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that were designed to examine the benefit of specific dietary interventions in the management of dependency on opioids among chronic pain patients, which was the theme of the special issue of *Anesthesia & Analgesia*. We appreciate the interest Drs Taekman and Bonakdar¹ have in promoting integrative medicine to improve the lifestyle of chronic pain patients. We agree with them that a healthy lifestyle, including proper diet and exercise, is very important for all persons, including those with chronic pain. We would greatly encourage continued rigorous evaluation regarding this area of study.

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Potential Benefits of Sodium-Glucose Cotransporter-2 Inhibitors in the Perioperative Period

To the Editor

With great interest, we read the review article by Peacock et al¹ on the perioperative concerns for patients with type 2 diabetes mellitus (DM2) treated with sodium-glucose cotransporter-2 (SGLT2) inhibitors. It raises well-deserved attention for a new class of medication. Some valuable concerns are raised by the authors, and these concerns led them to advise withholding SGLT2 inhibitors from the day before surgery. In support of future research of these drugs in the perioperative period, we would like to highlight some beneficial aspects and possible advantages of SGLT2 inhibitors in the perioperative period.

Because of their mechanism of action, stimulation of glycosuria by the kidneys, SGLT2 inhibitors lower glucose concentrations and glycated hemoglobin levels as well as cause weight loss because of the concurrent loss in calories. In addition, SGLT2 inhibition also causes natriuresis with an associated reduction in blood pressure. The Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) trial found a reduced event rate of cardiovascular (CV) death, myocardial infarction, and stroke in patients treated with empagliflozin compared to placebo (37.4 vs 43.9 events/1000 patient-years group; $P = .04$) and a reduced rate of hospitalization for cardiac failure (9.4 vs 14.5 events/1000 patient-years; $P = .002$).² This beneficial effect on CV outcomes was confirmed in the canagliflozin cardiovascular assessment study (CANVAS), in which canagliflozin reduced the composite outcome of CV death, myocardial infarction, and stroke (26.9 vs 31.5 events/1000 patient-years; $P = .02$).³

The improvement in CV outcomes in these trials is higher than expected based on the improvement of glycemic control. Several complementary mechanisms are proposed as an explanation, such as changes in arterial stiffness, cardiac function, and cardiac oxygen demand.^{2,3} This is supported by findings from our colleagues, who found a direct effect of SGLT2 inhibitors on mouse cardiac myocytes through inhibition of the cardiac Na^+/H^+ exchanger that lowered sodium concentrations and induced coronary vasodilation in the intact heart.⁴

In patients >65 years of age undergoing noncardiac surgery, 18% have a diagnosis of heart failure.⁵ These patients have a significantly increased risk of death and complications compared to other patients.⁵ This risk is higher than that in patients with coronary artery disease.^{5,6} Among patients with heart failure presenting for surgery, the diagnosis of DM2 has a prevalence of 40%.⁵ We certainly share the concerns of euglycemic diabetic ketoacidosis, hypovolemia, and hypotension put forth by Peacock et al.¹ However, we see an interesting potential of SGLT2 inhibitors for patients with DM2 undergoing surgery, especially in the presence of cardiac comorbidities, heart failure in particular. As such, we would welcome studies on the effect of SGLT2 inhibitors during surgery in these patients.

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In Response

We thank Hulst et al¹ for their commentary, which highlighted our key message about the benefits of sodium-glucose cotransporter-2 inhibitors (SGLT2is) on renal and cardiovascular risk reduction in stable outpatients.^{2,3} The results of the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) trial have, for example, resulted in regulatory changes around the use of empagliflozin as a cardiovascular-protective therapy.⁴ As we highlighted, due to both glycemic (hemoglobin A1C [HbA1c] lowering, weight reduction) and nonglycemic (antihypertensive, antiproteinuric, and possibly cardiorenal protective) effects associated with SGLT2i agents, anesthesiologists will likely encounter these drugs more frequently in the perioperative period in patients with type 2 diabetes.² Accordingly, anesthesiologists should be familiar with both their clinical use, and also the risks and benefits associated with this class of medications.

Despite cardiovascular and renal benefits observed in EMPA-REG OUTCOME and the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program in stable outpatients at high cardiovascular risk, it is not yet known if these salutary effects—including heart failure benefits—will extend to patients in the perioperative period. The EMPA-REG OUTCOME and CANVAS Program trials were not heart failure trials, and only approximately 10% of patients had heart failure at baseline.^{3,5} Hence, the results of ongoing, dedicated heart failure trials such as the Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure (NCT03036124), the Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction (NCT03057951),

and the Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction (NCT03057977) will better inform us on how to use these agents more broadly in the setting of heart failure. In conjunction with studies in hospitalized patients with heart failure (NCT03292653), these large, dedicated clinical trials will provide critical data about the role of SGLT2i in hospitalized patients and/or those with recent hemodynamic instability. Unfortunately, these studies will not give us specific insight into the safety of these agents in the perioperative setting.

Based on the current available evidence, the risks and benefits of SGLT2i use in the perioperative period are unknown. Accordingly, we caution that the use of these drugs during the perioperative period be carefully assessed and understood because of potential safety concerns outlined in our manuscript. These potential risks include hypovolemia due to fluid shifts and poor oral intake, acute kidney injury due to hemodynamic instability and reduced renal perfusion, and diabetic ketoacidosis due to hypovolemia, poor oral intake, underinsulinization, and increased levels of circulating counterregulatory hormones (glucagon, adrenaline, and noradrenaline). Until the use of SGLT2i agents is more completely understood in hospitalized patients, especially in the perioperative setting, we suggest that current guidelines around sick-day management pertaining to SGLT2i should be adhered to maximize the benefits and minimize the potential risks associated with this class of antihyperglycemic agents.²

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