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Response to Letter Regarding the Article: "Sodium Glucose Cotransporter-2 Inhibition in Heart Failure: Potential Mechanisms, Clinical Applications and Summary of Clinical Trials"

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To the Editor

We thank Dr. Grocott for his comments regarding our recent review of sodium-glucose cotransporter-2 (SGLT2) inhibitors in *Circulation*[1]. We fully agree that although rare, there is a potential increased risk for the development of serious adverse effects with SGLT2 inhibitors that warrant special attention and monitoring in the perioperative setting, such as diabetic ketoacidosis and issues related to volume depletion[1]. As outlined elsewhere, we have discussed possible contributory mechanisms and have suggested management approaches for patients taking SGLT2 inhibitors perioperatively to avoid these rare but potentially serious adverse effects[2, 3]. In brief, in addition to reduced carbohydrate availability due to glucosuria leading to ketogenesis, patients with type 2 diabetes are frequently instructed to reduce or hold basal insulin doses to avoid hypoglycemia in the perioperatively and are frequently asked to fast – both of these physiological factors can increase the risk of ketoacidosis due to insufficient insulinization. Furthermore, SGLT2 inhibitors increase glucagon secretion from alpha cells. The net decrease in the ratio of insulin to glucagon levels in plasma promotes ketone generation. As indicated by Dr. Grocott, due to ongoing SGLT2 inhibitor-induced glucosuria, clinicians also need to be

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aware of the possibility that ketogenesis can progress to ketoacidosis, even in the presence of relatively normal blood glucose levels. This unusual, relatively "euglycemic" presentation of diabetic ketoacidosis, with blood glucose levels in the 8–15 mmol/L (145–270 mg/dl) range, could delay the timely diagnosis and treatment of this complication due to overlap between non-specific post-operative symptoms with those of diabetic ketoacidosis[2, 3].

Aside from being aware of this rare but potentially serious risk with SGLT2 inhibitor use and the atypical clinical presentation, clinicians might be able to mitigate the risk of ketoacidosis and/or volume depletion perioperatively by counseling patients about "sick day" management strategies[4]. For example, clinical practice guidelines from Diabetes Canada contain important advice about classes of drugs that should be stopped in the setting of illness, hospitalization or perioperatively. This guideline recommended the mnemonic tool "**SADMANS**" (**S**ulfonylureas, **A**CE inhibitors, **D**iuretics/**D**irect renin inhibitors, **M**etformin, **A**ngiotensin receptor blockers, **N**on-steroidal anti-inflammatories, **S**GLT2 inhibitors) to advise patients about medication classes that should be held under these clinical conditions, including during the perioperative period[5]. Finally, as discussed elsewhere[3, 4], in the event of SGLT2 inhibitor-associated diabetic ketoacidosis, aside from stopping (and not restarting) the offending agent, management should follow routine diabetic ketoacidosis guidelines.

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