Perioperative Management of Glucose-lowering Drugs: Comment

To the Editor:

I would like to commend Preiser *et al.* for an excellent review of oral glucose-management drugs in the perioperative period.[1] I want to draw attention to a recent U.S. Food and Drug Administration safety labeling change for the management of patients taking sodium glucose cotransporter–2 inhibitor medications that was released after the acceptance of this manuscript for publication. In March 2020, the Food and Drug Administration issued an advisory suggesting that canagliflozin, dapagliflozin, and empagliflozin should all be discontinued 3 days before elective surgery, and ertugliflozin should be discontinued 4 days before elective surgery due to the risk of postoperative euglycemic diabetic ketoacidosis.[2] The additional recommended day for discontinuation of ertugliflozin appears to be related to its slightly longer half-life relative to canagliflozin, dapagliflozin, and empagliflozin to ensure appropriate elimination of the medication before the day of surgery. In light of this guidance and existing literature, we believe that it may be appropriate to hold these medications for 3 to 4 days before surgery, especially in patients who may have a prolonged decrease in nutritional intake in the postoperative period.

Competing Interests

The author declares no competing interests.

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Perioperative Management of Glucose-lowering Drugs: Comment

To the Editor:

We read with interest the review by Prieser *et al.* on the perioperative management of oral glucose-lowering agents in patients with type 2 diabetes mellitus.[1] The authors recommend (table 1) that sodium glucose cotransporter–2 inhibitors be ceased 24 h before elective interventions.[1] No allowance is made for the severity of the procedure (minor *vs.* major surgery) or type of procedure. However, the authors do acknowledge that other sources recommend a longer duration of withholding these medications before elective procedures. Ceasing them just on the day of the procedure may be suitable for minor interventions where early oral intake is possible. For procedures where return to preoperative state is expected to be delayed, some governing bodies recommend withholding these agents more than 24 h. The Australian Diabetes Society (Melbourne, Australia) recommends withholding 2 days before surgery and also on the day of the procedure in such scenarios.[2] The half-lives of canagliflozin, dapagliflozin, and empagliflozin range between 12 to 13 h, and hence, withholding them for four to five half-lives (around 50 to 65 h) is likely to ensure complete washout of the drug at the time of surgery.[3] As the half-life of ertugliflozin is 16 h, a more prolonged interruption may be required. The U.S. Food and Drug Administration (Silver Spring, Maryland) has recently approved a label change to sodium glucose cotransporter–2 inhibitors interruption before elective surgery. It recommends a 3-day cessation for canagliflozin, dapagliflozin, and empagliflozin, and 4 days for ertugliflozin.[4]

Euglycemic ketoacidosis is a rare, but serious complication associated with perioperative sodium glucose cotransporter–2 inhibitors therapy.[5] Few reports have shown that

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the pharmacologic effects of sodium glucose cotransporter–2 inhibitors are likely to last beyond five half-lives of elimination (2 to 3 days).[6–8] Prolonged glycosuria and ketonemia persisting up to 9 to 10 days after discontinuation of sodium glucose cotransporter–2 inhibitors therapy have been described with euglycemic ketoacidosis presentations both in the surgical[6,7] and nonsurgical settings.[8] Persistent glycosuria with minimal elevation of blood glucose was a key manifestation in those cases, highlighting an ongoing effect of these agents. Considering the half-lives of these agents, the renal effects should not have lasted beyond 2 to 3 days. Nonetheless, glycosuria (and metabolic effects) continued until 8 to 9 days with blood glucose values below the renal threshold of glucose. Sustained binding of these medications to renal transport proteins despite plasma elimination has been suggested as a possible mechanism of this prolonged effect.[7]

Competing Interests

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Perioperative Management of Glucose-lowering Drugs: Reply

In Reply:

We thank Dr. Gregory and Thiruvenkatarajan *et al.* for their positive comments on our review[1] and for pointing out the label change by the U.S. Food and Drug Administration (Silver Spring, Maryland), which appeared after our review was accepted for publication. We fully agree that it is appropriate and to be recommended to withhold sodium glucose cotransporter–2 inhibitors 3 to 4 days before surgery to avoid euglycemic diabetic ketoacidosis. Ketoacidosis in people with diabetes is not proportional to the degree of hyperglycemia[2] and may be, treacherously, euglycemic in patients taking sodium glucose cotransporter–2 inhibitors. Anesthesiologists should be aware of the risk of this serious complication.

Competing Interests

The authors declare no competing interests.

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Burst-suppression and Postoperative Delirium: Comment

To the Editor:

The recent report by Pedemonte *et al.*[1] of their substudy of the Minimizing ICU Neurologic Dysfunction with Dexmedetomidine-induced Sleep (MINDDS) study[2] emphasized the relationship between electroencephalogram (EEG) burst-suppression during cardiopulmonary bypass and delirium in elderly patients undergoing cardiac surgery. It raises several important points regarding the potential for cerebral monitoring to identify patients who may be at risk for significant postoperative neurologic complications, including delirium and postoperative cognitive dysfunction. However, interpreting these complex relationships requires certain safeguards to minimize the risk of potential false discovery, and thus maximize the confidence in a study's conclusions. These safeguards include, but are not limited to, clear adherence to the prespecified substudy aims and *a priori* hypotheses, the development of a data statistical analytic plan before accessing the data, and consideration to the potential moderating effects in the substudy from the intervention of the parent trial. In this case, for example, the data from the substudy were derived from an ongoing randomized controlled trial investigating the potential effects of dexmedetomidine on postoperative delirium. It would seem reasonable then for any analysis in the substudy to be adjusted for the use of dexmedetomidine. Clarification as to whether and how this was done would be useful.

Several other aspects of their study might also benefit from additional clarity. For example, adherence of reporting to the ordered prestated hypotheses seems to have been modified. For example, the primary hypothesis stated in their introduction was that "preexisting cognitive impairment accounts for electroencephalogram burst-suppression during CPB."[1] It is curious, then, that the article's title, and the subsequent analysis and reporting of the study, principally focuses on postoperative delirium as opposed to preexisting cognitive impairment. This is particularly notable because their power analysis states that the "primary objective of the study was to detect the difference in mean preoperative cognitive scores between the burst-suppression and no burst-suppression groups."[1] The current delirium analysis, as they state, was likely underpowered.

Although there is a potentially important relationship between preexisting cognitive impairment and delirium, and one that could be plausibly mediated *via* EEG burst-suppression, the primary analysis reported should have been the relationship between baseline cognition and EEG burst suppression, with the delirium-related analyses being secondary, and/or exploratory, and fully adjusted for multiple comparisons. Indeed, although some mention is made of adjustments to reduce false discovery, it is not clear where and how these were done. Furthermore, as the authors stated that the "data and statistical analyses plans were defined and written after the data were accessed,"[1] it is not clear how much data and analyses mining might have been undertaken before these complex analyses were settled on and which results were chosen to be reported. The study's actual primary objective found that the relationship between preexisting cognition (assessed using the abbreviated Montreal cognitive assessment) and EEG burst-suppression was not statistically significant ($P = 0.965$ in their table 1).

These limitations should not dissuade the reader from considering the potentially important relationships that the authors have described, because they may in fact be quite meaningful. However, without adequate adjustment for the unit of randomization, consideration for the analytical plan being developed after the data was accessed, and the subsequent organization of the results around a hypothesis that was not the primary one, it does raise the question as to whether undue emphasis is being placed on the "positive"