mechanistic strength of these data sets varies widely. The bioinformatic associations of RNA sequencing data with biological signals and mechanisms should not be taken for real data because they are based on often unknown and in part only remotely related literature. Importantly, therefore, the reduced expression of intercellular adhesion molecule and matrix metalloproteinases by empagliflozin pretreatment was confirmed on the protein level after 48 hours of reperfusion. Still, proof for a causal role of these proteins would then require their genetic knockout or pharmacologic antagonism. The ambivalent role of STAT3 in myocardial ischemia/reperfusion with a protective role of activation in early reperfusion and a deleterious role of activation in later reperfusion is in line with current concepts on STAT3.[9] Still, it is somewhat surprising that empagliflozin would activate STAT3 at early reperfusion[5,6] and inhibit STAT3 at later reperfusion (as in the present study[8])—a new enigma.

The clinical data are derived from only a small cohort of diabetic patients who were pretreated with metformin, which is cardioprotective per se, and empagliflozin was compared to insulin, which is also cardioprotective per se. The perfusion boundary data of sublingual microvessels and carotid-femoral pulse wave velocity data are only remotely related to cardioprotection. Improvement of flow-mediated dilation in the forearm by empagliflozin is more solid evidence for better endothelial function, and circulating biomarkers are supportive but still no proof for better coronary endothelial function in infarcting myocardium. The strongest and most robust data are the in vivo mouse data on infarct size, no-reflow, inflammation, and capillary integrity/injury, which clearly demonstrate reduced injury both with pre- and posttreatment with empagliflozin. Here, the posttreatment effect of empagliflozin is opposite to the current notion that cardioprotective interventions must be installed in the first few minutes of reperfusion and no later to be effective[10]—another new enigma. At this point, it is not clear which one of these itemized mechanisms is causal for cardioprotection by SGLT2 inhibition, and—if several of them are involved—how they interact (Figure 1).

It is definitely important to further consider the protective effects of SGLT2 inhibition not only on cardiomyocytes but also on endothelial and other vascular cells, and such vasculoprotective effects may—as in cardiomyocytes—include sodium-proton exchange inhibition, attenuation of oxidative stress, and early STAT3 activation or later STAT3 inhibition. Coronary microvascular injury must now be considered as an integral part of the injury by acute myocardial infarction. It remains to be seen how the novel and important data of the present study translate to larger animal models and, finally, to humans who would receive empagliflozin after reperfused acute myocardial infarction.

FIGURE 1 Potential Mechanisms of SGLT2 Inhibition in Protection of Cardiomyocytes and Endothelial Cells From Myocardial Ischemia/Reperfusion Injury



Created with BioRender.com. ROS = reactive oxygen species, SGLT2 = sodium-glucose cotransporter 2; STAT3 = signal transducer and activator of transcription 3.

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