Perioperative Management of Oral Glucose-lowering Drugs in the Patient with Type 2 Diabetes

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Diabetes mellitus is a group of metabolic disorders, characterized by hyperglycemia, resulting from relative insulin deficiency, often on a background of insulin resistance (type 2 diabetes), or (near) absolute insulin deficiency related to autoimmune pathophysiology (type 1 diabetes). The most common form is type 2 diabetes, and its global prevalence is rising as a result of changes in lifestyle and lengthening of life expectancy.[1,2] An estimated 463 million people aged 20 to 79 yr have diabetes,[3] which corresponds to 9.3% of the adult population and represents a four-fold increase in diabetes prevalence since 1980.[4] Patients with type 2 diabetes often have comorbidities such as arterial hypertension, obesity, ischemic heart disease, renal failure, and atherosclerosis. Ischemic heart disease in particular may affect younger patients compared to nondiabetic populations and may have silent ischemia. Hence, assessing the preoperative risk of diabetic patients is challenging, and can be underestimated. As shown outside the perioperative setting, these patients have equivalent or higher risk for cardiovascular events and mortality as patients with typical angina.[5,6] However, current guidelines recommend against systematic stress testing in individuals without symptoms.[7,8]

The number of type 2 diabetes patients undergoing surgical procedures is rising worldwide. An American review from 2004 estimated that 15 to 20% of surgical patients are diabetic.[4] Twenty-five percent of type 2 diabetes patients will require a surgical procedure during their lifetime[9] related to chronic complications that affect the cardiovascular, ophthalmologic, renal or orthopedic systems. The risk of postoperative complications (*i.e.,* gastroparesis, cardiovascular events, and postoperative infection) in type 2 diabetes patients is higher than in nondiabetic patients, as reported by large-scale studies.[4,5,9–12] In order to adjust for potential confounders, the adverse outcomes occurring after major surgery have been compared with a propensity-matched cohort of non-diabetic patients in a cohort of more than 33,000 patients in Taiwan.[13] In this study, Lin *et al.* found a higher risk of postoperative sepsis (odds ratio, 1.33; 95% CI, 1.01 to 1.74) and in-hospital mortality (odds ratio, 1.51; 95% CI, 1.07 to 2.13) when compared to nondiabetic patients. Karamanos *et al.*[14] demonstrated higher mortality, cardiovascular and renal complications after urgent cholecystectomy in insulin-requiring diabetic patients than in orally treated diabetic patients, possibly pointing to worse outcomes in people with more advanced diabetes and/or more severe comorbidities.

Surgical stress induces insulin resistance and increased endogenous glucose production, resulting in stress hyperglycemia characterized by blood glucose level greater than 180 mg/dl (10 mM).[15–18] When this persists, elevated glucose levels become deleterious, promoting immune dysfunction and susceptibility to infections, endothelial dysfunction and thrombosis that can culminate in stroke and acute myocardial infarction, and oxidative stress caused by enhanced reactive oxygen species production.[19]

In the intensive care setting, stress hyperglycemia, spontaneous or drug-related hypoglycemia (glucose less than 70 mg/dl [3.89 mM]) and high glycemic variability (coefficient of variation greater than 20%) constitute the three features of dysglycemia syndrome. All are associated with worse outcomes in acutely injured patients.[20–22] Badawi *et al.*[22] analyzed a large cohort of critically ill patients from 344 American intensive care units to evaluate the association between intensive care unit–acquired dysglycemia and in-hospital mortality. The results showed that hypoglycemia as well as hyperglycemia and glucose variability are deleterious to critically ill patients. The longer the duration of this variability, the greater is the impact on in-hospital mortality. The adjusted relative risk (95% CI) of mortality for hyperglycemia (glucose, 180 to 240 mg/dl [10 to 13.3 mM]) was 1.63 (1.47 to 1.81). The relative risk for glycemic variability was 1.61 (1.47 to 1.78), and for hypoglycemia (glucose, 40 to 60 mg/dl [2.2 to 3.3 mM]) it was 1.53 (1.37 to 1.70). The optimal glycemic control in diabetic patients should also consider the prior level of glucose control, indicated by the level of glycated hemoglobin. The "stress hyperglycemia ratio" and the "glycemic ratio" were introduced to calculate the difference between actual and average glycemia.[23,24] The estimated average glucose value derived from glycated hemoglobin could be the optimal target range, as suggested by reports of lower mortality or reduced need for intensive care when glucose was closer to the average value.[23,24] In surgical intensive care patients, and in particular for

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scheduled surgeries, perioperative care should focus on the prevention of dysglycemia in order to improve outcomes. The proper management of oral glucose-lowering treatment in type 2 diabetic patients is therefore crucial.

New Oral Glucose-lowering Drugs

Type 2 diabetes treatment has undergone major changes with the development of new drug classes, such as sodium-glucose cotransporter-2 inhibitors, and demonstration of their safety and efficacy in large-scale clinical trials. In recent trials primary outcomes were cardiovascular, whereas the primary outcome of previous trials was glycemic control.[25] This change in paradigm was mandated by the United States Food and Drug Administration, which, since 2008, has required data on cardiovascular safety for new glucose-lowering drugs, after the finding increased rates of myocardial infarction and cardiovascular mortality in patients randomized to rosiglitazone in a meta-analysis of 42 studies.[26] These changes show the complexity of oral glucose-lowering drug use in type 2 diabetic patients.

In practice, the current recommendations for the management of type 2 diabetes are simple for the initiation of pharmacologic treatment: metformin is the first agent to be started, unless contraindicated (such as a reduction in glomerular filtration rate less than 30 ml/min). Therapeutic efficacy is monitored by the level of glycated hemoglobin. Once metformin is no longer sufficient despite adequate dosing, a second oral medication (*e.g.,* sulfonylurea, thiazolidinedione, a sodium-glucose cotransporter-2 inhibitor, a dipeptidyl peptidase-4 inhibitor) or a glucagon-like peptide 1 analog should be selected, taking into consideration the individual patient's risk of atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease.[27] If combination therapy does not suffice, combination therapy with a third oral glucose-lowering drug or insulin must be considered. It is not uncommon therefore that type 2 diabetic patients are polymedicated. Knowledge of the mechanisms of action is important for the proper management of these drugs.

Types of Oral Glucose-lowering Drugs

Oral glucose-lowering drugs can be divided according to their mode of action: those lowering blood glucose by increasing insulin release (sulfonylurea, meglitinides, dipeptidyl peptidase-4 inhibitor), those lowering glycemia by increasing insulin action (biguanides, thiazolidinediones), those reducing glucose absorption (alpha-glucosidase inhibitors), and those increasing urinary glucose elimination (sodium glucose cotransporter-2 inhibitors). Different sites and modes of action of these medications are schematically displayed in figure 1.

Increasing Insulin Release

Sulfonylurea and Meglitinides. Historically, the first oral treatment available for type 2 diabetes was sulfonylurea, long-acting insulin secretagogues. Meglitinides constitute another class of insulin secretagogues that are taken with meals and are more rapid and short-acting. The currently available second generation sulfonylurea include gliclazide, glimepiride and glyburide or glibenclamide. The meglitinides include repaglinide and nateglinide. These drugs bind the sulfonylurea receptor, and thereby close potassium adenosine triphosphate channels in pancreatic β cells, resulting in membrane depolarization, calcium influx and insulin release. The American Diabetes Association (Arlington, Virginia) recommends sulfonylurea or meglitinides as add-on oral treatment when metformin does not suffice, in the absence of atherosclerotic cardiovascular disease or chronic kidney disease.

Clinical studies assessed the efficacy of sulfonylurea on glycemic control.[28] A meta-analysis of 31 trials with a median 16-week duration of showed that sulfonylurea in mono- or combination therapy with another drug lowered glycated hemoglobin by 1.5% (17 mmol/mol; 95% CI, 1.3 to 1.8) and 1.6% (18 mmol/mol; 95% CI, 1.0 to 2.2), respectively. Sulfonylurea are cheaper than other oral glucose-lowering drugs recommended as second step. Meglitinides were mostly tested as an adjunctive therapy to metformin, and combination therapy safely improved glycemic control (meta-analysis of 22 trials).[29]

As the effects of sulfonylurea are independent of circulating glucose levels, there is an increased risk of hypoglycemic events. The rate of hypoglycemia was increased by 2.4-fold in patients treated with sulfonylurea as compared with other glucose-lowering agents.[28] This risk can further increase in the hospital, as a result of differences between hospital diets and usual dietary habits. Hypoglycemia appears to be less of a risk for meglitinides[30] but still is relatively high. Besides the risk of hypoglycemia, the incidence of cardiovascular events and mortality has been reported to be increased in patients treated with sulfonylurea in some,[31] but not all meta-analyses. Increased cardiovascular morbidity was first reported in 1970 with tolbutamide (a first generation sulfonylurea),[32] and was related to weight gain and fluid retention. A recently suggested mechanism of cardiovascular toxicity of sulfonylurea relates to the prevention of preconditioning induced by ischemia or volatile anesthesia.[33] Clinically, this could translate to an enlarged necrotic myocardial area.

Regarding the perioperative period (table 1), withholding of the drug depends on the time of surgery and fasting duration, according to medication half-life and risk of hypoglycemia. In case of minor or major surgery with fasting, patients should omit the dose of the day.[34–39] In the case of ambulatory surgery with short-term fasting (fewer than 6 h for solid food, or fewer than 2 h for fluids) or with maltodextrin use before surgery, guidelines suggest that it is possible to continue sulfonylurea, but glycemia should be carefully monitored, with special attention to the risk of hypoglycemia.

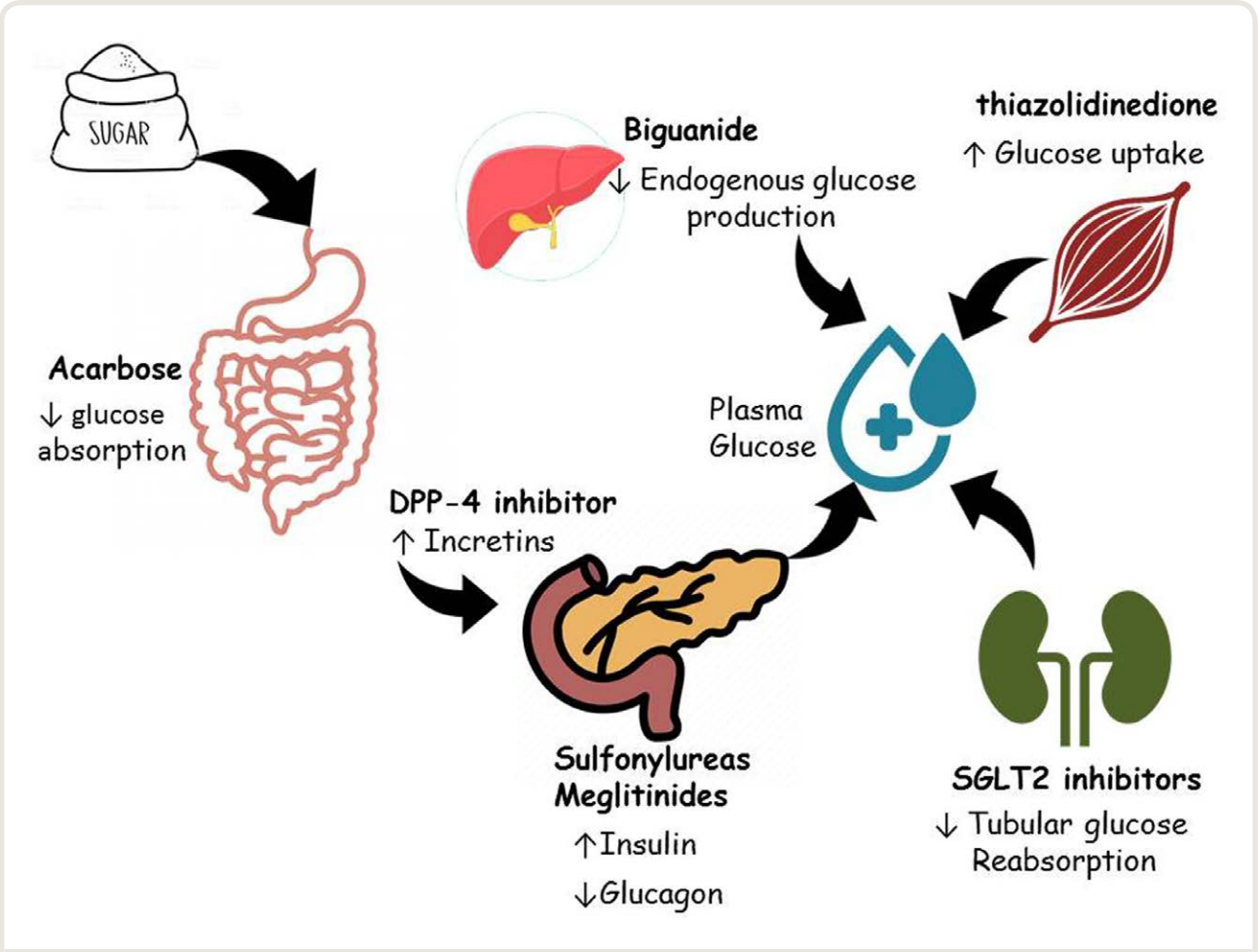

Fig. 1. Schematic representation of the sites of action of glucose-lowering drug (*bold characters*) and modes of action. DPP-4 inhibitor, dipeptidyl peptidase-4 inhibitor. SGLT2 inhibitor, sodium glucose cotransporter-2 inhibitor.

Dipeptidyl Peptidase-4 Inhibitors. Dipeptidyl peptidase-4 inhibitors (linagliptine, saxagliptine, sitagliptine, alogliptine) prevent the degradation of the incretin hormone glucagon-like peptide 1 by the serine protease dipeptidyl peptidase-4. By inhibiting this enzyme, dipeptidyl peptidase-4 inhibitors potentiate the incretin effect of endogenous glucagon-like peptide 1 and enhance glucose-dependent insulin secretion by pancreatic β cells. The risk of hypoglycemia associated with the use of dipeptidyl peptidase-4 inhibitors is very low. In patients undergoing noncardiac surgery, dipeptidyl peptidase-4 inhibitors lowered blood glucose to the same extent as insulin therapy with fewer hypoglycemic events[40,41]; in combination with basal insulin it was noninferior to basal–prandial insulin treatment.[42] Ogawa et al showed benefits of dipeptidyl peptidase-4 inhibitors compared to other glucose-lowering drugs on long-term cardiac and cerebrovascular complications in patients undergoing cardiac surgery.[43] Dipeptidyl peptidase-4 inhibitors should not be stopped before surgeries of any kind, independently of fasting duration.[2,35,36]

Increasing Insulin Action

Thiazolidinediones. Thiazolidinediones enhance insulin sensitivity in peripheral tissues as a result of their peroxisome proliferator-activated receptor agonistic effect. Peroxisome proliferator-activated receptor-γ is found predominantly in the central nervous system, macrophages, vascular endothelium, adipose tissue and pancreatic β cells, while peroxisome proliferator-activated receptor-α is found predominantly in the liver, skeletal muscle, heart, and vascular wall. Rosiglitazone and pioglitazone, the two available thiazolidinediones, bind either to peroxisome proliferator-activated receptor-γ only (rosiglitazone) or to both peroxisome proliferator-activated receptor-γ and -α (pioglitazone).

Due to potential risks of myocardial infarction, cardiovascular death and fluid retention,[44] rosiglitazone has been withdrawn from several markets. Pioglitazone was found safe in a recent meta-analysis of 16 studies.[45] The risk of hypoglycemia is low.[30] Recent publications demonstrated that thiazolidinediones were associated with lower incidence of atrial fibrillation compared with other glucose-lowering

Table 1. Oral Glucose-lowering Drugs, Mechanism of Action, Half-life, and Guidelines Based on the Type of Surgery

Class	Known Mechanism of Action	Generic Name	Half-life	Day before Ambulatory Surgery	Minor or Major Surgery	Emergency Surgery
Sulfonylurea	Stimulation of insulin secretion by inhibition of K-ATP channel, provoking calcium influx into the β cell	Chlorpropamide Gliclazide Gliclazide MR Glimepiride Glyburide (glibenclamide)	36 h 10 h 16 h 5–9 h 10 h	Should be continued (attention to the time of surgery and fasting)[2,35,37,38]	Stop the morning of the surgery and restart after food intake is resumed[35,37-40]	Stop
Meglitinides	Stimulation of insulin secretion by inhibition of K-ATP channel, provoking calcium influx into the β cell	Repaglinide	1 h	Should be continued (Attention to the time of surgery and fasting)[2,35,37,38]	Stop the morning of the surgery and restart after food intake is resumed[35,37-40]	Stop
Biguanides	Inhibition of mitochondrial respiratory chain and activation of AMPK, reduction in hepatic gluconeogenesis and insulin resistance	Metformin Metformin XR	6–18 h 24 h	Should be continued (attention in case of contrast use and renal failure)[2,35,37]	Restart after 24 h with stabilized renal function[35,37]; Exception: minor surgery without renal dysfunction or risk for acute kidney injury	Stop
Thiazolidinediones	Enhanced insulin sensitivity by activation of PPAR γ	Pioglitazone Rosiglitazone	3–7 h 3–4 h	Should be continued[37]	Should be continued[37]	Stop
α glucosidase inhibitor	Inhibition of intestinal glucose absorption	Acarbose	2–4 h	Should be continued[2,35,37]	Omit the dose if meal is skipped and restart after food intake is resumed[2,35,37]	Stop
Dipeptidyl peptidase-4 inhibitors	Inhibition of GLP-1 degradation	Linagliptine Saxagliptine Sitagliptine Alogliptine	12 h 2.5 h 12 h 21 h	Should be continued[2,35,37]	Should be continued[2,35,37]	Stop
Sodium glucose cotransporter 2 inhibitors	Inhibition of renal glucose reabsorption, promoting glucosuria	Canaglifozin Dapagliflozin Empagliflozin Ertugliflozin	13 h 13 h 12 h 16 h	Should be continued[35,37,70]	Stop the morning of the surgery and restart after food intake is resumed[2,35,37]	Stop

AMPK, 5' adenosine monophosphate–activated protein kinase; DDP4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide-1; K-ATP, potassium adenosine triphosphate; MR, modified release; PPAR, peroxisome proliferator-activated receptor; XR, extended release.

drugs, although in cardiothoracic surgery patients this was not confirmed.[46]

In case of elective surgery, thiazolidinediones can be taken on the day of surgery, independently of the time of surgery and fasting duration.[36]

Biguanides. Metformin, the only marketed biguanide, exerts its glucose-lowering effect *via* inhibition of endogenous hepatic glucose production, as a result of blockade of mitochondrial respiratory chain and activation of the 5' adenosine monophosphate–activated protein kinase. This drug has been used to treat type 2 diabetes for more than 60 yr and is still recommended as first-line therapy[38]; it is the most widely used glucose-lowering agent[47] and one of the top ten most prescribed drugs in the United States with a well-established safety and efficacy profile. The risk of metformin-associated lactic acidosis remains of some concern, mainly in patients with chronic kidney disease (glomerular filtration rate less than 30 ml/min), heart failure, or chronic liver disease, because those conditions result in plasma metformin levels well above the therapeutic range. The mechanisms of accumulation are reduced renal metformin clearance, impaired hepatic metabolism with reduced lactate clearance, and increased lactate production, as can occur in major surgeries.[48] In randomized controlled trials, metformin use in the perioperative period did not significantly affect lactate levels in coronary artery bypass or noncardiac surgery patients with type 2 diabetes and it improved glycemic control.[49,50] Overall, the risk of metformin-associated lactic acidosis is extremely small (fewer than 10 cases per 100,000 patient-years) and mortality rates have improved.[48,51–53]

Other mechanisms of action possibly unrelated to the glucose-lowering effects of metformin could explain intriguing and partially unexplained findings of a higher survival rate in patients with diabetes and sepsis who used metformin than in those who did not (meta-analysis of five studies).[54] In surgical settings, there was no difference on mortality and postoperative complications between metformin users and nonusers. The effects of metformin on mitochondrial respiratory chain and 5' adenosine

monophosphate–activated protein kinase cause increased nitric oxide and adenosine diphosphate levels, resulting in endothelial protection in the setting of ischemia/reperfusion injury.[55] In the United Kingdom Prospective Diabetes Study, fewer metformin-allocated patients had diabetes-related endpoints (*i.e.,* sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal myocardial infarction, angina, heart failure, stroke, renal failure, amputation [of at least one digit], vitreous hemorrhage, retinopathy requiring photocoagulation, blindness in one eye, or cataract extraction [risk reduction, 19% (95% CI, 2 to 33)]), and the risk reduction persisted for 10 yr (also for myocardial infarction, 33% risk reduction[56,57]). Meta-regression analyses suggest that metformin is more beneficial in longer trials that enroll younger patients.[32] Hence, it is important to avoid unnecessary withdrawal to maintain the benefits of this drug.[55]

The recommendations for perioperative use depend on the type of surgery, renal function and the potential risk for metformin-associated lactic acidosis. For 1-day minor surgery, it is recommended to continue metformin, except in patients with renal dysfunction or in interventions requiring a contrast medium administration or use of nonsteroidal antiinflammatory drugs, angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists.[2,34–36] For major surgeries, it is recommended that metformin be stopped the day before. For both scenarios, metformin should be resumed once oral intake has been re-established and renal function is stabilized.[34,36,58] Some reports of safe postoperative use of metformin in combination with insulin have recently been published.[49,59]

Reducing Glucose Absorption

Alpha Glucosidase Inhibitors. This class of agents (acarbose, miglitol, voglibose) prevents intestinal glucose absorption and primarily reduces the rise in postprandial glucose. Hence, glucose-lowering efficacy depends on carbohydrate intake.[60,61] The risk of hypoglycemia is very low.

In the preoperative setting, if the patient eats in the morning, the drug should be taken. Nevertheless, with fasting, this drug should be withheld and resumed when nutrition is resumed.[2,34,36,60]

Increasing Urinary Elimination of Glucose

Sodium Glucose Cotransporter-2 Inhibitors. Sodium glucose cotransporter-2 inhibitors (canaglifozin, dapagliflozin, empagliflozin, ertugliflozin) are the newest oral type 2 diabetes drugs that are increasingly being prescribed. Their mechanism of action is to block the sodium glucose cotransporter-2 in the kidneys and promote glucosuria by inhibiting renal glucose reabsorption. This confers glycemia-dependent control, not leading to hypoglycemia. Beneficial effects on the cardiovascular system were observed for all sodium glucose cotransporter-2 inhibitors tested so far: data collected in more than 70,000 patients suggest a net protection against cardiovascular outcomes and death.[62] A series of case reports describes euglycemic ketoacidosis in sodium glucose cotransporter-2 inhibitor–treated patients. Ketoacidosis probably develops due to insulinopenia, increased levels of counter-regulating hormones (glucagon, cortisol, epinephrine), and hypovolemia,[63,64] and the risk increases with fasting.

Patients using sodium glucose cotransporter-2 inhibitors should therefore be considered at risk of ketoacidosis in the perioperative period. Cases have been described and the main challenge is that in some patients the event occurred at euglycemia. It is essential to have a high degree of suspicion.[65,66] It is recommended to not take this drug on the day of surgery because of the risk of dehydration; some have recommended cessation several days before surgery.[67] When food intake is resumed, the sodium glucose cotransporter-2 inhibitor can be restarted.[2,36]

Summary of the Recommendations for the Preoperative Period

During the perioperative period, table 1 summarizes recommendations for each drug class, based on guidelines from the Association of Anesthetists of Great Britain and Ireland (London, United Kingdom), a joint statement of the French Society of Anesthesia and Intensive Care Medicine and the French Society for the Study of Diabetes (Paris, Fance), a joint recommendation of the German Society for Anesthesiology and Intensive Care Medicine (Nuremberg, Germany), German Society for Internal Medicine (Wiesbaden, Germany), German Society for Surgery (Berlin, Germany), the American Diabetes Association, and the European Medicines Agency (Amsterdam, The Netherlands), and recent reviews.[2,35–37,68–70] These recommendations are often based on expert opinion, as relatively few randomized controlled trials have assessed the management of oral type 2 diabetes treatment in the perioperative period. Specific considerations will help to decide whether a medication should be continued or withheld.

Guidelines suggest that insulin should be started when blood glucose is greater than 180 mg/dl (10 mM).[72] Individualized insulin therapy targeting average glycemia should be assessed in clinical trials.

Conclusions

Patients with type 2 diabetes are commonly referred for elective or emergency surgery. In case of scheduled surgical procedures, previous guidelines recommended to withhold oral glucose-lowering drugs.[35,72] Based on recent literature, this tendency has shifted toward treatment continuation.

In most cases, the continuation of glucose-lowering drugs seems safe, although it may be recommended to temporarily interrupt treatment, *e.g.,* on the day of surgery, when there is fasting, reduced food intake, or risk of renal

dysfunction. Inadvertent discontinuation may worsen glycemic control and increase complication rates, whereas an inappropriate continuation of sulfonylurea or sodium glucose cotransporter-2 inhibitors may induce hypoglycemia or ketoacidosis.

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Competing Interests

The authors declare no competing interests.

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References

1. Dimas AS, Lagou V, Barker A, Knowles JW, Mägi R, Hivert MF, Benazzo A, Rybin D, Jackson AU, Stringham HM, Song C, Fischer-Rosinsky A, Boesgaard TW, Grarup N, Abbasi FA, Assimes TL, Hao K, Yang X, Lecoeur C, Barroso I, Bonnycastle LL, Böttcher Y, Bumpstead S, Chines PS, Erdos MR, Graessler J, Kovacs P, Morken MA, Narisu N, Payne F, Stancakova A, Swift AJ, Tönjes A, Bornstein SR, Cauchi S, Froguel P, Meyre D, Schwarz PE, Häring HU, Smith U, Boehnke M, Bergman RN, Collins FS, Mohlke KL, Tuomilehto J, Quertemous T, Lind L, Hansen T, Pedersen O, Walker M, Pfeiffer AF, Spranger J, Stumvoll M, Meigs JB, Wareham NJ, Kuusisto J, Laakso M, Langenberg C, Dupuis J, Watanabe RM, Florez JC, Ingelsson E, McCarthy MI, Prokopenko I; MAGIC Investigators: Impact of type 2 diabetes susceptibility variants on quantitative glycemic traits reveals mechanistic heterogeneity. Diabetes 2014; 63:2158–71
2. Cheisson G, Jacqueminet S, Cosson E, Ichai C, Leguerrier AM, Nicolescu-Catargi B, Ouattara A, Tauveron I, Valensi P, Benhamou D; working party approved by the French Society of Anaesthesia and Intensive Care Medicine (SFAR), the French Society for the study of Diabetes (SFD): Perioperative management of adult diabetic patients. Review of hyperglycaemia: Definitions and pathophysiology. Anaesth Crit Care Pain Med 2018; 37 Suppl 1:5–8
3. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, Colagiuri S, Guariguata L, Motala AA, Ogurtsova K, Shaw JE, Bright D, Williams R; IDF Diabetes Atlas Committee: Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract 2019; 157:107843
4. Clement S, Braithwaite SS, Magee MF, Ahmann A, Smith EP, Schafer RG, Hirsch IB, Hirsh IB; American Diabetes Association Diabetes in Hospitals Writing Committee: Management of diabetes and hyperglycemia in hospitals. Diabetes Care 2004; 27:553–91
5. Frisch A, Chandra P, Smiley D, Peng L, Rizzo M, Gatcliffe C, Hudson M, Mendoza J, Johnson R, Lin E, Umpierrez GE: Prevalence and clinical outcome of hyperglycemia in the perioperative period in noncardiac surgery. Diabetes Care 2010; 33:1783–8
6. Stacey RB, Vera T, Morgan TM, Jordan JH, Whitlock MC, Hall ME, Vasu S, Hamilton C, Kitzman DW, Hundley WG: Asymptomatic myocardial ischemia forecasts adverse events in cardiovascular magnetic resonance dobutamine stress testing of high-risk middle-aged and elderly individuals. J Cardiovasc Magn Reson 2018; 20:75
7. Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, Davila-Roman VG, Gerhard-Herman MD, Holly TA, Kane GC, Marine JE, Nelson MT, Spencer CC, Thompson A, Ting HH, Uretsky BF, Wijeysundera DN; American College of Cardiology; American Heart Association: 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol 2014; 64:e77–137
8. Rydén L, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N, Deaton C, Escaned J, Hammes HP, Huikuri H, Marre M, Marx N, Mellbin L, Ostergren J, Patrono C, Seferovic P, Uva MS, Taskinen MR, Tendera M, Tuomilehto J, Valensi P, Zamorano JL; ESC Committee for Practice Guidelines (CPG), Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S; Document Reviewers, De Backer G, Sirnes PA, Ezquerra EA, Avogaro A, Badimon L, Baranova E, Baumgartner H, Betteridge J, Ceriello A, Fagard R, Funck-Brentano C, Gulba DC, Hasdai D, Hoes AW, Kjekshus JK, Knuuti J, Kolh P, Lev E, Mueller C, Neyses L, Nilsson PM, Perk J, Ponikowski P, Reiner Z, Sattar N, Schächinger V, Scheen A, Schirmer H, Strömberg A, Sudzhaeva S, Tamargo JL, Viigimaa M, Vlachopoulos C, Xuereb RG: Diabetes,

pre-diabetes, and cardiovascular diseases. Eur Heart J 2013; 34:3035–87
9. Halkos ME, Lattouf OM, Puskas JD, Kilgo P, Cooper WA, Morris CD, Guyton RA, Thourani VH: Elevated preoperative hemoglobin A1c level is associated with reduced long-term survival after coronary artery bypass surgery. Ann Thorac Surg 2008; 86:1431–7
10. Kreutziger J, Schlaepfer J, Wenzel V, Constantinescu MA: The role of Admission blood glucose in outcome prediction of surviving patients with multiple injuries. J Trauma Inj Infect Crit Care 2009;67:704–8
11. Vilar-Compte D, Alvarez de Iturbe I, Martín-Onraet A, Pérez-Amador M, Sánchez-Hernández C, Volkow P: Hyperglycemia as a risk factor for surgical site infections in patients undergoing mastectomy. Am J Infect Control 2008; 36:192–8
12. Abdelmalak B, Maheshwari A, Kovaci B, Mascha EJ, Cywinski JB, Kurz A, Kashyap VS, Sessler DI: Validation of the DeLiT Trial intravenous insulin infusion algorithm for intraoperative glucose control in noncardiac surgery: A randomized controlled trial. Can J Anaesth 2011; 58:606–16
13. Lin C-S, Chang C-C, Lee Y-W, Liu C-C, Yeh C-C, Chang Y-C, Chuang MT, Chang TH, Chen TL, Liao CC: Adverse outcomes after major surgeries in patients with diabetes: A multicenter matched study. J Clin Med 2019;8:100.
14. Karamanos E, Sivrikoz E, Beale E, Chan L, Inaba K, Demetriades D: Effect of diabetes on outcomes in patients undergoing emergent cholecystectomy for acute cholecystitis. World J Surg 2013; 37:2257–64
15. Preiser JC, Ichai C, Orban JC, Groeneveld AB: Metabolic response to the stress of critical illness. Br J Anaesth 2014; 113:945–54
16. Lena D, Kalfon P, Preiser JC, Ichai C: Glycemic control in the intensive care unit and during the postoperative period. Anesthesiology 2011; 114:438–44
17. Dungan KM, Braithwaite SS, Preiser JC: Stress hyperglycaemia. Lancet 2009; 373:1798–807
18. Mesotten D, Preiser JC, Kosiborod M: Glucose management in critically ill adults and children. Lancet Diabetes Endocrinol 2015; 3:723–33
19. Mongkolpun W, Provenzano B, Preiser JC: Updates in glycemic management in the hospital. Curr Diab Rep 2019; 19:133
20. Krinsley JS, Egi M, Kiss A, Devendra AN, Schuetz P, Maurer PM, Schultz MJ, van Hooijdonk RT, Kiyoshi M, Mackenzie IM, Annane D, Stow P, Nasraway SA, Holewinski S, Holzinger U, Preiser JC, Vincent JL, Bellomo R: Diabetic status and the relation of the three domains of glycemic control to mortality in critically ill patients: An international multicenter cohort study. Crit Care 2013; 17:R37
21. Finfer S, Liu B, Chittock DR, Norton R, Myburgh JA, McArthur C, Mitchell I, Foster D, Dhingra V, Henderson WR, Ronco JJ, Bellomo R, Cook D, McDonald E, Dodek P, Hébert PC, Heyland DK, Robinson BG; NICE-SUGAR Study Investigators: Hypoglycemia and risk of death in critically ill patients. N Engl J Med 2012; 367:1108–18
22. Badawi O, Waite MD, Fuhrman SA, Zuckerman IH: Association between intensive care unit-acquired dysglycemia and in-hospital mortality. Crit Care Med 2012; 40:3180–8
23. Roberts GW, Quinn SJ, Valentine N, Alhawassi T, O'Dea H, Stranks SN, Burt MG, Doogue MP: Relative hyperglycemia, a marker of critical illness: Introducing the stress hyperglycemia ratio. J Clin Endocrinol Metab 2015; 100:4490–7
24. Preiser JC, Lheureux O, Prevedello D: A step toward personalized glycemic control. Crit Care Med 2018; 46:1019–20
25. Rodriguez-Gutierrez R, McCoy RG: Measuring what matters in diabetes. JAMA 2019; 321:1865–6
26. Nissen SE, Wolski K: Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007; 356:2457–71
27. Buse JB, Wexler DJ, Tsapas A, Rossing P, Mingrone G, Mathieu C, D'Alessio DA, Davies MJ: 2019 update to: Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2019; https://doi.org/10.1007/s00125-019-05039-w
28. Hirst JA, Farmer AJ, Dyar A, Lung TW, Stevens RJ: Estimating the effect of sulfonylurea on HbA1c in diabetes: A systematic review and meta-analysis. Diabetologia 2013; 56:973–84
29. Yin J, Deng H, Qin S, Tang W, Zeng L, Zhou B: Comparison of repaglinide and metformin *versus* metformin alone for type 2 diabetes: A meta-analysis of randomized controlled trials. Diabetes Res Clin Pract 2014; 105:e10–5
30. Leonard CE, Han X, Brensinger CM, Bilker WB, Cardillo S, Flory JH, Hennessy S: Comparative risk of serious hypoglycemia with oral antidiabetic monotherapy: A retrospective cohort study. Pharmacoepidemiol Drug Saf 2018; 27:9–18
31. Azoulay L, Suissa S: Sulfonylureas and the risks of cardiovascular events and death: A methodological meta-regression analysis of the observational studies. Diabetes Care 2017; 40:706–14
32. Meinert CL, Knatterud GL, Prout TE, Klimt CR: A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. II. Mortality results. Diabetes 1970; 19:Suppl:789–830
33. Forlani S, Tomai F, De Paulis R, Turani F, Colella DF, Nardi P, De Notaris S, Moscarelli M, Magliano G, Crea F, Chiariello L: Preoperative shift from glibenclamide to insulin is cardioprotective in diabetic

patients undergoing coronary artery bypass surgery. J Cardiovasc Surg (Torino) 2004; 45:117–22
34. Cosson E, Catargi B, Cheisson G, Jacqueminet S, Ichai C, Leguerrier AM, Ouattara A, Tauveron I, Bismuth E, Benhamou D, Valensi P: Practical management of diabetes patients before, during and after surgery: A joint French diabetology and anaesthesiology position statement. Diabetes Metab 2018; 44:200–16
35. Kuzulugil D, Papeix G, Luu J, Kerridge RK: Recent advances in diabetes treatments and their perioperative implications. Curr Opin Anaesthesiol 2019; 32:398–404
36. Membership of the Working Party P, Barker P, Creasey PE, Dhatariya K, Levy N, Lipp A, Nathanson MH, Penfold N, Watson B, Woodcock T: Peri-operative management of the surgical patient with diabetes 2015: Association of Anaesthetists of Great Britain and Ireland. Anaesthesia 2015;70:1427–40
37. Australian Diabetes Society: Peri-operative diabetes management guidelines. Available at: https://diabetessociety.com.au/documents/PerioperativeDiabetesManagementGuidelinesFINALCleanJuly2012.pdf. Accessed January 28, 2020.
38. American Diabetes Association: Pharmacologic approaches to glycemic treatment: Standards of medical care in diabetes—2020. Diabetes Care 2020; 43(Supplement 1):S98–110
39. Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin (DGAI), Deutsche Gesellschaft für Innere Medizin (DGIM), Deutsche Gesellschaft für Chirurgie (DGCH), Zwissler B: Preoperative evaluation of adult patients before elective, noncardiothoracic surgery: Joint recommendation of the German Society of Anesthesiology and Intensive Care Medicine, the German Society of Surgery, and the German Society of Internal Medicine. Anaesthesist 2019; 68(Suppl 1):25–39
40. Vellanki P, Rasouli N, Baldwin D, Alexanian S, Anzola I, Urrutia M, Cardona S, Peng L, Pasquel FJ, Umpierrez GE, Linagliptin Inpatient Research Group: Glycaemic efficacy and safety of linagliptin compared to basal-bolus insulin regimen in patients with type 2 diabetes undergoing non-cardiac surgery: A multicenter randomized clinical trial. Diabetes Obes Metab 2019; 21:837–43
41. Garg R, Schuman B, Hurwitz S, Metzger C, Bhandari S: Safety and efficacy of saxagliptin for glycemic control in non-critically ill hospitalized patients. BMJ Open Diabetes Res Care 2017; 5:e000394
42. Pasquel FJ, Gianchandani R, Rubin DJ, Dungan KM, Anzola I, Gomez PC, Peng L, Hodish I, Bodnar T, Wesorick D, Balakrishnan V, Osei K, Umpierrez GE: Efficacy of sitagliptin for the hospital management of general medicine and surgery patients with type 2 diabetes (Sita-Hospital): A multicentre, prospective, open-label, non-inferiority randomised trial. Lancet Diabetes Endocrinol 2017; 5:125–33
43. Ogawa S, Okawa Y, Sawada K, Goto Y, Fukaya S, Suzuki T: Effect of dipeptidyl peptidase-4 inhibitor in patients undergoing bypass surgery. Asian Cardiovasc Thorac Ann 2016; 24:863–7
44. Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, Jones NP, Komajda M, McMurray JJ; RECORD Study Team: Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): A multicentre, randomised, open-label trial. Lancet 2009; 373:2125–35
45. Alam F, Islam MA, Mohamed M, Ahmad I, Kamal MA, Donnelly R, Idris I, Gan SH: Efficacy and safety of pioglitazone monotherapy in type 2 diabetes mellitus: A systematic review and meta-analysis of randomised controlled trials. Sci Rep 2019; 9:5389
46. Anglade MW, Kluger J, White CM, Aberle J, Coleman CI: Thiazolidinedione use and post-operative atrial fibrillation: A US nested case-control study. Curr Med Res Opin 2007; 23:2849–55
47. Wilkinson S, Douglas I, Stirnadel-Farrant H, Fogarty D, Pokrajac A, Smeeth L, Tomlinson L: Changing use of antidiabetic drugs in the UK: Trends in prescribing 2000-2017. BMJ Open 2018; 8:e022768
48. DeFronzo R, Fleming GA, Chen K, Bicsak TA: Metformin-associated lactic acidosis: Current perspectives on causes and risk. Metabolism 2016; 65:20–9
49. Baradari AG, Emami Zeydi A, Aarabi M, Ghafari R: Metformin as an adjunct to insulin for glycemic control in patients with type 2 diabetes after CABG surgery: A randomized double blind clinical trial. Pak J Biol Sci 2011; 14:1047–54
50. Hulst AH, Polderman JAW, Ouweneel E, Pijl AJ, Hollmann MW, DeVries JH, Preckel B, Hermanides J: Peri-operative continuation of metformin does not improve glycaemic control in patients with type 2 diabetes: A randomized controlled trial. Diabetes Obes Metab 2018; 20:749–52
51. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE: Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane database Syst Rev 2010; (4):CD002967
52. Holstein A, Nahrwold D, Hinze S, Egberts EH: Contraindications to metformin therapy are largely disregarded. Diabet Med 1999; 16:692–6
53. Kajbaf F, Lalau JD: Mortality rate in so-called "metformin-associated lactic acidosis": A review of the data since the 1960s. Pharmacoepidemiol Drug Saf 2014; 23:1123–7
54. Liang H, Ding X, Li L, Wang T, Kan Q, Wang L, Sun T: Association of preadmission metformin use and mortality in patients with sepsis and diabetes mellitus: A

systematic review and meta-analysis of cohort studies. Crit Care 2019; 23:50
55. Varjabedian L, Bourji M, Pourafkari L, Nader ND: Cardioprotection by metformin: Beneficial effects beyond glucose reduction. Am J Cardiovasc Drugs 2018; 18:181–93
56. Turner R: Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998;352:854–65
57. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA: 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008; 359:1577–89
58. Duncan AI, Koch CG, Xu M, Manlapaz M, Batdorf B, Pitas G, Starr N: Recent metformin ingestion does not increase in-hospital morbidity or mortality after cardiac surgery. Anesth Analg 2007; 104:42–50
59. Ghods K, Davari H, Ebrahimian A: Evaluation of the effect of metformin and insulin in hyperglycemia treatment after coronary artery bypass surgery in nondiabetic patients. Ann Card Anaesth 2017; 20:427–31
60. Joshi SR, Standl E, Tong N, Shah P, Kalra S, Rathod R: Therapeutic potential of α-glucosidase inhibitors in type 2 diabetes mellitus: An evidence-based review. Expert Opin Pharmacother 2015; 16:1959–81
61. van de Laar FA, Lucassen PL, Akkermans RP, van de Lisdonk EH, Rutten GE, van Weel C: Alpha-glucosidase inhibitors for patients with type 2 diabetes: Results from a Cochrane systematic review and meta-analysis. Diabetes Care 2005; 28:154–63
62. Wu JH, Foote C, Blomster J, Toyama T, Perkovic V, Sundström J, Neal B: Effects of sodium-glucose cotransporter-2 inhibitors on cardiovascular events, death, and major safety outcomes in adults with type 2 diabetes: A systematic review and meta-analysis. Lancet Diabetes Endocrinol 2016; 4:411–9
63. Peters AL, Buschur EO, Buse JB, Cohan P, Diner JC, Hirsch IB: Euglycemic diabetic ketoacidosis: A potential complication of treatment with sodium-glucose cotransporter 2 inhibition. Diabetes Care 2015; 38:1687–93
64. Ueda P, Svanström H, Melbye M, Eliasson B, Svensson AM, Franzén S, Gudbjörnsdottir S, Hveem K, Jonasson C, Pasternak B: Sodium glucose cotransporter 2 inhibitors and risk of serious adverse events: Nationwide register based cohort study. BMJ 2018; 363:k4365
65. Thiruvenkatarajan V, Meyer EJ, Nanjappa N, Van Wijk RM, Jesudason D: Perioperative diabetic ketoacidosis associated with sodium-glucose co-transporter-2 inhibitors: A systematic review. Br J Anaesth 2019; 123:27–36
66. Bardia A, Wai M, Fontes ML: Sodium-glucose cotransporter-2 inhibitors: An overview and perioperative implications. Curr Opin Anaesthesiol 2019; 32:80–5
67. Chacko B, Whitley M, Beckmann U, Murray K, Rowley M: Postoperative euglycaemic diabetic ketoacidosis associated with sodium-glucose cotransporter-2 inhibitors (gliflozins): A report of two cases and review of the literature. Anaesth Intensive Care 2018; 46:215–9
68. American Diabetes Association: 15. Diabetes care in the hospital: Standards of medical care in diabetes-2020. Diabetes Care 2020; 43(Suppl 1):S193–202
69. EMA: EMA confirms recommendations to minimise ketoacidosis risk with SGLT2 inhibitors for diabetes | European Medicines Agency. Available at: https://www.ema.europa.eu/en/news/ema-confirms-recommendations-minimise-ketoacidosis-risk-sglt2-inhibitors-diabetes. Accessed January 28, 2020.
70. Pasquel FJ, Fayfman M, Umpierrez GE: Debate on insulin vs non-insulin use in the Hhospital setting-Is it time to revise the guidelines for the management of inpatient diabetes? Curr Diab Rep 2019; 19:65
71. Ichai C, Preiser JC; Société Française d'Anesthésie-Réanimation; Société de Réanimation de langue Française; Experts group: International recommendations for glucose control in adult non diabetic critically ill patients. Crit Care 2010; 14:R166
72. Song X, Wang J, Gao Y, Yu Y, Zhang J, Wang Q, Ma X, Estille J, Jin X, Chen Y, Mu Y: Critical appraisal and systematic review of guidelines for perioperative diabetes management: 2011-2017. Endocrine 2019; 63:204–12