Recommendations for Practical Use of Metformin, a Central Pharmacological Therapy in Type 2 Diabetes

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Metformin is a biguanide derived from the plant *Galega officinalis*. Originally synthesized nearly 100 years ago in 1922 (1), it has been used in humans for more than 60 years (2). Interestingly, and despite its long history, the mechanism of action of metformin is not well understood (2). A decrease in hepatic neoglycogenesis has been the most frequently highlighted action (3,4). Metformin can influence AMP-activated protein kinase and the fructose-1,6-bisphosphatase pathway, leading to a decrease in the AMP/ATP ratio and reducing the energy available for neoglycogenesis (4). Recently, however, it has been suggested that its main mechanism of action resides in the gastrointestinal (GI) tract (5). Using delayed-release metformin that acts predominantly in the gut, Buse et al. (5) found that, despite lower bioavailability, this formulation had greater efficacy than immediate- and extended-release formulations. These findings support the idea that the distal intestine is responsible for most of metformin's glucose-lowering effect. Proposed mechanisms are an increment in intestinal glucose expenditure and an increase in the secretion of GI incretins (6), as metformin seems to enhance secretion of glucagon-like peptide 1 (GLP-1) and peptide YY. In fact, metformin and dipeptidyl peptidase 4 (DPP-4) inhibitors may increase GLP-1 to a similar extent through different and complementary mechanisms (7).

When administered orally, metformin is absorbed mainly in the small intestine, with a bioavailability of 55 ± 16%. The drug is eliminated unchanged by the kidney, with an average half-life of 5 hours in individuals with normal renal function (8).

Metformin currently plays a central role in the treatment of type 2 diabetes and may also have benefits in other pathologies. Although it is generally considered to have a good safety profile, some precautions are essential for its correct use. This article reviews the advantages and applications of metformin, but its main focus is on the drug's adverse effects and on providing practical recommendations for its use.

Role of Metformin

Type 2 Diabetes

The importance of metformin in the treatment of type 2 diabetes is well established. In joint guidelines from the American Diabetes Association and the European Association for the Study of Diabetes (9), it is recommended as the first-line pharmacological therapy. The positioning of this drug within the treatment algorithm is not the result of chance, but rather of the numerous advantages attributed to it. Its long history of use translates into vast experience, greater safety, and lower cost (2,10).

Metformin has considerable efficacy in reducing A1C (by ~1.12% as monotherapy and 0.95% when added to other drugs) (11). The UK Prospective Diabetes Study (UKPDS) documented its beneficial effects on glycemic control, which were similar to those obtained in groups treated with a sulfonylurea or insulin (12,13). However, metformin monotherapy in patients with type 2 diabetes and overweight/obesity yielded a greater reduction in all-cause mortality and other diabetes-related end points with less hypoglycemia and without inducing weight gain (13). In two randomized controlled trials (RCTs), DeFronzo and Goodman (14) verified that metformin, both as monotherapy or in combination with a sulfonylurea, had beneficial effects on both glycemic control and the lipid profile. Furthermore, a meta-analysis of studies performed between 1957 and 1994 revealed that metformin reduces fasting plasma glucose (FPG) and A1C to a similar extent as sulfonylureas and with a 5% net weight loss (15). Several trials have also shown glycemic benefits from

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https://doi.org/10.2337/cd21-0043

combination therapy with metformin and pioglitazone (16–18), DPP-4 inhibitors (19–22), GLP-1 receptor agonists (21,23,24) and sodium–glucose cotransporter 2 inhibitors (25–29).

A meta-analysis comparing metformin with this wider range of noninsulin antidiabetic agents found similar efficacy on glycemic control for all classes in monotherapy and in combination with metformin, except for DPP-4 inhibitors, which was less effective) (30). However, a Cochrane systematic review of metformin as monotherapy (31) found no high-quality RCTs to evaluate data on cardiovascular outcomes, all-cause mortality, or severe adverse effects (31).

In the metformin arm in UKPDS, there was a 30% lower risk of macrovascular complications compared with the group treated exclusively with diet (13), which was confirmed with data from the post-trial follow-up at 10 years (32). Cardiovascular benefit was supported by other large studies (33,34). A meta-analysis by Griffin S et al. (11), showed favorable results for metformin in all cardiovascular end points except for stroke, however these results were not statistically significant. Two subsequent, larger meta-analyzes showed statistically significant reductions in the risks of cardiovascular and all-cause death (35) and a reduction in the risk of cardiovascular events and cardiovascular death (36). An assessment of the role of metformin in reducing these complications, similar to the cardiovascular outcomes trials carried out with more recently introduced drugs, is unlikely with such a well-established drug.

Cognitive decline and dementia are also frequently associated with diabetes (37), and a possible protective role for metformin in this regard has been proposed. Data obtained to date are inconsistent (38). A Cochrane systematic review (39) found no good evidence that any specific treatment strategy for type 2 diabetes prevents or delays cognitive decline. Nevertheless, two subsequent meta-analyzes (40,41) support the existence of a neuroprotective role for metformin. Animal studies also indicate a possible benefit of metformin on peripheral neuropathy—namely, reduction of neuropathic symptoms, protection against ethanol-induced neuronal apoptosis, and increased neurogenesis (42).

Diabetes is also accompanied by an increased risk of fractures (37), and metformin has the theoretical potential to have bone benefits (43,44). However, the studies that analyzed this possibility yielded contradictory results, and a neutral effect of the drug on bone health is likely (45).

The dosing of metformin for maximum benefit has been evaluated in a few studies. With doses ranging from 500 to 3,000 mg, there seems to be a dose-dependent effect on glycemic control, mainly on FPG (46,47). Cardiovascular benefit may be associated, in part, with regulation of the lipid profile, thus having an antiatherosclerotic effect (35,46,48). Regulation of fibrinolysis through decreases in plasminogen activator inhibitor may also have a role (13). A study comparing dosages of 1,500 and 3,000 mg and placebo found a decrease in plasma triglycerides and cholesterol of a similar magnitude in both metformin groups that only reached statistical significance in the group taking the higher metformin dose. Both dosages had similar and statistically significant effects on tests of fibrinolysis, with a trend toward enhanced global fibrinolysis (46). Additional data, however, suggest that a beneficial effect on plasma triglycerides is observed only with dosages >1,700 mg/dL, suggesting the higher dosages may be necessary to affect the lipid profile and attain an antiatherosclerotic effect (48).

Other Indications and Potential Benefits

Additional indications for the use of metformin have been proposed. It is an option in prediabetes to prevent progression to type 2 diabetes, especially in patients with a BMI ≥35 kg/m^2, those <60 years of age, and women with a history of gestational diabetes mellitus (GDM). In the Diabetes Prevention Program (DPP) and its follow-up Diabetes Prevention Program Outcomes Study (DPPOS), a dosage of 850 mg twice daily was used for this purpose. More recently, in a 15-year analysis of these studies, it was found that patients with higher A1C, higher FPG, or prior GDM benefited the most (49).

In individuals with type 1 diabetes and overweight/obesity, metformin may have an adjuvant role in reducing insulin resistance (50). Several studies have been performed using doses between 1,000 and 2,000 mg, and its use seems to be associated with reduced insulin requirements and less weight gain, with little effect on A1C (51,52). The results of the REMOVAL (Reducing With Metformin Vascular Adverse Lesions in Type 1 Diabetes trial of metformin 1,000 mg twice daily corroborate that there is little effect on glycemic control, but suggest a reduction in cardiovascular risk factors (i.e., weight, LDL cholesterol, insulin dose per kilogram of body weight, and progression of atherosclerosis) (53).

The use of metformin in GDM and type 2 diabetes during pregnancy has been studied; however, there are

some doubts regarding its effects on offspring (54,55), especially with regard to metabolic effects and body composition (55). Regarding type 2 diabetes in pregnancy, results of the multicenter RCT MiTy (Metformin in Women with Type 2 Diabetes in Pregnancy) suggest that the use of metformin 1,000 mg twice daily in addition to insulin is associated with better maternal metabolic control, reduced insulin requirements, less maternal weight gain, and fewer large-for-gestational-age newborns. There was, however, a greater proportion of small-for-gestational-age babies born to women in the metformin group (56). The SUGAR-DIP (Oral Medication Strategy Versus Insulin for Diabetes in Pregnancy) trial is currently underway and aims to provide more data about the use of oral antidiabetic agents in GDM (57).

Metformin also finds utility as a therapy for the metabolic changes and menstrual irregularities associated with polycystic ovary syndrome, at a dose of 850 mg twice daily in most studies (58–61). Its use was also considered in nonalcoholic fatty liver disease (62); however, there is evidence of limited efficacy in improving liver histology, and it is therefore not recommended in current guidelines (63). Additional benefits have been proposed, including a reduction in the incidence and mortality of neoplastic disease (38,64–66), an antiaging effect (38,67), and modification of the intestinal microbiota and immunomodulation (68). Regarding the latter, and taking into account the current pandemic context, it should be noted that the immunomodulatory role of this drug may suppress the inflammatory response responsible for severe disease caused by severe acute respiratory syndrome coronavirus 2. It has also been suggested that metformin can directly inhibit infection by interfering with the interaction between viral and human proteins, and, in animal studies, it appears to improve varying degrees of lung injury (69). However, in view of the increased risk of lactic acidosis (LA) in the context of acute illness (discussed further below), its use in individuals with severe disease may be limited (70).

Proposals for new applications and benefits of this drug are numerous. Table 1 summarizes the most frequently cited of these.

TABLE 1 Possible Applications for Metformin

- First-line pharmacological therapy for type 2 diabetes
  - Low cost, long experience, significant efficacy, safety
  - Possible cardio- and neuroprotective effects
- Prevention of type 2 diabetes
  - Mainly in those with BMI $\geq$35 kg/m^2, age $<$60 years, or previous GDM
- Adjuvant therapy in type 1 diabetes
  - Reduced need for insulin and reduced weight gain
- GDM therapy
  - Doubts regarding effects on offspring
- Polycystic ovary syndrome
  - Improvement in metabolic changes and menstrual irregularities
- Nonalcoholic fatty liver disease
  - Not recommended in current guidelines
- Neoplastic disease
- Improving aging outcomes
- Modification of the intestinal microbiota
- Immunomodulatory role

Potential Adverse Effects

Adverse effects of metformin are common, but mostly not serious, with GI intolerance being the most frequently described, occurring in >20–30% (71). Diarrhea is especially common, with reported incidences varying from 20 to 60%. Nausea, flatulence, dyspepsia, vomiting, and abdominal discomfort are also frequently reported. These side effects may lead to nonadherence in a significant proportion of affected patients (72).

Vitamin B12 deficiency is also a possible side effect of metformin, likely because of malabsorption. Several mechanisms have been proposed, including alteration of motility in the small intestine, leading to bacterial overgrowth; changes of membrane potential, leading to calcium channel blockage with impairment of calcium-dependent absorption of intrinsic factor (73); competitive inhibition of B12 absorption; and alterations of cubulin or intrinsic factor (74). The main consequences of this deficiency are hematological (megaloblastic anemia) and neurological (irritability; impairment of reflexes, cognition, gait, olfaction, proprioception, and vibratory sense; dementia-like disease; and peripheral neuropathy). Hyperpigmentation, jaundice, vitiligo, and glossitis may also emerge (75). In people with diabetes, B12 deficiency may contribute to exacerbation of diabetic peripheral neuropathy and, if left untreated, may contribute to permanent nerve damage (76).

In an analysis of the DPP/DPPOS (77), there was a 13% increase in the risk of B12 deficiency for each year of metformin use. Increased levels of homocysteine, suggesting deficiency at the tissue level, and a higher prevalence of anemia and neuropathy were also detected. In a recent meta-analysis (78), although metformin use was associated with a decrease in B12 concentrations, no significant association with anemia or neuropathy was found. The authors argued, however, that an impact in hemoglobin may take longer to occur than

the follow-up period in the studies included in the meta-analysis. Different tools to diagnose neuropathy may have prevented the detection of a significant effect, and the possibility of the neuroprotective effects of metformin balancing the negative effects of B12 deficiency was also raised (78).

Metformin may be associated with a precocious decrease in hemoglobin without an increase in mean corpuscular volume and therefore not explained by B12 deficiency (79).

Metformin-associated lactic acidosis (MALA) is the most feared complication. Experience with other biguanides such as phenformin and buformin contributed to this concern, as LA was much more frequent with these drugs, which were ultimately withdrawn from the market (80,81), than with metformin. However, this concern persists, and it is important to recognize who may be truly more susceptible to this complication.

Lactate levels result from a balance between lactate production and elimination (82). In glycolysis, glucose generates pyruvate that can be transported into the mitochondria and undergo oxidative phosphorylation or be converted into lactate in the cytosol (83). Metformin inhibits the mitochondrial respiratory chain, with the potential to increase lactate genesis. Because the drug is eliminated unchanged by the kidney (84), theoretically, an accumulation would be expected in the setting of impaired renal function. Other factors can contribute, including hypoxemia, sepsis, shock, alcohol abuse, liver failure, radiological contrast, and ischemic events (85).

Until 2016, metformin was contraindicated for individuals with creatinine levels >1.4 mg/dL in women and 1.5 mg/dL in men. The use of this drug was rarely recommended for patients with a glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 (2).

However, the relationship between metformin levels and renal failure is uncertain (86). There seems to be a substantial reduction (~75%) in the clearance of this drug for GFRs <60 mL/min/1.73 m^2, with little increase up to GFRs of 30 mL/min/1.73 m^2, but the drug's blood levels generally do not reach those observed in the MALA (87). When metformin was dosed in patients with LA, normal or elevated serum levels were reported, with no correlation with the degree of LA (88). This finding legitimizes the question of whether metformin is the cause of LA or if it simply coexists with this complication.

Several studies have demonstrated metformin's safety for 30–60 mL/min/1.73 m^2 without increased incidence of LA (34,89,90). In a systematic review, Inzucchi et al. (88) concluded that the incidence of MALA varies from 3 to 10 per 100,000 person-years and is generally indistinguishable from the rate in the general population, especially when patients with a GFR <30 mL/min/1.73 m^2 are excluded. Although it is clear that the rate of LA is much lower with metformin than with phenformin, the actual incidence of MALA is extremely hard to define, as it occurs in the context of triggering factors, making it is difficult to determine in which cases the drug is one of the contributors to the lactate elevation (81).

In 2016, because of the accumulation of data such as those mentioned above, first the U.S. Food and Drug Administration (FDA) (91) and later the European Medicines Agency (EMA) (92) extended the use of metformin in individuals with a GFR >30 mL/min/1.73 m^2. For those with a GFR <30 mL/min/1.73 m^2, an increased risk of MALA continues to be described (93,94).

Because the liver is responsible for most lactate elimination, there is also the possibility that the use of metformin is not safe in the setting of chronic liver disease (95), and the drug is often discontinued in cirrhotic individuals (96). Conversely, in a retrospective evaluation of 250 individuals diagnosed with cirrhosis, continuation of metformin was associated with a 57% reduction in the risk of death, which was limited to those with nonalcoholic steatohepatitis–related cirrhosis (96). In a comparison of different therapies for diabetes in 100 individuals with cirrhosis caused by hepatitis C virus, metformin therapy was associated with a lower occurrence of hepatocellular carcinoma and death associated with liver disease (97). More recently, Smith et al. (95) found that both metformin and lactate levels remained in the safe range (<5 mg/L and 5 mmol/L, respectively) in a group of individuals with chronic liver disease, suggesting the safety of metformin therapy in this group of patients (95). These studies, however, make no specific mention of the use of metformin in patients who maintain excessive alcohol consumption.

Crowley et al. (98) performed a meta-analysis on the use of metformin in settings in which caution was traditionally recommended. When compared with the alternatives, metformin's use in the setting of chronic kidney disease (CKD) was associated with 22% lower mortality and less hypoglycemia. In patients with heart failure,

20% less mortality and a 13% reduction in heart failure–related readmissions were found. Available data on chronic liver failure did not allow the performance of meta-analysis; however, a tendency toward lower mortality was observed in the included studies (98).

Hypoglycemia is one of the adverse effects most feared by people with diabetes. By not directly stimulating insulin secretion, metformin has a low risk of hypoglycemia. Nevertheless, it can occur in the context of intense physical activity or fasting (99).

Other adverse reactions include weakness, myalgia, chest discomfort, palpitation, flushing, headache, dizziness, dyspnea, and flu-like syndrome. Skin side effects have also been reported, including leukocytoclastic vasculitis, bullous pemphigoid, psoriasiform rash, lichen planus, and acute alopecia (100). The adverse effects of metformin are summarized in Table 2.

Precautions With the Use of Metformin

Prevention of GI Adverse Effects

Adverse GI effects of metformin may be lessened with extended-release formulations. Another good way to promote tolerance to the drug is a progressive introduction with low initial doses, increased progressively over the course of weeks to months (72). One possible regimen is to start with 500 or 850 mg and increase by 500–850 mg every 7 days (101). Taking metformin with meals also seems to reduce discomfort (102). Greenway et al. (103) reported a case in which using the drug in combination with prebiotics seemed to improve its tolerability.

Prevention of Vitamin B12 Deficiency and Its Consequences

Regarding the possible development of vitamin B12 deficiency, regular monitoring of blood count and measurement of this micronutrient is suggested, especially in the presence of symptoms or signs such as anemia or symptoms of neuropathy (77). The Kidney Diseases Improving Global Outcomes (KDIGO) guidelines (101) recommend annual monitoring of this micronutrient in patients on metformin for >4 years or those with risk factors for the development of B12 deficiency (i.e., malabsorption syndrome or low dietary intake).

Several studies suggest that multivitamin supplementation may be associated with a lower incidence of vitamin B12 deficiency, but this strategy remains controversial (76). When B12 deficiency is identified, supplementation will be necessary. Yang et al. (78) suggest prophylactic B12 prescription for levels between 150 and 300 pmol/L, especially in patients with poor glycemic control in whom metformin's neuroprotective action may be compromised (78).

Avoidance of MALA

The possibility of MALA is the main concern with metformin use. Given the importance of renal function to ensure the safety of metformin, it is recommended to evaluate this parameter before starting the drug. For individuals with a GFR >60 mL/min/1.73 m^2, the safety of metformin use has long been established, and dosages up to 2,550 mg (according to FDA [104]) or up to 3,000 mg (according to the EMA [105]) may be used. However, the need to monitor renal function at least annually is emphasized.

As mentioned above, for GFRs ranging from <60 to 30 mL/min/1.73 m^2, the use of metformin is now considered appropriate. However, some adjustments are needed, and recommendations have only recently emerged that establish how to use it safely in this setting. In 2018, Lalau et al. (106) carried out a study to define a safe dose for each stage of CKD. The authors suggested a maximum dose of 1,500 mg/day for individuals with a GFR of 45–60 mL/min/1.73 m^2 and 1,000 mg/day for those with a GFR of 30–45 mL/min/1.73 m^2. Although

TABLE 2 Adverse Effects of Metformin

Adverse Effect	Description
GI effects	Diarrhea, nausea, flatulence, dyspepsia, vomiting, and abdominal discomfort; these are the most frequent adverse effects and lead to discontinuation of the drug in a significant percentage of patients
Cutaneous effects	Leukocytoclastic vasculitis, bullous pemphigoid, psoriasiform rash, lichen planus, and acute alopecia
Vitamin B12 deficiency	May be accompanied by consequent anemia and neuropathy
MALA	Risk increased in patients with GFRs <30 mL/min/1.73 m^2 (in context of a chronic kidney dysfunction or AKI; a serious and potentially fatal adverse effect)
Hypoglycemia	Low risk, but it may occur in the context of strenuous physical exercise or fasting
Other effects	Weakness, myalgia, chest discomfort, palpitation, flushing, headache, dizziness, dyspnea, and flu-like syndrome

the data obtained suggested that the use of 500 mg/day for patients with a GFR of 15–30 mL/min/1.73 m^2 might be safe, the number of patients with this GFR did not allow the authors to safely conclude so, and the authors reiterated the contraindication for those with a GFR <30 mL/min/1.73 m^2. Given the greater plasmatic accumulation in these stages of kidney dysfunction, the authors suggested that there is no decrease in efficacy with dose reduction.

In 2019, the KDIGO recommendations brought a slightly more permissive adjustment strategy. For individuals with a GFR of 45–59 mL/min/1.73 m^2, dose adjustment should be considered only in the presence of conditions that predispose to hypoperfusion and hypoxemia. The maximum dose should be halved for those with a GFR of 30–45 mL/min/1.73 m^2. Treatment must be stopped when the GFR decreases to <30 mL/min/1.73 m^2 or when dialysis is started (101).

In addition to adjusting for the various levels of GFR, it is essential to recognize other situations in which the use of metformin may carry an increased risk.

In the context of acute illness, there is often dehydration, and consequent worsening of renal function may occur. Older age, CKD, heart failure, and diabetes itself are known risk factors for acute kidney injury (AKI) (107). Thus, particularly in patients susceptible to the development of AKI, drug suspension is recommended in the setting of acute disease. Lalau et al. (106) suggest that the lactate concentration may be useful in this decision; a value >2.5 mmol/L should be repeated soon, and, if maintained, the drug should be suspended, whereas a value >5 mmol/L should lead to the immediate suspension of the drug. Importantly, given the potential worsening of metabolic control from both acute illness and drug suspension, more frequent monitoring is needed, and consideration should be given to introducing or increasing insulin therapy in these instances.

In patients hospitalized with acute illness, insulin is the treatment of choice, with the risk of LA being an especially important obstacle to the use of metformin in this context (108). The drug may be reintroduced during preparation for discharge if renal function is optimized and stable.

Exams using iodinated contrast represent an additional challenge. When extending the use of metformin to individuals with lower GFRs, the FDA suggested discontinuing the drug at the time of or before such exams in all of the following situations: GFR of 30–60 mL/min/1.73 m^2; history of liver disease, alcoholism, or heart failure; or intra-arterial iodinated contrast. Metformin could be restarted 48 hours after the procedure only if the patient has stable renal function (91). More recently, the European Society of Urogenital Radiology has issued recommendations for an absolute need to discontinue metformin and reassess kidney function only in patients with an GFR <30 mL/min/1.73 m^2, with AKI, or for any test in which the contrast has first renal passage (109). The joint recommendations of the American College of Radiology and the National Kidney Foundation also indicate the absolute need to suspend the drug for those with a GFR <30 mL/min/1.73 m^2 or AKI. For those with a GFR of 30–60 mL/min/1.73 m^2, the decision to temporarily interrupt the drug should be individualized (110).

Surgical procedures can also be associated with worsening renal function (111). The ADA recommends that metformin be discontinued on the day of surgery (112). The analytical control usually performed postoperatively will allow the detection of situations in which immediate reintroduction is not advised.

Table 3 summarizes important recommendations for the use of metformin.

Conclusion

Metformin is a drug of unquestionable importance in the treatment of type 2 diabetes. However, some precautions are necessary for its safe use. The progressive introduction of the drug and use of different formulations may promote GI tolerance in a larger group of patients. Periodic monitoring of the blood count and B12 levels allows early detection of deficiency of this micronutrient and prevents the onset of its consequences.

MALA is the most serious complication associated with the use of metformin; however, the risk seems more limited than initially assumed. Of utmost importance is the periodic surveillance of renal function and the adjustment of the drug dose accordingly. Some situations (e.g., acute illness, iodinated contrast exams, and surgical procedures) may predispose to a worsening of renal function and indicate the need to suspend the drug and/or perform early monitoring of renal function.

DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

TABLE 3 Practical Recommendations for the Use of Metformin

When starting metformin

- Evaluate GFR before starting the drug
  - Check that there is no contraindication to its use
  - Adjust the maximum target dose to patient's GFR (see below)
- Assess the patient's accessibility to health care and compliance with the monitoring required for the use of the drug
- Introduce progressively, starting with a low dose (500–850 mg) and increasing every 7 days until the target dose is reached

While taking with metformin

- Monitor patient's renal function and adjust the dosage accordingly, as follows:

For GFR >60 mL/min/1.73 m^2	• Maximum dosage: 2,550–3,000 mg/day (per FDA and EMA, respectively) • Monitor kidney function at least annually
For GFR 45–60 mL/min/1.73 m^2	• Recommended maximum dose: 1,500 mg/day (dosages up to 2,000 mg/dL may be considered in patients without other comorbidities and good adherence to monitoring) • Assess renal function every 3–6 months
For GFR 30–45 mL/min/1.73 m^2	• Reduced maximum dose: 1,000 mg/day • Assess renal function every 3–6 months • Evaluate periodically the risk-benefit ratio of maintaining or starting the drug in patients with significant comorbidities, risk of sudden worsening of renal function, poor access to health care, or difficulty monitoring renal function as required
For GFR <30 mL/min/1.73 m^2	• Contraindicated

- Monitor for vitamin B12 deficiency
  - Monitor blood count periodically
  - Consider monitoring vitamin B12 annually if ≥4 years on metformin and/or additional risk factors for deficiency
  - Evaluate vitamin B12 earlier if there are changes in complete blood count or symptoms of neuropathy
- Monitor for possible side effects

In special situations

• Acute illness	• Monitor renal function and consider discontinuing metformin, especially if severe acute illness and/or risk factors for the development of AKI exist • Monitor blood glucose levels and assess the need for the introduction or adjustment of insulin therapy
• Contrast-enhanced imaging	• Assess renal function if there is no recent evaluation and/or risk of recent worsening • Suspend drug if GFR is <30 mL/min/1.73 m^2 and/or AKI exists and/or for any exam with first renal passage of the contrast • Make a case-by-case decision on the need for suspension of metformin for GFR of 30–60 mL/min/1.73 m^2 in the absence of other risk factors for worsening renal function • If the drug needs to be discontinued, assess renal function within 48 hours
• Surgery	• Discontinue on the day of surgery • Evaluate the presence of contraindications to subsequent reintroduction

AUTHOR CONTRIBUTIONS

I.H.V. researched the data and wrote the manuscript. L.M.B., C.F.B., D.M.R., and I.M.P. reviewed/edited the manuscript. I.H.V. is the guarantor of this work and, as such, had full access to all the data reported and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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