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Metformin Use in Patients With Historical Contraindications

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Patients with type 2 diabetes rarely have just 1 chronic condition to manage (1). Some comorbid conditions, such as kidney disease, heart failure, and liver dysfunction, greatly reduce the number of drugs that can be used safely to lower blood glucose levels. As a result, patients with these conditions often end up on medications that increase the risk for hypoglycemia and weight gain (sulfonylureas or insulin), result in a high treatment burden (insulin), or substantially increase the cost of treatment (all newer, branded products). For these patients, a safe and inexpensive oral agent, minimally disruptive to their routines, would be a clear win.

Metformin fits that bill and is recommended widely as a first-line treatment for type 2 diabetes. However, when metformin was first approved in 1994, it was contraindicated in patients with kidney disease as well as in those with clinical or laboratory evidence of liver disease because of concerns about lactic acidosis. Several years later, the U.S. Food and Drug Administration (FDA) advised against its use in persons with congestive heart failure because of reports of lactic acidosis occurring in this setting (2). However, in 2006, the FDA eliminated the heart failure warning in response to 2 large observational studies (3) that suggested that metformin is safe and may be beneficial in patients with compensated heart failure. In April 2016, the FDA issued another safety communication, this time relaxing the renal contraindications (4). Metformin use is now allowed in patients with mild to moderate kidney dysfunction, defined as an estimated glomerular filtration rate (eGFR) of 30 to 60 mL/min/1.73 m², but not in those with severe kidney dysfunction (eGFR <30 mL/min/1.73 m²). The FDA's decision to require this label change came as a result of 2 citizen petitions and again was based primarily on observational data (4). As a result of this decision, many patients with historical contraindications to metformin are now eligible for its use.

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Metformin effectively lowers blood glucose levels, does not typically cause hypoglycemia or weight gain, and usually is well-tolerated. However, aside from those advantages, it is important to consider whether its use actually leads to improved clinical outcomes. After all, the goal of diabetes care is to reduce complications, not just blood glucose levels. What is the evidence that the potential benefits of metformin with respect to cardiovascular events and mortality (5, 6) extend to patients with traditional contraindications, such as heart, kidney, or liver failure?

Crowley and colleagues (7) conducted a systematic review of metformin use and its effect on several relevant clinical outcomes, including all-cause mortality and major cardiovascular events in patients with kidney disease (eGFR <60 mL/min/1.73 m²), congestive heart failure, or chronic liver disease with hepatic impairment. The authors found no eligible studies evaluating other outcomes of interest, such as glycemic and lipid control, hypoglycemia, and weight gain. They reviewed 17 studies comparing treatment regimens that included metformin with those that did not and found that metformin use was associated with lower all-cause mortality among patients with each of the 3 chronic conditions. In addition, metformin was associated with a lower risk for heart failure readmission in patients with heart failure and kidney disease, but it did not confer a lower risk for major cardiovascular events in those patients.

Despite this well-conducted review, the benefits of metformin use in patients with kidney, heart, or liver dysfunction remain somewhat uncertain. The available studies were all observational and could not completely account for confounding by indication or other biases. Moreover, metformin use was determined primarily at baseline, attrition was not evaluated completely, and outcome assessment was not blinded. As a result, the authors correctly concluded that the strength of the evidence remains low.

To make smart decisions about glucose-lowering therapies, clinicians and patients need higher-quality evidence regarding the benefits and harms of various treatment options. In addition, they need to consider how each treatment will affect patients' daily routines, whether it fits with their self-management capacity, and what associated out-of-pocket costs it will incur. The particularly vulnerable patients with kidney, heart, or liver failure need specific information about the safety and effectiveness of treatment in the context of these comorbid conditions and about any interactions between drugs or conditions that may nullify the benefits or accentuate the harms of treatment. This type of evidence is sorely lacking.

Because metformin is widely used and inexpensive, a better understanding of its effect on outcomes in contemporary practice, as well as among subgroups of patients with commonly occurring comorbid conditions, is imperative. The often-cited evidence concerning metformin's cardiovascular benefits for relatively healthy patients with newly diagnosed diabetes stems primarily from a small subgroup of the UKPDS (United Kingdom Prospective Diabetes Study) conducted more than 2 decades ago, before the widespread use of many cardioprotective therapies, such as statins and renin–angiotensin system inhibitors (6). Comparative effectiveness evidence for metformin with respect to cardiovascular disease in the modern era is either insufficient or of low quality (8). In contrast, evidence for newer

glucose-lowering agents (that is, those introduced after 2008) is now emerging from several modern cardiovascular outcomes trials, which typically include thousands of high-risk diabetic patients with many prespecified and independently adjudicated outcomes (9). These postapproval trials are required by the FDA to reasonably exclude cardiovascular risk associated with new glucose-lowering agents (10). The resulting imbalance in the available evidence may potentially lead to greater use of newer medications, in lieu of metformin, and cost an already-taxed health care system billions of dollars. In light of the recently relaxed contraindications for its use, bolstering the evidence base for metformin might be a wise investment.

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