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Review

Towards ending the perioperative metformin controversy: a narrative review

Van Hove K.[1], Coremans P.[1], Van Oers F.[1], De Block C.[2]

[1]Department of diabetology-endocrinology, Vitaz, Sint-Niklaas, Belgium; [2]Department of Endocrinology, Diabetology and Metabolism, Antwerp University Hospital, Edegem, Belgium.

Corresponding author: K. Van Hove, Moerlandstraat 1, 9100 Sint-Niklaas, Belgium. E-mail: kobe.vanhove@hotmail.com

Abstract

Metformin is the most widely prescribed oral glucose-lowering medication and serves as the first-line treatment for type 2 diabetes mellitus due to its efficacy, cost-effectiveness, and favourable safety profile. Given its widespread use, perioperative management of metformin is a common clinical challenge. Concerns regarding metformin and lactic acidosis have historically led to recommendations for its preoperative discontinuation. Recent studies, including randomized controlled trials, have found no significant difference in lactic acidosis risk between patients who continue or discontinue metformin perioperatively. However, these studies are highly heterogeneous, and the randomized controlled trials include a limited number of patients; on the other hand, metformin-induced and metformin-associated lactic acidosis are uncommon. We conducted an extensive narrative review of perioperative metformin guidelines, including ten publications from 2015 to 2024. Seven out of ten guidelines support continuing metformin in patients without risk factors, such as impaired renal function or the use of contrast agents. When risk factors are present, most guidelines recommend withholding metformin on the morning of surgery. There has been a notable shift in recommendations regarding resumption. Guidelines published before 2020 advised waiting 48 hours postoperatively, but more recent guidance suggests metformin can be restarted once adequate oral intake is established and renal function is confirmed to be stable. However, definitive large-scale randomized trials are still needed to establish standardized recommendations.

Keywords: **Metformin, Perioperative Care, Anesthesia / adverse effects, Guidelines.**

Introduction

Metformin is the most commonly prescribed oral glucose-lowering medication. It is widely regarded as the first-line treatment of choice for individuals with type 2 diabetes mellitus[1,2]. Advantages include low cost, high efficacy, and a favourable safety profile. Furthermore, evidence suggests a modest cardioprotective effect independent of glucose-lowering properties. The fact that the effect on weight ranges from neutral to modest weight loss is a benefit compared with insulin and sulfonylureas[1,3].

Given the widespread use of metformin, it is frequently encountered in the preoperative setting. Historically, it was recommended to discontinue metformin before surgery due to concerns about lactic acidosis. However, in recent years, this recommendation has been increasingly challenged as new evidence emerges. This article aims to explore the current literature and examine the most recent guidelines regarding the perioperative use of metformin. Should it be withheld, or is it safe to continue? And when is it appropriate to resume metformin after surgery?

Methodology

An extensive search for preoperative, perioperative, and postoperative metformin guidelines was conducted using PubMed, Embase, and Google Scholar. Recognizing that many official guidelines may not be indexed in traditional medical databases like PubMed or Embase, we also explored additional online sources. The search terms were "perioperative metformin guidelines", "metformin preoperative management", "metformin postoperative management", "diabetes perioperative guidelines", and "anesthesia guidelines for diabetic patients". Only guidelines published in English and between January 2014 and January 2025 were included.

To evaluate the scientific basis of the guidelines, a comprehensive literature search for clinical trials was performed in PubMed, Embase, and ClinicalTrials.gov, using the search terms "perioperative metformin," "metformin surgery," and "metformin lactic acidosis surgery." Only studies published in English between January 2004 and November 2025 were included.

Background

Mechanism of action

Metformin was first introduced as a glucose-lowering agent in 1957 due to its remarkable ability to reduce blood glucose levels. Despite its long-standing clinical use, the exact mechanism of action remains under investigation. The primary effect is the inhibition of hepatic gluconeogenesis.The main target organelles involved are mitochondria and lysosomes. The glucose-lowering effect occurs through both AMP-activated protein kinase (AMPK)-dependent and AMPK-independent pathways. sosomes, and the glucose-lowering effect occurs through both AMP-activated protein kinase (AMPK)-dependent and AMPK-independent pathways. There is strong evidence that the gut and microbiota also contribute to glucose regulation, for instance by stimulating intestinal L-cells to release incretins such as glucagon-like peptide 1 (GLP-1) and peptide YY. Notably, metformin is not metabolized by the liver; its elimination relies entirely on renal function[1,4-6].

Side effects

Adverse effects of metformin are relatively common but generally mild and transient, with gastrointestinal intolerance being the most frequently reported (20-30%). Other potential side effects include vitamin B12 deficiency (approximately 10%), lactic acidosis (3–10 cases per 100,000 patient-years), and hypoglycemia, the latter depending on concomitant use of other glucose-lowering medications[1,2,4].

Gastrointestinal

Gastrointestinal effects of metformin include diarrhea, nausea, flatulence, abdominal discomfort, and a metallic taste. These symptoms are typically mild, dose-dependent, and transient. The underlying mechanism is thought to involve the accumulation of metformin in enterocytes of the small intestine, leading to local irritation and increased fluid retention in the large intestine. Gradual dose titration, dose reduction, or taking medication with meals has been shown to alleviate symptoms. Switching to an extended-release formulation may further reduce gastrointestinal side effects by reducing intestinal metformin accumulation[1,4,7,8].

Lactic acidosis

A potentially lethal, though rare, complication of metformin therapy is the so-called metformin-associated lactic acidosis (MALA). The estimated incidence is low, with 3–10 cases per 100,000 person-years, yet the reported mortality remains high, ranging from 30% to 50% depending on the clinical setting[1,2,4,9].

Historically, MALA is commonly defined as a lactic acidosis (blood pH < 7.35 and lactate > 5.0 mmol/L) in the context of metformin use or overdose. Importantly, this definition lacks nuance, as it does not establish causality between metformin and lactic acidosis[9,10].

This underlines the importance of distinguishing between metformin-induced lactic acidosis (MILA), metformin-unrelated lactic acidosis (MULA), and MALA. MILA is defined as lactic acidosis that results directly and exclusively from the toxic accumulation of metformin, with no other contributing comorbidities. In contrast, MULA refers to lactic acidosis occurring in a patient taking metformin, but without metformin accumulation, where the acidosis is entirely attributable to other causes (e.g., sepsis or hypoperfusion). Finally, MALA is a mixed form, in which both metformin accumulation and underlying comorbid conditions contribute to lactic acidosis. Accurate classification is essential, as it directly guides prognosis and management[10].

Thus, diagnosing lactic acidosis in metformin using patients is challenging and prone to pitfalls. The first step is to establish whether true metformin accumulation is present, for example due to renal failure or overdose. The second is to determine whether lactic acidosis is directly attributable to metformin or to another precipitating factor such as sepsis, shock, or hepatic dysfunction. Nevertheless, therapeutic levels of metformin vary widely between individuals, and high concentrations do not consistently correlate with lactic acidosis[10].

Measuring both plasma and erythrocyte metformin concentrations can be informative: plasma levels mainly reflect recent intake, whereas erythrocyte concentrations better indicate tissue accumulation. While no universally accepted toxic threshold has been established, a recent retrospective observational study proposed a plasma concentration of 9.9 mg/L[11].

The mechanism causing this metabolic acidosis involves the stimulation of anaerobic metabolism at the earlier mentioned mitochondria and

lysosomes, which leads to elevated lactate levels in the body. Patients often present with nonspecific symptoms, including gastrointestinal complaints such as nausea, vomiting, and diarrhea[1,2,4,9].

Precipitating factors for MALA include sepsis, heart failure, chronic liver disease, and renal impairment. This is because these conditions can elevate metformin levels beyond the therapeutic range by reducing renal clearance or impairing hepatic lactate metabolism, thereby increasing overall lactate levels. In addition, deteriorating kidney and liver function, as well as increased lactate production due to tissue damage, can occur during surgery and be contributing factors, especially in major procedures[1,2,4,12].

Although the recommendation to discontinue metformin perioperatively has been in place since a 1997 case report of MALA following minor surgery, the association between surgery, anesthesia, and MALA remains unclear, with evidence limited to sporadic clinical cases[13,14].

The treatment for lactic acidosis is mainly supportive, as no specific antidote exists, and centers on correcting acid-base disturbances, addressing contributing comorbidities, and promoting metformin clearance when indicated. In cases of intoxication, early presentation may allow for activated charcoal. The severity of the condition will guide therapy, which may include bicarbonate infusion if the pH is below 7.20, hemodialysis, or continuous venovenous hemofiltration[9,15].

Role in the treatment of diabetes mellitus

If diet and lifestyle interventions fail to achieve glycemic goals, metformin is the recommended first-line pharmacological therapy in type 2 diabetes mellitus if there is no history of atherosclerosis cardiovascular disease or chronic kidney disease (CKD), as endorsed by the American Diabetes Association (ADA)[3].

Metformin, known for its ability to reduce A1C levels by 1-2% as monotherapy or in combination therapy, is both cost-effective and well-established due to its long history of use and favorable safety profile. It has shown significant cardiovascular benefits, as demonstrated by a 30% reduction in the risk of macrovascular complications in the United Kingdom Prospective Diabetes Study (UKPDS) study in a small subgroup of the total cohort treated with metformin compared to the diet-only group. This finding was later confirmed by studies such as the Dutch HOME trial. Unlike insulin and sulfonylureas, metformin is weight-neutral or may even promote weight loss[3,4,16].

Research indicates that the efficacy of metformin is dose dependent. Up to 2000-2500 mg/day, there is a linear relationship between the dose of metformin and a reduction in A1C values. With a maximal dose of 2500 mg, one can achieve an A1C reduction of up to 2.0%[1].

Contra indications

Metformin is contraindicated if the estimated glomerular filtration rate (eGFR) is < 30 ml/min/1.73 m², as the kidneys are unable to adequately clear metformin, increasing the risk of lactic acidosis. When the eGFR is between 30 and 60 ml/min/1.73 m², metformin may be used at a reduced dose, as recommended by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA). However, in recent years, there is increasing evidence that metformin can be used in patients with stable CKD even up to CKD stage 4. A dose adjustment is required in the following stages: CKD 3A: 1500 mg/day, CKD 3B: 1000 mg/day, and CKD 4: 500 mg/day[1,4,17].

Other contraindications include liver disease, acute unstable congestive heart failure, conditions with decreased perfusion or hemodynamic instability, alcoholism, and acidosis-related conditions[1,4].

Pregnancy is not a contra-indication, nevertheless, there are some concerns regarding the metabolic effects on the child, according to the ADA[4].

Other indications for discontinuing metformin

Other indications for temporarily stopping metformin are related to acute kidney injury. Acute illness, often combined with dehydration, can worsen kidney function and potentially lead to MALA[4].

Iodinated contrast is another potential reason to discontinue metformin. Nearly all major organizations — including the FDA, the European Society of Urogenital Radiology, the American College of Radiology, the ADA, and the National Kidney Foundation — agree that metformin should be discontinued when the estimated eGFR falls below 30 mL/min/1.73 m². Although, for eGFR values between 30 and 60 mL/min/1.73 m², each organization offers its own specific recommendations. The ADA recommends making a case-by-case decision on the need to suspend metformin for an eGFR of 30–60 mL/min/1.73 m² in the absence of other risk factors for worsening renal function. An overview of these guidelines is summarized in Table I[4,18].

Perioperative management

Patients with diabetes undergo surgical procedures more frequently than those without, and poor

Table I. — Guidelines regarding the management of metformin in contrast-enhanced imaging: continuation or discontinuation – last updated 16 June 2025.

	eGFR < 30 ml/ min/1.73m²		eGFR 30 – 60 ml/ min/1.73m²		eGFR > 60 ml/ min/1.73m²	
	Continue	Stop	Continue	Stop	Continue	Stop
FDA [4]		✓		✓	✓*[a]	
European Society of Urogenital Radiology [4]		✓	✓*[b]		✓*[b]	
American College of Radiology [18]		✓	Individual decision		✓	
National Kidney Foundation [18]		✓	Individual decision		✓	
ADA [4]		✓	Individual decision		✓*[b]	

*a If there is no history of liver disease, alcoholism, heart failure; or intra-arterial iodinated contrast; *b If there is no AKI; or first renal passage of contrast.
Abbreviations: FDA, Food and Drug Administration; ADA, The American Diabetes Association; AKI, acute kidney impairment; eGFR, estimated glomerular filtration rate.

glycemic control is associated with increased postoperative morbidity and mortality following surgery. Historically, metformin was recommended to be stopped the day before or the day of surgery due to the higher risk of lactic acidosis and the potential worsening of renal function associated with surgery. However, evidence regarding the perioperative management of metformin remains limited and is primarily based on expert opinion and consensus[19,20]. So, what is the current state of affairs at this moment?

Scientific background

In recent years, several clinical studies have sought to address the concern of metformin and lactic acidosis in the postoperative setting. Data extracted from these clinical investigations and available scientific research provide valuable insights into the safety of metformin use in the postoperative setting.

Randomized controlled trials

Below, we synthesize the key findings from randomized clinical trials conducted over the past 20 years that investigated the use of metformin in the perioperative context.

A double-blind randomized clinical trial conducted in 2011 compared the effects of high-dose metformin (1000 mg twice daily with insulin) (n = 94) versus insulin alone (n = 96) in type 2 diabetic patients following coronary artery bypass surgery. No significant differences in lactate levels or lactic acidosis were observed between the groups. However, no cases of lactic acidosis occurred in either group, and metformin was not initiated preoperatively[21].

Another double-blind randomized clinical trial conducted in 2011 compared metformin plus insulin (n = 46) with insulin alone (n = 47) during the postoperative period (from 3 hours after extubation). There was a significant difference in glycemic control, with more episodes of both hyperglycemia and hypoglycemia observed in the insulin alone group. No significant differences in lactate levels were observed up to 5 days postoperatively, and no cases of lactic acidosis were reported. The main limitations of this study were again the small sample size and the discontinuation of oral hypoglycemic agents 48 hours before surgery[22].

In 2015, a placebo-controlled, double-blind study was conducted in non-diabetic adults undergoing elective on-pump CABG surgery. The study compared metformin (n = 52) and placebo (n = 48) administered three days before surgery to evaluate myocardial injury, assessed by troponin measurement. No difference in troponin levels was found, indicating no beneficial effect of metformin in preventing myocardial injury. However, metformin appeared safe, as no differences were observed in secondary endpoints such as inotropic support, time to extubation, duration of stay in the intensive care unit, or postoperative insulin use. Data on lactic acid levels or glycemic control were not reported[23].

Furthermore, in 2017, a randomized controlled trial was conducted in patients with type 2 diabetes mellitus scheduled for non-cardiac surgery (n metformin group = 37, n control group = 33). Postoperative glucose levels were similar between groups, and postoperative lactate levels did not differ significantly. The authors concluded that metformin did not raise lactate levels to a clinically relevant degree. Nevertheless, the number of patients was limited, and no cases of lactic acidosis occurred, which is unsurprising given the rarity of this complication[24].

In 2018, a randomized controlled trial was carried out in patients with type 2 diabetes who were taking oral antidiabetic medications (metformin and/or sulfonylureas) and were scheduled for ambulatory surgery (n stop medication on the day of surgery

= 73, n continue medication = 69). Perioperative blood glucose levels were significantly lower in the group that continued their medication. Although a clear difference in blood glucose levels was observed, the study does not demonstrate whether this translates into a clinically relevant effect. Additional limitations include the mixed inclusion of sulfonylurea users and the absence of lactate measurements[25].

A recent double-blind randomized controlled trial was conducted in elective colon cancer patients without diabetes. One group received metformin (n = 23), while the control group received no placebo (n = 25), to investigate postoperative hyperglycemia. Treatment was initiated 20 days before and continued for 10 days after surgery (restarting with the first postoperative meal). The study found a significant reduction in postoperative hyperglycemia, defined as blood glucose levels >180 mg/dL, in the metformin group. However, no significant difference was observed when hyperglycemia was defined as >138 mg/dL. Study limitations included inconsistent timing of blood glucose measurements across patients, lack of routine measurement of lactate levels, and discontinuation of metformin on the morning of surgery[26].

Two randomized controlled trials are still ongoing. One is examining metformin versus placebo in patients undergoing total joint replacement surgery. In this study, metformin is continued on the day of surgery, and both patients with and without diabetes are eligible for inclusion. A limitation is the small sample size (n = 40)[27]. The other trial will compare continuation of metformin therapy versus preoperative cessation of oral metformin 24 hours before non-cardiac surgery to evaluate the effects on perioperative glycemic control[28].

Prospective and retrospective trials

A 2010 Cochrane review, including 347 prospective comparative trials and observational cohort studies with a total of 96,295 patients with type 2 diabetes, was conducted. This large-scale analysis found no increased incidence of lactic acidosis in patients treated with metformin compared with those receiving other antihyperglycemic agents. However, this Cochrane review was not performed in a perioperative setting, and the included studies were highly heterogeneous[29].

In total, four studies—retrospective or prospective—found no significant difference in postoperative mortality or the incidence of lactic acidosis among metformin users. Nevertheless, these studies were highly heterogeneous; metformin was mostly discontinued on the morning of surgery, and routine lactate measurements were not consistently performed[20,30-32].

A summary of all studies, including randomized controlled trials, on perioperative metformin use over the past two decades is presented in Table II.

Guidelines

This section describes the differences among existing guidelines concerning the perioperative management of metformin, indicating when the medication should be withheld and when it should be restarted. The guidelines are discussed in order of the date of publication.

1. The Association of Anaesthetists of Great Britain and Ireland (AAGBI) states that metformin can be continued on the day of surgery. If the patient has an eGFR below 60 mL/min/1.73m² and/or contrast medium is used, metformin should be discontinued on the day of the procedure and for the next 48 hours[33].
2. The Association of British Clinical Diabetologists (ABCD), similar to the AAGBI, recommends continuing metformin on the day of surgery, with the exception of skipping the lunch dose if there are three doses. As with the AAGBI, if the patient's eGFR is below 60 mL/min/1.73m² and/or contrast media is used during the procedure, metformin should be discontinued on the day of surgery and for the following 48 hours[34].
3. The Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) recommends continuing metformin if iodinated contrast imaging is not used, the patient has an eGFR > 60 mL/min/1.73 m², and there is no history of liver disease, alcoholism, or heart failure. If metformin was stopped due to the presence of any of the aforementioned conditions, it should be withheld on the day of surgery and restarted 48 hours later if renal function is stable (reassess eGFR after 48 hours) and the patient has a normal intake[35].
4. The French Society of Anaesthesia and Intensive Care Medicine (SFAR) and the French Society for the Study of Diabetes (FSD) recommend discontinuing metformin the night before major surgery. Their reasoning is that there is no urgency to resume metformin, and that insulin can be used safely for in-hospital patients during the interim period. In the case of minor or outpatient surgery, metformin may be continued, provided there is no severe renal impairment (with no specific eGFR threshold mentioned)[36].
5. Diabetes Australia and the Royal Australian and the College of General Practitioners (RACGP)

Table II. — Clinical trials on perioperative metformin use and lactic acidosis.

Randomized controlled trials					
Article	Year	Trial design	Number of patients	Conclusion	Comments
Does high-dose metformin cause lactic acidosis in type 2 diabetic patients after CABG surgery? A double blind randomized clinical trial[21]	2011	Randomized controlled trial	$n_{\text{metformin and insulin}} = 94$ $n_{\text{insulin}} = 96$	No significant differences in lactate levels or lactic acidosis were observed between the groups	No cases of lactic acidosis occurred in either group. Metformin was not initiated preoperatively.
Metformin as an adjunct to insulin for glycemic control in patients with type 2 diabetes after CABG surgery: a randomized double blind clinical trial[22]	2011	Randomized controlled trial	$n_{\text{metformin and insulin}} = 46$ $n_{\text{insulin}} = 47$	There was a significant difference in glycemic control, with more episodes of both hyperglycemia and hypoglycemia observed in the insulin alone group.	No cases of lactic acidosis occurred in either group. Discontinuation of metformin 48 hours before surgery.
Effect of metformin pretreatment on myocardial injury during coronary artery bypass surgery in patients without diabetes (MetCAB): a double-blind, randomised controlled trial[23]	2015	Randomized placebo-controlled trial	$n_{\text{metformin}} = 52$ $n_{\text{placebo}} = 48$	Metformin is safe, as no differences were observed in secondary endpoints such as inotropic support, time to extubation, duration of stay in the intensive care unit, or postoperative insulin use.	Non-diabetic adults. Metformin was initiated three days before surgery and therefore cannot be considered chronic use. There was no data on lactic acid levels or glycemic control.
Perioperative continuation of metformin does not improve glycaemic control in patients with type 2 diabetes: A randomized controlled trial [24]	2017	Randomized controlled trial	$n_{\text{metformin continued}} = 37$ $n_{\text{metformin withheld}} = 33$	Metformin did not raise lactate levels to a clinically relevant degree.	Postoperative glucose levels were similar between groups. No cases of lactic acidosis occurred in either group. Small sample size.
Preoperative Continuation Versus Interruption of Oral Hypoglycemics in Type 2 Diabetic Patients Undergoing Ambulatory Surgery: A Randomized Controlled Trial[25]	2018	Randomized controlled trial	$n_{\text{stop medication on the day of surgery}} = 73$ $n_{\text{continue medication}} = 69$	Perioperative blood glucose levels were significantly lower in the group that continued their medication.	Both metformin and sulfonylurea users were included. Absence of lactate measurements.
Perioperative Continuation of Metformin Therapy in Patients With Type 2 Diabetes Mellitus Undergoing Non-cardiac Surgery[28]	2020	Randomized controlled trial	$n_{\text{continue metformin}} = ?$ $n_{\text{discontinue 24 hours before surgery}} = ?$	No results available yet; the study is still ongoing (last update on ClinicalTrials.gov was in 2020).	

Table II. — Clinical trials on perioperative metformin use and lactic acidosis - continued.

Randomized controlled trials					
Article	Year	Trial design	Number of patients	Conclusion	Comments
Perioperative Metformin Treatment to Reduce Postoperative Hyperglycemia After Colon Cancer Surgery: A Randomized Clinical Trial[26]	2024	Randomized placebo-controlled trial	$n_{metformin} = 23$ $n_{placebo} = 25$	Significant reduction in postoperative hyperglycemia, defined as blood glucose levels >180 mg/dL.	Non-diabetic adults. Metformin was initiated ten days before surgery and therefore cannot be considered chronic use. No significant reduction in postoperative hyperglycemia, defined as blood glucose levels >138 mg/dL. Inconsistent timing of blood glucose measurements across patients. Absence of routine lactate measurements. Discontinuation of metformin on the morning of surgery.
Perioperative metformin use in patients undergoing total joint replacement surgery: protocol for a randomized, placebo-controlled pilot study[27]	2025	Randomized placebo-controlled trial	$n_{metformin} = 20$ $n_{placebo} = 20$	No results available yet; the study is still ongoing.	Diabetic and non-diabetic adults. Metformin will be initiated two weeks before surgery and therefore cannot be considered chronic use.
Prospective and retrospective trials					
Article	Year	Trial design	Number of patients	Conclusion	Comments
Recent Metformin Ingestion Does Not Increase In-Hospital Morbidity or Mortality After Cardiac Surgery[30]	2007	Retrospective study	$n_{metformin\ treated} = 443$ $n_{not\ metformin\ treated} = 443$	Metformin users do not have a higher risk of in-hospital mortality or postoperative complications after cardiac surgery compared with non-metformin-treated patients.	The last dose was administered 8 to 24 hours postoperatively. Routine measurement of lactic acid was not performed. Medication was restarted after extubation once the patient tolerated oral intake.

Table II. — Clinical trials on perioperative metformin use and lactic acidosis - continued.

Prospective and retrospective trials					
Article	Year	Trial design	Number of patients	Conclusion	Comments
Metformin is not associated with lactic acidosis in patients with diabetes undergoing coronary artery bypass graft surgery: a case control study[31]	2017	Case control study	$n_{\text{metformin group}} = 41$ $n_{\text{other hypoglycemic agents}} = 68$	Metformin combined with insulin provides better glycemic control without causing lactic acidosis after CABG surgery.	Metformin was discontinued the morning of the surgery and was restarted 3 hours after extubation. The incidence of lactic acidosis (defined as arterial lactate level ≥ 5 mmol/L and serum bicarbonate ≤ 22 mmol/L) was significantly higher in the group treated with other hypoglycemic agents.
Continuation of Metformin Till Night Before Surgery and Lactate Levels in Patients Undergoing Coronary Artery Bypass Graft Surgery[32]	2019	Prospective cohort study	$n_{\text{metformin group}} = 387$ $n_{\text{non-metformin group}} = 239$ $n_{\text{non-diabetic group}} = 164$	Continuation of metformin does not significantly elevate lactate levels after CABG surgery.	87% of the patients were males. The incidence of lactic acidosis (defined as arterial lactate lactate > 5 mmol/L, pH <7.35) was higher in the non-metformin group, but not significant compared to the metformin group. Metformin was continued untill night before surgery and restarted if the patient could tolerate a normal diet.
Metformin and mortality after surgery: a systematic review and meta-analysis[20]	2022	Systematic review (2 retrospective studies and 1 cohort study)	$n_{\text{metformin group}} = 3911$ $n_{\text{control group}} = 8760$	The analysis found no difference in 30-day mortality between the metformin group and the non-metformin group.	This review was only based on 3 studies. There is no measurement of lactate or mention of the numbers of lactic acidosis.
Abbreviations: CABG, Coronary Artery Bypass Grafting.					

recommend withholding oral glucose-lowering medications on the morning of surgery, irrespective of whether they are on the morning or afternoon list. Postoperatively, metformin can be restarted 24 hours after major surgery, provided there has been no deterioration in serum creatinine[37].

6. The American Society of Anesthesiologists (ASA) differentiates between two types of surgery: in minor surgery metformin can be continued, except in patients with renal dysfunction (no specific eGFR threshold provided), procedures requiring contrast medium administration or when using nonsteroidal medications. While in major surgery metformin should be stopped the day before surgery. In both situations, metformin should be restarted once oral intake is restored and kidney function is stable[2].

7. Just like the ABCD and the AAGBI, the Centre for Perioperative Care (CPOC) recommend continuing metformin on the day of surgery. If the patient has an eGFR below 60 mL/min/1.73m² and/or contrast medium is used, metformin should be discontinued on the day of the procedure and for the next 48 hours. Similar to the ABCD, the CPOC recommends omitting the lunchtime dose if the patient is on a three-times-daily regimen[38,39].

8. The American Diabetes Association (ADA) recommends discontinuing metformin on the day of surgery, without distinguishing between major and ambulatory surgery or taking risk factors into account. Postoperatively, assess the presence of contraindications before considering its reintroduction[4].

9. The Australian and New Zealand College of Anaesthetists (ANZCA) and the Australian Diabetes Society (ADS) recommend discontinuing metformin on the day of surgery and restarting it once the patient resumes eating. In patients with renal impairment (CKD stage 3B or below / eGFR < 45 mL/min/1.73 m²) or those undergoing major surgery, metformin should be restarted once renal function is deemed adequate[40].

10. The Society for Ambulatory Anesthesia advises patients undergoing ambulatory surgery to continue metformin unless the eGFR is below 45 mL/min/1.73 m² and/or the procedure involves nephrotoxic agents (e.g., contrast dye). If metformin was stopped, it can be resumed once food intake is adequate[33].

An overview of these guidelines for the preoperative and postoperative management of metformin is summarized in Table III.

Discussion

Our review of current international guidelines reveals a consistent recommendation to continue metformin in the perioperative period, provided there are no significant risk factors. Specifically, seven out of ten guidelines support the continuation of metformin in patients with preserved renal function (eGFR > 60 mL/min/1.73 m²) and no exposure to iodinated contrast media. Only a few still advocate for routine discontinuation without considering individual risk profiles. In cases where risk factors are present—such as impaired renal function or the planned use of contrast agents—most guidelines (8 out of 9) advise withholding metformin the morning before surgery. Only the guideline of ASA is more cautiously and advises to stop 24 hours before[2,4,33-41].

The latest guidelines are supported by current scientific evidence. Multiple studies, including randomized controlled trials, have demonstrated no increased incidence of lactic acidosis with continued metformin use in the perioperative setting, provided that contraindications are absent. So the longstanding concern over metformin and lactic acidosis, largely based on anecdotal reports of biguanide-associated lactic acidosis is thus increasingly challenged[12,20-26,29].

However, these findings have limitations. The randomized controlled trials generally have small sample sizes; because MALA and MILA are rare conditions, the studies are clearly underpowered to draw a definitive conclusion. Only 2 out of the 6 randomized controlled trials continued metformin perioperatively. Furthermore, the studies exhibited significant heterogeneity in primary endpoints, trial design, types of surgery, and patient populations, with some including non-diabetic individuals[21-26].

Current evidence suggests that metformin can be safely restarted once oral intake is tolerated, provided no additional risk factors are present. Indeed, in patients with identifiable risk factors, guidelines before 2020 recommend restarting after 48 hours, while more recent guidelines tend to restart when patients resume oral intake. We anticipate that continuing or promptly restarting metformin in the perioperative period may enhance glycaemic control and reduce the (temporary) need for insulin. From the patient's perspective, uninterrupted metformin use may also help prevent post-operative medication errors, making treatment plans easier to follow. The majority, but not all, studies show better glycemic control when using

Table III. — Guidelines regarding the perioperative management of metformin: continuation or discontinuation, and timing of resumption– last updated 13 May 2025.

Year	Organization	Subgroup	Continue	Stop		Restart		
				Day of surgery	24h before	If oral intake	24h after	48h after
2015	AAGBII [39]	No contrast and eGFR >60 ml/min/1.73m²	✓					
		Contrast or eGFR < 60 ml/min/1.73m²		✓				✓
2016	ABCD [34]	No contrast and eGFR >60 ml/min/1.73m²	✓*[a]					
		Contrast or eGFR < 60 ml/min/1.73m²		✓				✓
2017	SEMDSA [35]	eGFR > 60 mL/minute/1.73m² and no history of liver disease, alcoholism, or heart failure	✓					
		eGFR < 60 mL/minute/1.73m², history of liver disease, alcoholism, or heart failure		✓				✓*[b]
2018	SFAR - SFD [36]	Minor surgery	✓*[c]					
		Major surgery		✓				✓*[c]
2020	RACGP [37]			✓			✓*[e]	
2020	ASA [2]	1-day minor surgery	✓*[d]			✓*[b]		
		Major surgery		✓		✓*[b]		
2021	COPC [38]	No contrast and eGFR >60 ml/min/1.73m²	✓*[a]					
		Contrast or eGFR < 60 ml/min/1.73m²		✓				✓
2022	ADA [4]			✓		?*[e]	?*[e]	?*[e]
2022	ANZCA - ADS [40]	No major surgery and eGFR > 45 ml/min/1.73m2		✓		✓		
		Major surgery or eGFR < 45 ml/min/1.73m²		✓		?*[c]	?*[c]	?*[c]
2024	Society for Ambulatory Anesthesia [33]	No contrast and eGFR > 45 ml/min/1.73m²	✓					
		Contrast or eGFR < 45 ml/min/1.73m²		?		✓		

*a: If taken three times per day, omit lunchtime dose.
*b: If renal function is stable and patient is eating normally.
*c: If there is no severe renal impairment.
*d: Except if there is renal dysfunction or use of contrast, NSAID, ACE-inhibitor or ARB.
*e: Evaluate the presence of contraindications to subsequent reintroduction.
Abbreviations: AAGBI, The Association of Anaesthetists of Great Britain and Ireland; ABCD, The Association of British Clinical Diabetologists; SEMDSA, The Society for Endocrinology, Metabolism and Diabetes of South Africa; SFAR, The French Society of Anaesthesia and Intensive Care Medicine; SFD, The French Society for the Study of Diabetes; RACGP, The Royal Australian and the College of General Practitioners; ASA, The American Society of Anesthesiologists; COPC, The Centre for Perioperative Care; ADA, The American Diabetes Association; ANZCA, The Australian and New Zealand College of Anaesthetists; ADS, the Australian Diabetes Society; eGFR, estimated glomerular filtration rate; NSAID, non-steroidal anti-inflammatory drug; ACE-inhibitor, angiotensin-converting enzyme inhibitor; ARB, Angiotensin-receptor bl.

metformin in combination with insulin versus insulin alone. However, the true safety benefit of an earlier versus delayed reintroduction remains uncertain, as no clinical studies have yet assessed its effectiveness or necessity. Further research is needed to determine whether immediate reinitiation upon resumption of oral intake or a more cautious delay offers the best balance between safety and glycemic control[2,4,21,22,24-26,33-40].

Conclusion

In this review, we have outlined the mechanism of action of metformin and its role in current clinical practice. Given the potential for adverse events, its use in the perioperative setting requires careful consideration. To help guide clinical decision-making, we have conducted a comprehensive review of current international guidelines regarding the use of metformin in the perioperative period. The vast majority of professional societies now recommend continuing metformin perioperatively in patients with normal renal function (eGFR > 60 mL/min/1.73 m²) and no anticipated use of iodinated contrast media. However, if metformin needs to be discontinued—such as in cases of impaired renal function (eGFR < 60 mL/min/1.73 m²) or contrast exposure—it is typically withheld the morning before surgery. Resuming of metformin is recommend after 24 hours later or once oral intake is tolerated by most guidelines. These recommendations are expected to significantly impact the management of diabetic patients on metformin by making perioperative guidelines more practical and easier to implement. Despite growing support for the safety of continuing metformin in low-risk patients, there is a lack of large, high-quality randomized controlled trials to robustly support current recommendations.

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References

1. Sanchez-Rangel E, Inzucchi SE. Metformin: clinical use in type 2 diabetes. Diabetologia. 2017;60(9):1586–93.
2. Preiser JC, Provenzano B, Mongkolpun W, Halenarova K, Cnop M. Perioperative Management of Oral Glucose-lowering Drugs in the Patient with Type 2 Diabetes. Anesthesiology. 2020;133(2):430–8.
3. Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, et al. Management of Hyperglycemia in Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2022;45(11):2753–86.
4. Vieira IH, Barros LM, Baptista CF, Rodrigues DM, Paiva IM. Recommendations for Practical Use of Metformin, a Central Pharmacological Therapy in Type 2 Diabetes. Clin Diabetes. 2022;40(1):97–107.
5. Buse JB, DeFronzo RA, Rosenstock J, Kim T, Burns C, Skare S, et al. The Primary Glucose-Lowering Effect of Metformin Resides in the Gut, Not the Circulation: Results From Short-term Pharmacokinetic and 12-Week Dose-Ranging Studies. Diabetes Care. 2016;39(2):198–205.
6. Foretz M, Guigas B, Viollet B. Metformin: update on mechanisms of action and repurposing potential. Nat Rev Endocrinol. 2023;19(8):460–76.
7. Nasri H, Rafieian-Kopaei M. Metformin: Current knowledge. J Res Med Sci. 2014;19(7):658–64.
8. Oh JR, Song HC, Chong A, Ha JM, Jeong SY, Min JJ, et al. Impact of medication discontinuation on increased intestinal FDG accumulation in diabetic patients treated with metformin. AJR Am J Roentgenol. 2010;195(6):1404–10.
9. Dyatlova N, Tobarran NV, Kannan L, North R, Wills BK. Metformin-Associated Lactic Acidosis (MALA). StatPearls. Treasure Island (FL) ineligible companies. : StatPearls Publishing. Copyright © 2025, StatPearls Publishing LLC.; 2025.
10. Lalau JD, Kajbaf F, Protti A, Christensen MM, De Broe ME, Wiernsperger N. Metformin-associated lactic acidosis (MALA): Moving towards a new paradigm. Diabetes Obes Metab. 2017;19(11):1502–12.
11. Bennis Y, Bodeau S, Batteux B, Gras-Champel V, Masmoudi K, Maizel J, et al. A Study of Associations Between Plasma Metformin Concentration, Lactic Acidosis, and Mortality in an Emergency Hospitalization Context. Crit Care Med. 2020;48(12):e1194–e202.
12. DeFronzo R, Fleming GA, Chen K, Bicsak TA. Metformin-associated lactic acidosis: Current perspectives on causes and risk. Metabolism. 2016;65(2):20–9.
13. Angeletti C, Vergani C, Troili S, Carrocci C, De Martinis G, Venturoni F, et al. Two cases of metformin-associated lactic acidosis in post-operative period in emergency department: time to be aware-case reports. AME Case Rep. 2023;7:39.
14. Vreven R, De Kock M. Metformin lactic acidosis and anaesthesia: myth or reality? Acta Anaesthesiol Belg. 2005;56(3):297–302.
15. Alotaibi M, Ali F, Leung S, Kent R. Metformin Induced Lactic Acidosis What Is the Effective Treatment? Open Journal of Nephrology. 2020;10(1):11–7.
16. Kooy A, de Jager J, Lehert P, Bets D, Wulffelé MG, Donker AJ, et al. Long-term effects of metformin on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus. Arch Intern Med. 2009;169(6):616–25.
17. De Broe ME, Jouret F. Does metformin do more benefit or harm in chronic kidney disease patients? Kidney Int. 2020;98(5):1098–101.
18. Davenport MS, Perazella MA, Yee J, Dillman JR, Fine D, McDonald RJ, et al. Use of Intravenous Iodinated Contrast Media in Patients With Kidney Disease: Consensus Statements from the American College of Radiology and the National Kidney Foundation. Kidney Med. 2020;2(1):85–93.
19. Crowley K, Scanaill P, Hermanides J, Buggy DJ. Current practice in the perioperative management of patients with diabetes mellitus: a narrative review. Br J Anaesth. 2023;131(2):242–52.
20. Jones TF, Iakovou D, Makariou N, Fowler AJ, Ackland GL. Metformin and mortality after surgery: a systematic review and meta-analysis. Br J Anaesth. 2022;128(4):e277–e9.

21. Baradari AG, Habibi MR, Khezri HD, Aarabi M, Khademloo M, Jalali Z, et al. Does high-dose metformin cause lactic acidosis in type 2 diabetic patients after CABG surgery? A double blind randomized clinical trial. Heart Int. 2011;6(1):e8.
22. 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(23):1047–54.
23. El Messaoudi S, Nederlof R, Zuurbier CJ, van Swieten HA, Pickkers P, Noyez L, et al. Effect of metformin pretreatment on myocardial injury during coronary artery bypass surgery in patients without diabetes (MetCAB): a double-blind, randomised controlled trial. Lancet Diabetes Endocrinol. 2015;3(8):615–23.
24. Hulst AH, Polderman JAW, Ouweneel E, Pijl AJ, Hollmann MW, DeVries JH, et al. Perioperative continuation of metformin does not improve glycaemic control in patients with type 2 diabetes: A randomized controlled trial. Diabetes Obes Metab. 2018;20(3):749–52.
25. Gasanova I, Meng J, Minhajuddin A, Melikman E, Alexander JC, Joshi GP. Preoperative Continuation Versus Interruption of Oral Hypoglycemics in Type 2 Diabetic Patients Undergoing Ambulatory Surgery: A Randomized Controlled Trial. Anesthesia & Analgesia. 2018;127(4):e54–e6.
26. Colov Tauby EP, Bojesen RD, Grube C, Miedzianogora REG, Buzquurz F, Fransgaard T, et al. Perioperative Metformin Treatment to Reduce Postoperative Hyperglycemia After Colon Cancer Surgery: A Randomized Clinical Trial. Dis Colon Rectum. 2024;67(11):1403–12.
27. Morrell A, Shelofsky S, Hoffman H, McCallister C, Huff TW, Schabel KL, et al. Perioperative metformin use in patients undergoing total joint replacement surgery: protocol for a randomised, placebo-controlled pilot study. BMJ Open. 2025;15(4):e091446.
28. Jens Meier KUHRP. Perioperative Continuation of Metformin Therapy in Patients With Typ 2 Diabetes Mellitus Undergoing Non-cardiac Surgery ClinicalTrials.gov2020. Date of last access: 23-11-2025. Available from: https://clinicaltrials.gov/study/NCT04284722?cond=Operation&intr=Metformin&rank=4.
29. 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;2010(4):Cd002967.
30. Duncan AI, Koch CG, Xu M, Manlapaz M, Batdorf B, Pitas G, et al. Recent metformin ingestion does not increase in-hospital morbidity or mortality after cardiac surgery. Anesth Analg. 2007;104(1):42–50.
31. Nazer RI, Alburikan KA. Metformin is not associated with lactic acidosis in patients with diabetes undergoing coronary artery bypass graft surgery: a case control study. BMC Pharmacol Toxicol. 2017;18(1):38.
32. Bano T, Mishra SK, Kuchay MS, Mehta Y, Trehan N, Sharma P, et al. Continuation of Metformin Till Night Before Surgery and Lactate Levels in Patients Undergoing Coronary Artery Bypass Graft Surgery. Indian J Endocrinol Metab. 2019;23(4):416–21.
33. Rajan N, Duggan EW, Abdelmalak BB, Butz S, Rodriguez LV, Vann MA, et al. Society for Ambulatory Anesthesia Updated Consensus Statement on Perioperative Blood Glucose Management in Adult Patients With Diabetes Mellitus Undergoing Ambulatory Surgery. Anesth Analg. 2024;139(3):459–77.
34. JBDS. Management of adults with diabetes undergoing surgery and elective procedures: improving standards 2016. Date of last access: 15-03-2025. Available from: https://abcd.care/sites/default/files/site_uploads/JBDS_Guidelines_Archive/JBDS_03_Surgical_guidelines_2015_full_FINAL_amended_Mar_2016_Archive.pdf.
35. SEMDSA 2017 Guidelines for the Management of Type 2 diabetes mellitus 2017. Date of last access: 23-11-2025. Available from: https://www2.kznhealth.gov.za/family/SEMDS-2017-Guidelines.pdf.
36. Cheisson G, Jacqueminet S, Cosson E, Ichai C, Leguerrier AM, Nicolescu-Catargi B, et al. Perioperative management of adult diabetic patients. Preoperative period. Anaesth Crit Care Pain Med. 2018;37 Suppl 1:S9–s19.
37. Management of type 2 diabetes: A handbook for general practice: Diabetes Australia; 2020. Date of last access: 23-11-2025. Available from: https://www.diabetesaustralia.com.au/wp-content/uploads/Available-here.pdf.
38. Guideline for Perioperative Care for People with Diabetes Mellitus Undergoing Elective and Emergency Surgery: Centre for Perioperative Care; 2021. Date of last access: 23-11-2025. Available from: https://www.cpoc.org.uk/sites/cpoc/files/documents/2021-03/CPOC-Guideline%20for%20Perioperative%20Care%20for%20People%20with%20Diabetes%20Mellitus%20Undergoing%20Elective%20and%20Emergency%20Surgery.pdf.
39. Barker P, Creasey PE, Dhatariya K, Levy N, Lipp A, Nathanson MH, et al. Perioperative management of the surgical patient with diabetes 2015: Association of Anaesthetists of Great Britain and Ireland. Anaesthesia. 2015;70(12):1427–40.
40. ADS-ANZCA Perioperative Diabetes and Hyperglycaemia Guidelines (Adults) 2022 [updated 2025. Date of last access: 23-11-2025. Available from: https://www.diabetessociety.com.au/wp-content/uploads/2023/03/ADS-ANZCA-Perioperative-Diabetes-and-Hyperglycaemia-Guidelines-Adults-November-2022-v2-Final.pdf.
41. JBDS. Management of adults with diabetes undergoing surgery and elective procedures: improving standards: Joint British Diabetes Societies (JBDS); 2016. Date of last access: 15-03-2025. Available from: https://abcd.care/sites/default/files/site_uploads/JBDS_Guidelines_Archive/JBDS_03_Surgical_guidelines_2015_full_FINAL_amended_Mar_2016_Archive.pdf.

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