



# Recent advances in diabetes treatments and their perioperative implications

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## Purpose of review

The implications for perioperative management of new oral antihyperglycemic medications and new insulin treatment technologies are reviewed.

## Recent findings

The preoperative period represents an opportunity to optimize glycemic control and potentially to reduce adverse outcomes. There is now general consensus that the optimal blood glucose target for hospitalized patients is approximately 106–180 mg/dl (6–10 mmol/l). Recommendations for the management of antihyperglycemic medications vary among national guidelines. It may not be necessary to cease all antihyperglycemic agents prior to surgery. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are associated with higher rates of ketoacidosis especially in acutely unwell and postsurgical patients. The clinical practice implications of new insulin formulations, and new systems for insulin delivery, are not clear. The optimal perioperative management of these will vary depending on local institutional factors such as staff skills and existing clinical practices. Improved hospital care delivery standards, quality assurance, process improvements, consistency in clinical practice, and coordinated multidisciplinary teamwork should be a major focus for improving outcomes of perioperative patients with diabetes.

## Summary

Sulfonylureas and SGLT2i should be ceased before moderate or major surgery. Other oral antihyperglycemic therapies may be continued or ceased. Complex patients and/or new therapies require specialized multidisciplinary management.

## Keywords

antihyperglycemic, diabetes, insulin, perioperative, surgery

## INTRODUCTION

In 2017, the International Diabetes Federation estimated that 425 million people worldwide aged 18–99 years have diabetes mellitus with this number projected to increase to 693 million by 2045 [1<sup>•</sup>]. People with diabetes having surgical procedures are more likely to require complex hospitalization and experience perioperative complications. Up to half of people with diabetes are undiagnosed [1<sup>•</sup>]. The perioperative period represents an ideal opportunity to identify patients with hyperglycemia with or without a diagnosis of diabetes, to optimize treatment of diabetes perioperatively, and to modify their postsurgical course.

The introduction of different classes of antihyperglycemic agents has made traditional recommendations to cease all treatment on the day of surgery over-simplistic. Newer agents such as sodium-glucose cotransporter 2 inhibitors (SGLT2i) may require longer periods of cessation prior to surgery. It may be safe to continue other drugs in patients with adequate renal function.

Advances in technology such as continuous glucose monitoring (CGM) systems and continuous

subcutaneous insulin infusion therapy provides new opportunities for improving glycemic control but also carries new challenges. Ongoing work is required to determine their effectiveness in the acute setting.

Medications used to treat diabetes and its complications must be reviewed perioperatively with regard

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## KEY POINTS

- The perioperative period is a key time to identify patients with hyperglycemia and provide management to improve the postsurgical course.
- SGLT2i may provoke euglycemic diabetic ketoacidosis in the perioperative period and should be withheld until the patient is well and eating normally.
- Reducing variation in practice and adherence to standardized clinical pathways should be key goals to improve perioperative outcomes.

to effect on fluid homeostasis, electrolyte balance, cardiovascular stability, and with regard to interactions with common associated comorbidities such as renal failure, autonomic dysfunction, ischemic heart disease, vascular disease and hypertension.

### Preoperative patient preparation and blood glucose targets

All patients presenting for surgery should be screened for diabetes. A recent measurement of Hemoglobin A1c (HbA1c) should be reviewed for all patients with diabetes preoperatively to allow for risk assessment and optimization of glycemic control (HbA1c <69 mmol/mol) [2,3].

Several studies have demonstrated a relationship between glycemic control and adverse outcomes, although this not a simple relationship [4,5,6<sup>•</sup>,7].

A recent report is one of few prospective randomized trials demonstrating improved outcomes with preoperative diabetes optimization [8<sup>•</sup>].

A retrospective study suggests that improved preoperative diabetes control is associated with better pre and postsurgery glycemic control with reduced incidence of hypoglycemic events and reduction in length of stay [9<sup>••</sup>].

A meta-analysis of studies including only surgical patients with diabetes reported that perioperative blood glucose level (BGL) control of between 150 and 200 mg/dl (8.3–11.1 mmol/l) was associated with reduced perioperative mortality and stroke compared with more liberal targets (BGL > 200 mg/dl; 11.1 mmol/l), but no additional benefit was gained from tighter control (101–150 mg/dl; 5.6–8.3 mmol/l) [10<sup>•</sup>].

Some studies have observed that perioperative hyperglycemia is more predictive of harm in patients without a previous diagnosis of diabetes [3,11<sup>••</sup>]. Although perioperative hyperglycemia is associated with adverse outcomes, it is not clear if this is an epiphenomena or a therapeutic target [11<sup>••</sup>].

To avoid harm from both hypoglycemia and hyperglycemia, international guidelines recommend

targeting BGL less than 180 mg/dl (10 mmol/l) in the majority of adult inpatients, with recommendations for a minimum BGL target of between 79 and 144 mg/dl (4.4–8 mmol/l) [2,3,12<sup>•</sup>–16<sup>•</sup>].

### Perioperative management of antihyperglycemic medications

Conventional practice has been to withhold all oral antihyperglycemic medications on the day of surgery [12<sup>•</sup>]. This approach may be less appropriate for patients having ambulatory surgery or being managed using ERAS (enhanced recovery after surgery) principles emphasizing minimized fasting preoperatively and rapid return to normal diet [17<sup>•</sup>].

The Association of Anaesthetists of Great Britain and Ireland (AAGBI) guideline suggests that for surgery with a short starvation period, medications may be individualized, and that diabetes drugs that do not cause hypoglycemia may be continued, including metformin [16<sup>•</sup>]. A joint anesthesiology and diabetology position statement from France suggest all noninsulin drugs should be continued for ambulatory surgical patients, and be withheld for major surgery [13<sup>•</sup>].

A recent statement from multiple German specialty societies avoids a definitive recommendation, concluding that ‘overall, the decision on whether to continue or discontinue oral antidiabetic drugs should be based primarily on blood glucose management and less on potential adverse effects’ [15<sup>•</sup>].

A recent small randomized study showed lower blood glucose levels were maintained perioperatively if oral medications (including sulfonylureas) were continued. The study was not powered to demonstrate the incidence of hypoglycemia, nor any effect to improve patient outcomes [18<sup>•</sup>].

Given the multiplicity of guidelines and differing recommendations, it is unsurprising that variability of ‘real-world’ clinical practice with regard to perioperative management of oral antihyperglycemic medications has been noted in audits such as the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) study [19<sup>••</sup>], and even in trial settings [18<sup>•</sup>].

### Metformin

Metformin is first line oral therapy for type 2 diabetes. Withholding metformin for 48 h preoperatively was previously recommended to reduce the risk of lactic acidosis, but it now appears this risk was greatly overestimated [20<sup>•</sup>,21<sup>•</sup>]. The US Food and Drug Administration has recently changed metformin contraindications to allow its use until an estimated glomerular filtration rate (eGFR) of less than 30 ml/min/1.73 m<sup>2</sup>.

The American Diabetes Association (ADA) continues to recommend withholding metformin on the day of surgery [12<sup>•</sup>] but the AAGBI guideline notes that metformin does not cause hypoglycemia, and therefore recommends metformin may be given on day of surgery, along with most oral antihyperglycemic drugs other than sulfonylureas and SGLT2i [18<sup>•</sup>].

A recent randomized study did not show a significant difference in perioperative glycemic control when perioperative metformin was continued [22<sup>•</sup>].

### Sulfonylureas

Sulfonylureas have been in clinical use since the early 1950s and remain second-line therapy for type 2 diabetes in many guidelines.

A CGM study has demonstrated a higher risk of asymptomatic hypoglycemia than other classes of oral antidiabetic agents [23<sup>•</sup>]. The conventional recommendation to withhold sulfonylureas on day of surgery remains appropriate.

In a recent meta-analysis sulfonylureas were associated with an increased risk of hospitalization, congestive heart failure and all-cause mortality [24<sup>•</sup>]. Israel has recently updated its diabetes management guidelines to place sulfonylureas as a third line agent due to the high cost of treatment of side effects despite the low cost of the medication itself [25<sup>•</sup>].

### Sodium-glucose cotransporter-2 inhibitors

SGLT2i or 'gliflozins' act by promoting glycosuria and natriuresis in an insulin-independent manner [26]. They are associated with improved glycemic control, reduced plasma volume and blood pressure, renoprotective effects and promote weight loss [27<sup>•</sup>–29<sup>•</sup>]. Their popularity has increased since the publication of the EMPA-REG OUTCOME trial, which demonstrated a reduction in cardiovascular mortality, myocardial infarction, all-cause mortality and hospitalizations for heart failure [27<sup>•</sup>].

Of concern, SGLT2i therapy is associated with an increased risk of genitourinary tract infections [30<sup>•</sup>]. Of greater concern are the increasing reports of SGLT2i-associated diabetic ketoacidosis (DKA). This syndrome has been recognized in nonhospitalized patients since 2015 [31<sup>•</sup>,32<sup>•</sup>]. Of particular concern, 71% of patients experience euglycemic DKA [33<sup>•</sup>].

The perioperative period appears to be a precipitating factor and the risk may be further increased if SGLT2i therapy is not discontinued or is reintroduced too early in the postoperative phase [31<sup>•</sup>,32<sup>•</sup>,34<sup>•</sup>,35<sup>•</sup>,36<sup>•</sup>,37<sup>•</sup>,38<sup>•</sup>]. There have recently been a number of case reports of euglycemic ketoacidosis in the perioperative setting [39<sup>•</sup>–42<sup>•</sup>,43,44,45<sup>•</sup>]. These have been reviewed and discussed in detail [34<sup>•</sup>,36<sup>•</sup>,37<sup>•</sup>].

There is currently no universal consensus for the perioperative management of SGLT2i. The benefits of SGLT2i are from long-term therapy, and there is no hazard from short-term cessation. Recommendations on the appropriate period of cessation prior to surgery range from 24 to 72 h or longer, with some suggesting a more nuanced approach [34<sup>•</sup>,36<sup>•</sup>,37<sup>•</sup>,46<sup>•</sup>–48<sup>•</sup>].

Where patients being treated with SGLT2i undergo surgery, staff awareness of the potential development of perioperative euglycemic ketoacidosis (euDKA) is paramount. There should be a low threshold to screen for and treat ketoacidosis [34<sup>•</sup>,36<sup>•</sup>,37<sup>•</sup>]. There should be no rush to recommence SGLT2i therapy postoperatively, until the patient is feeling well and eating normally.

The role of SGLT2i in the acute hospital setting remains unclear and until further safety data are available it may be prudent to avoid their use in all hospitalized patients [12<sup>•</sup>].

### Dipeptidyl peptidase 4 inhibitors (-gliptins)

Dipeptidyl peptidase 4 inhibitors (DPP4i) act by preventing breakdown of endogenous gastric inhibitory polypeptide and glucagon-like peptide-1 (GLP-1). They have a low risk of hypoglycemia. There is no evidence of advantage over insulin therapy in hospitalized patients; however, DPP4i therapy may be a management option in settings in which insulin therapy is logistically challenging [49<sup>•</sup>]. A small study demonstrated noninferiority between basal-bolus insulin regimen and basal insulin with DPP4i in hospitalized patients [49<sup>•</sup>].

Withholding or continuing DPP4i therapy during the immediate perioperative period is unlikely to have major clinical impact, and either approach is reasonable.

### Glucagon-like peptide-1 receptor agonists

GLP-1 is an incretin hormone that promotes glucose-dependent insulin secretion, suppresses pancreatic glucagon production, slows gastric emptying and suppresses appetite. GLP-1 agonist medications are usually given by daily or weekly injection. They do not cause hypoglycemia [50,51]. Recent cardiovascular outcome trials have shown long-term cardiovascular benefit [52–54,55<sup>•</sup>–57<sup>•</sup>].

Two randomized controlled trials in cardiac and noncardiac surgical patients have demonstrated improved perioperative glycemic control with the addition of a GLP-1 receptor agonists (GLP-1RA) to insulin therapy [58<sup>•</sup>,59<sup>•</sup>]. However, their use is associated with more nausea and vomiting [59<sup>•</sup>,60<sup>•</sup>].

The gastrointestinal effects may be a reason to withhold this therapy preoperatively, or to modify anesthetic management.

Either withholding or continuing GLP-1RA therapy perioperatively period is clinically reasonable.

### Insulin management

Discussion of perioperative management of insulin therapy should recognize the benefits of institutional consistency in clinical management and the need to avoid medication errors.

Basal bolus regimens for insulin administration are more successful than intermittent subcutaneous rapid acting insulin bolus regimens in achieving optimal BGL control in surgical patients with type 2 diabetes [61]. Basal bolus regimens are also associated with reduced postoperative complications and reduced inpatient costs per day [62<sup>■</sup>].

Variable rate intravenous insulin infusion (VRIII) has traditionally been limited to use in critical care settings, although multiple centers have been using VRIII safely and effectively based on nurse-led protocols in noncritical care settings for many years [63,64]. British guidelines support the use of VRIII in noncritical care patients. The safety of these regimens relies on strict use of institutional protocols [65<sup>■</sup>].

Continuation of basal insulin at 80% of the usual dosage while fasting or on VRIII is recommended [2,12<sup>■</sup>]. Some modern basal insulins such as insulin degludec and insulin detemir bind to albumin. Degludec in particular forms a subcutaneous multimeric depot with biological activity exceeding 42h [66]. There are limited studies to show how this impacts upon the perioperative glucose control although one study of patients undergoing fasting for colonoscopy did not demonstrate an increase in hypoglycemia [67].

### Advances in technology

Continuous glucose monitoring (CGM) of interstitial glucose, and automated insulin delivery devices, are now commonly used. Results suggest improvements in diabetes control with use of CGM, with greatest benefits seen with near-continuous use [68<sup>■</sup>].

Sensor-augmented pumps incorporate alarms to alert the user to actual or predicted hypoglycemia, with some devices ceasing insulin administration at certain thresholds. Hybrid closed-loop devices are now available. These systems employ an open loop for a patient-initiated premeal bolus but a computer-controlled closed loop for basal periods between meals and overnight, including hyperglycemia-initiated insulin dose increases. Embedded bolus calculators assist patients to manage their meal-time insulin requirements [68<sup>■</sup>].

Overall results from community-based studies of hybrid devices suggest equal or improved glycemic

control, less hypoglycemic events, less hyperglycemia, reduced HbA1c and reduced mean sensor glucose concentrations, particularly overnight [69<sup>■</sup>,70<sup>■</sup>].

Evidence for inpatient use of CGMs and insulin pumps is promising, particularly regarding earlier identification of hypoglycemia. However, concerns remain about their independent use in perioperative and inpatient setting due to acute alterations in physiologic and pharmacologic conditions, and patient capacity. Institutional guidelines are needed to address staff education, appropriate use, calibration and recording of values. Current recommendations are for early endocrine team involvement, potential removal of the device and confirmation of all patient-reported BGL values with a hospital point-of-care testing device [68<sup>■</sup>,71<sup>■</sup>]. However, it is worth noting that the accuracy of commercially available point-of-care blood glucose testing devices has been found to have wide variation in two recent studies, particularly in the hypoglycemic range. Many devices were not found to meet both international and US-based standards on meter accuracy. It is suggested this may be due to devices reaching the market prior to current, more stringent, standards being enacted, or due to postmarketing performance deterioration [72,73].

During ambulant and short-stay surgery, it may be appropriate to continue the use of advanced insulin pumps, in which the anesthesiologist (and the institution) is able and prepared to take temporary responsibility for managing the device. In other circumstances, the device should be removed and insulin infusion used instead.

Although some experts support the continuation of insulin pump use for minor procedures, some manufacturers advise that insulin pumps, and CGM sensors and transmitters, should not be used in association with MRI, computed tomography scanners, fluoroscopy and diathermy is being used [74<sup>■</sup>].

### Carbohydrate loading before surgery

ERAS programs commonly encourage preoperative administration of carbohydrate-rich drinks [16<sup>■</sup>]. Noting the equivocal evidence in support of carbohydrate loading in all patients, and concern about the safety of this practice in patients with diabetes, some have called for a moratorium pending further research [75<sup>■</sup>].

### Improving clinical processes, standards and quality

Despite the common focus on optimizing perioperative glycemic targets, the annual ADA 'Standards of

Medical Care in Diabetes' highlights that the prevention of adverse patient outcomes may be most dependent on reducing deficiencies and confusion about hospital processes, clinical standards and improving quality of care [12<sup>■</sup>]. With regard to surgical patients, the recent NCEPOD report highlights the significant unwarranted variations in standards and quality of care of patients with diabetes in the United Kingdom [19<sup>■</sup>].

The multiplicity of different guidelines (even within single institutions), and lack of clarity about institutional clinical responsibility for perioperative diabetes management, was highlighted in the NCEPOD report [19<sup>■</sup>]. Greater availability of computerized drug prescribing should facilitate improved medication management [12<sup>■</sup>]. Improvements in clinical information and patient management systems with decision support may provide a platform to reduce suboptimal patient care.

For complex hospital patients, dedicated inpatient management teams have been shown to reduce readmission rates, improve transition to outpatient care and to improve adherence to diabetes care follow-up, with best results if the patient was seen within 24 h of admission by the specialized diabetes team. This approach results in large cost reductions based on a reduced readmission rate [76<sup>■</sup>], although this result was most pronounced for medical patients, not surgical.

## CONCLUSION

Over recent years, consensus regarding appropriate perioperative glucose target has been reached although robust prospective evidence of improved surgical outcomes remains lacking. Optimal medication regimens should avoid severe hyperglycemia while also avoiding hypoglycemia with the latter being increasingly recognized as a significant contributor to length of stay, adverse outcomes and potentially mortality. Advances in technology provide opportunities for improved glycemic control but ongoing studies are required. The lack of familiarity with newer technology among healthcare workers remains a barrier to their use in acute care settings. Therapeutic complexity, patient and staff confusion, and medication errors may result in adverse clinical outcomes. Quality activities such as clinical standardization, audit and process improvement maybe the most important strategy to improve patient outcomes.

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## Conflicts of interest

There are no conflicts of interest.

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- of special interest
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