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**BRIEF ANSWERS
TO SPECIFIC
CLINICAL
QUESTIONS**

Q: Should metformin be used in every patient with type 2 diabetes?

A: Most patients should receive it, with exceptions as noted below. Metformin is the cornerstone of diabetes therapy and should be considered in all patients with type 2 diabetes. Both the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE)^{1,2} recommend it as first-line treatment for type 2 diabetes. It lowers blood glucose levels by inhibiting hepatic glucose production, and it does not tend to cause hypoglycemia.

However, metformin is underused. A 2012 study showed that only 50% to 70% of patients with type 2 diabetes treated with a sulfonylurea, dipeptidyl peptidase-4 (DPP-4) inhibitor, thiazolidinedione, or glucagon-like peptide-1 analogue also received metformin.³ This occurred despite guidelines recommending continuing metformin when starting other diabetes drugs.⁴

■ EVIDENCE METFORMIN IS EFFECTIVE

The United Kingdom Prospective Diabetes Study (UKPDS)⁵ found that metformin significantly reduced the incidence of:

- Any diabetes-related end point (hazard ratio [HR] 0.68, 95% confidence interval [CI] 0.53–0.87)
- Myocardial infarction (HR 0.61, 95% CI 0.41–0.89)
- Diabetes-related death (HR 0.58, 95% CI 0.37–0.91)
- All-cause mortality (HR 0.64; 95% CI 0.45–0.91).

The Hyperinsulinemia: Outcomes of Its Metabolic Effects (HOME) trial,⁶ a multicenter trial conducted in the Netherlands,

evaluated the effect of adding metformin (vs placebo) to existing insulin regimens. Metformin recipients had a significantly lower rate of macrovascular mortality (HR 0.61, 95% CI 0.40–0.94, $P = .02$), but not of the primary end point, an aggregate of microvascular and macrovascular morbidity and mortality.

The Study on the Prognosis and Effect of Antidiabetic Drugs on Type 2 Diabetes Mellitus With Coronary Artery Disease trial,⁷ a multicenter trial conducted in China, compared the effects of metformin vs glipizide on cardiovascular outcomes. At about 3 years of treatment, the metformin group had a significantly lower rate of the composite primary end point of recurrent cardiovascular events (HR 0.54, 95% CI 0.30–0.90). This end point included nonfatal myocardial infarction, nonfatal stroke, arterial revascularization by percutaneous transluminal coronary angioplasty or by coronary artery bypass graft, death from a cardiovascular cause, and death from any cause.

These studies prompted the ADA to emphasize that metformin can reduce the risk of cardiovascular events or death. Metformin also has been shown to be weight-neutral or to induce slight weight loss. Furthermore, it is inexpensive.

■ WHAT ABOUT THE RENAL EFFECTS?

Because metformin is renally cleared, it has caused some concern about nephrotoxicity, especially lactic acidosis, in patients with impaired renal function. But the most recent guidelines have relaxed the criteria for metformin use in this patient population.

Revised labeling

Metformin's labeling,⁸ revised in 2016, states the following:

**Recent
guidelines
have relaxed
the criteria
for metformin
use in patients
with renal
impairment**

doi:10.3949/ccjm.86a.18039

- If the estimated glomerular filtration rate (eGFR) is below 30 mL/min/1.73 m², metformin is contraindicated
- If the eGFR is between 30 and 45 mL/min/1.73 m², metformin is not recommended
- If the eGFR is below 45 mL/min/1.73 m² in a patient taking metformin, the risks and benefits of continuing treatment should be assessed, the dosage may need to be adjusted, and renal function should be monitored more frequently.⁸

These labeling revisions were based on a systematic review by Inzucchi et al⁹ that found metformin is not associated with increased rates of lactic acidosis in patients with mild to moderate kidney disease. Subsequently, an observational study published in 2018 by Lazarus et al¹⁰ showed that metformin increases the risk of acidosis only at eGFR levels below 30 mL/min/1.73 m². Also, a Cochrane review published in 2003 did not find a single case of lactic acidosis in 347 trials with 70,490 patient-years of metformin treatment.¹¹

Previous guidelines used serum creatinine levels, with metformin contraindicated at levels of 1.5 mg/dL or above for men and 1.4 mg/dL for women, or with abnormal creatinine clearance. The ADA and the AACE now use the eGFR^{1,2} instead of the serum creatinine level to measure kidney function because it better accounts for factors such as the patient's age, sex, race, and weight.

Despite the evidence, the common patient perception is that metformin is nephrotoxic, and it is important for practitioners to dispel this myth during clinic visits.

What about metformin use with contrast agents?

Labeling has a precautionary note stating that metformin should be held at the time of, or prior to, any imaging procedure involving iodinated contrast agents in patients with an eGFR between 30 and 60 mL/min/1.73 m²; in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients who will receive intra-arterial iodinated contrast. The eGFR should be reevaluated 48 hours after the imaging procedure.⁸

Additionally, if the iodinated contrast

agent causes acute kidney injury, metformin could accumulate, with resultant lactate accumulation.

The American College of Radiology (ACR) has proposed less stringent guidelines for metformin during radiocontrast imaging studies. This change is based on evidence that lactic acidosis is rare—about 10 cases per 100,000 patient-years—and that there are no reports of lactic acidosis after intravenously administered iodinated contrast in properly selected patients.^{12,13}

The ACR divides patients taking metformin into 2 categories:

- No evidence of acute kidney injury and eGFR greater than 30 mL/min/1.73 m²
- Either acute kidney injury or chronic kidney disease with eGFR below 30 mL/min/1.73 m² or undergoing arterial catheter studies with a high chance of embolization to the renal arteries.¹⁴

For the first group, they recommend against discontinuing metformin before or after giving iodinated contrast or checking kidney function after the procedure.

For the second group, they recommend holding metformin before and 48 hours after the procedure. It should not be restarted until renal function is confirmed to be normal.

METFORMIN AND INSULIN

The ADA recommends¹ continuing metformin after initiating insulin. However, in clinical practice, it is often not done.

Clinical trials have shown that combining metformin with insulin significantly improves glycemic control, prevents weight gain, and decreases insulin requirements.^{15,16} One trial¹⁶ also looked at cardiovascular end points during a 4-year follow-up period; combining metformin with insulin decreased the macrovascular disease-related event rate compared with insulin alone.

In the HOME trial,⁶ which added metformin to the existing insulin regimen, both groups gained weight, but the metformin group had gained about 3 kg less than the placebo group at the end of the 4.3-year trial. Metformin did not increase the risk of hypoglycemia, but it also did not reduce the risk of microvascular disease.

The extended-release formulation may be more tolerable, with similar glycemic efficacy

Concomitant metformin reduces costs

These days, practitioners can choose from a large selection of diabetes drugs. These include insulins with better pharmacokinetic profiles, as well as newer classes of noninsulin agents such as sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 analogues.

Metformin is less expensive than these newer drugs, and using it concomitantly with other diabetes drugs can decrease their dosage requirements, which in turn decreases their monthly costs.

GASTROINTESTINAL EFFECTS

Metformin's gastrointestinal adverse effects such as diarrhea, flatulence, nausea, and vomiting are a barrier to its use. The actual incidence rate of diarrhea varies widely in randomized trials and observational studies, and gastrointestinal effects are worse in metformin-naïve patients, as well as those who have chronic gastritis or *Helicobacter pylori* infection.¹⁷

We have found that starting metformin at a low dose and up-titrating it over several weeks increases tolerability. We often start patients at 500 mg/day and increase the dosage by 1 500-mg tablet every 1 to 2 weeks. Also, we have noticed that intolerance is more likely in patients who eat a high-carbohydrate diet, but there is no high-level evidence to back this up because patients in clinical trials all undergo nutrition counseling and are therefore more likely to adhere to the low-carbohydrate diet.

Also, the extended-release formulation is more tolerable than the immediate-release formulation and has similar glycemic efficacy. It may be an option as first-line therapy or for

patients who have significant adverse effects from immediate-release metformin.¹⁸ For patients on the immediate-release formulation, taking it with meals helps lessen some gastrointestinal effects, and this should be emphasized at every visit.

Finally, we limit the metformin dose to 2,000 mg/day, rather than the 2,550 mg/day allowed on labeling. Garber et al¹⁹ found that the lower dosage still provides the maximum clinical efficacy.

OTHER CAUTIONS

Metformin should be avoided in patients with acute or unstable heart failure because of the increased risk of lactic acidosis.

It also should be avoided in patients with hepatic impairment, according to the labeling. But this remains controversial in practice. Zhang et al²⁰ showed that continuing metformin in patients with diabetes and cirrhosis decreases the mortality risk by 57% compared with those taken off metformin.

Diet and lifestyle measures need to be emphasized at each visit. Wing et al²¹ showed that calorie restriction regardless of weight loss is beneficial for glycemic control and insulin sensitivity in obese patients with diabetes.

TAKE-HOME POINTS

Metformin improves glycemic control without tending to cause weight gain or hypoglycemia. It may also have cardiovascular benefits. Metformin is an inexpensive agent that should be continued, if tolerated, in those who need additional agents for glycemic control. It should be considered in all adult patients with type 2 diabetes.

Metformin improves glycemic control without tending to cause weight gain or hypoglycemia

REFERENCES

1. American Diabetes Association. 8. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2018. *Diabetes Care* 2018; 41(suppl 1):S73–S85. doi:10.2337/dc18-S008
2. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm — 2018 executive summary. *Endocr Pract* 2018; 24(1):91–120. doi:10.4158/CS-2017-0153
3. Hampp C, Borders-Hemphill V, Moeny DG, Wysowski DK. Use of antidiabetic drugs in the US, 2003–2012. *Diabetes Care* 2014; 37(5):1367–1374. doi:10.2337/dc13-2289
4. Inzucchi SE, Bergenstal RM, Buse JB, et al; American Diabetes Association (ADA); European Association for the Study of Diabetes (EASD). Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2012; 35(6):1364–1379. doi:10.2337/dc12-0413
5. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998; 352(9131):854–865. pmid:9742977
6. Kooy A, de Jager J, Lehert P, 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):616–625. doi:10.1001/archinternmed.2009.20
7. Hong J, Zhang Y, Lai S, et al; SPREAD-DIMCAD Investigators. Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease. *Diabetes Care* 2013; 36(5):1304–1311. doi:10.2337/dc12-0719
 8. **Glucophage (metformin hydrochloride) and Glucophage XR (extended-release)** [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. www.accessdata.fda.gov/drugsatfda_docs/label/2018/020357s034,021202s0181bl.pdf. Accessed December 5, 2018.
 9. Inzucchi SE, Lipska KJ, Mayo H, Bailey CJ, McGuire DK. Metformin in patients with type 2 diabetes and kidney disease: a systematic review. *JAMA* 2014; 312(24):2668–2675. doi:10.1001/jama.2014.15298
 10. Lazarus B, Wu A, Shin JJ, et al. Association of metformin use with risk of lactic acidosis across the range of kidney function: a community-based cohort study. *JAMA Intern Med* 2018; 178(7):903–910. doi:10.1001/jamainternmed.2018.0292
 11. Salpeter S, Greyber E, Pasternak G, Salpeter E. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2003; (2):CD002967. doi:10.1002/14651858.CD002967
 12. Eppenga WL, Lalmohamed A, Geerts AF, et al. Risk of lactic acidosis or elevated lactate concentrations in metformin users with renal impairment: a population-based cohort study. *Diabetes Care* 2014; 37(8):2218–2224. doi:10.2337/dc13-3023
 13. Richy FF, Sabido-Espin M, Guedes S, Corvino FA, Gottwald-Hostalek U. Incidence of lactic acidosis in patients with type 2 diabetes with and without renal impairment treated with metformin: a retrospective cohort study. *Diabetes Care* 2014; 37(8):2291–2295. doi:10.2337/dc14-0464
 14. American College of Radiology (ACR). Manual on Contrast Media. Version 10.3. www.acr.org/Clinical-Resources/Contrast-Manual. Accessed December 5, 2018.
 15. Wulffele MG, Kooy A, Lehert P, et al. Combination of insulin and metformin in the treatment of type 2 diabetes. *Diabetes Care* 2002; 25(12):2133–2140. pmid:12453950
 16. Kooy A, de Jager J, Lehert P, 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):616–625. doi:10.1001/archinternmed.2009.20
 17. Bonnet F, Scheen A. Understanding and overcoming metformin gastrointestinal intolerance. *Diabetes Obes Metab* 2017; 19(4):473–481. doi:10.1111/dom.12854
 18. Jabbour S, Ziring B. Advantages of extended-release metformin in patients with type 2 diabetes mellitus. *Postgrad Med* 2011; 123(1):15–23. doi:10.3810/pgm.2011.01.2241
 19. Garber AJ, Duncan TG, Goodman AM, Mills DJ, Rohlf JL. Efficacy of metformin in type II diabetes: results of a double-blind, placebo-controlled, dose-response trial. *Am J Med* 1997; 103(6):491–497. pmid:9428832
 20. Zhang X, Harmsen WS, Mettler TA, et al. Continuation of metformin use after a diagnosis of cirrhosis significantly improves survival of patients with diabetes. *Hepatology* 2014; 60(6):2008–2016. doi:10.1002/hep.27199
 21. Wing RR, Blair EH, Bononi P, Marcus MD, Watanabe R, Bergman RN. Caloric restriction per se is a significant factor in improvements in glycemic control and insulin sensitivity during weight loss in obese NIDDM patients. *Diabetes Care* 1994; 17(1):30–36. pmid:8112186

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