



# Should you treat prediabetes? It's complicated

While treatment with metformin or lifestyle modification reduces risk for T2D in patients with prediabetes, neither intervention ultimately offers a mortality benefit.

## PRACTICE CHANGER

Adjust patient expectations when discussing metformin treatment and intensive lifestyle modification in patients with prediabetes. No long-term mortality benefit has been found with either, and it may be time to stop prescribing metformin in these patients.

### STRENGTH OF RECOMMENDATION

**B:** Based on a long-term follow-up of a randomized controlled trial.<sup>1</sup>

Lee CG, Heckman-Stoddard B, Dabelea D, et al; Diabetes Prevention Program Research Group. Effect of metformin and lifestyle interventions on mortality in the Diabetes Prevention Program and Diabetes Prevention Program Outcomes Study. *Diabetes Care*. 2021;44:2775-2782. doi: 10.2337/dc21-1046

## ILLUSTRATIVE CASE

A 51-year-old woman with a history of elevated cholesterol and a body mass index (BMI) of 31 presents to your clinic for a scheduled follow-up visit to review recent blood test results. Her A1C was elevated at 5.9%. She wants to know if she should start medication now.

**P**rediabetes is a high-risk state that confers increased risk for type 2 diabetes (T2D). It is identified by impaired fasting glucose (fasting plasma glucose [FPG], 100-125 mg/dL), impaired glucose tolerance (2-hour oral glucose tolerance test, 140-199 mg/dL), or an elevated A1C (between 5.7% and 6.4%).<sup>2</sup>

An estimated 96 million Americans—38% of the US adult population—have prediabetes, according to the Centers for Disease

Control and Prevention.<sup>3</sup> Family physicians frequently encounter this condition when screening for T2D in asymptomatic adults (ages 35 to 70 years) with overweight or obesity, as recommended by the US Preventive Services Task Force (grade “B”).<sup>4</sup>

**■ To treat, or not?** Studies have shown that interventions such as lifestyle modification and use of metformin by patients with prediabetes can decrease their risk for T2D.<sup>5,6</sup> In the Diabetes Prevention Program (DPP) study, progression from prediabetes to T2D was reduced to 14% with lifestyle modification and 22% with metformin use, vs 29% with placebo.<sup>7</sup>

However, there is disagreement about whether to treat prediabetes, particularly with medication. Some argue that metformin is a safe, effective, and cost-saving treatment to prevent T2D and its associated health consequences.<sup>8</sup> The current American Diabetes Association (ADA) guidelines suggest that metformin be considered in certain patients with prediabetes and high-risk factors, especially younger age, obesity or hyperglycemia, or a history of gestational diabetes.<sup>9</sup> However, only an estimated 1% to 4% of adults with prediabetes are prescribed metformin.<sup>10</sup>

Others argue that treating a preclinical condition is not a patient-centered approach, especially since not all patients with prediabetes progress to T2D and the risk for development or progression of retinopathy and microalbuminuria is extremely low if A1C levels remain < 7.0%.<sup>11</sup> By this standard,

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➤ **Both the metformin and lifestyle intervention groups experienced decreases in weight and cardiovascular risk factors but not in mortality.**

pharmacologic treatment should be initiated only if, or when, a patient develops T2D, with a focus on intensive lifestyle intervention for high-risk patients in the interim.<sup>11</sup>

Given the conflicting viewpoints, ongoing long-term studies on T2D prevention will help guide treatment decisions for patients with prediabetes. The study by Lee et al<sup>1</sup> was the first to evaluate the effect of metformin or intensive lifestyle modification on all-cause and cause-specific mortality in patients at high risk for T2D.

#### STUDY SUMMARY

##### **No mortality benefit from metformin or lifestyle modification**

This secondary analysis evaluated mortality outcomes for patients at risk for T2D who were part of the DPP trial and then were followed long term in the Diabetes Prevention Program Outcomes Study (DPPOS).<sup>1</sup> The initial DPP trial included 3234 adult patients at high risk for T2D (defined as having a BMI  $\geq 24$ ; an FPG of 95-125 mg/dL; and a 2-hour glucose level of 140-199 mg/dL). Participants were randomized into groups receiving either intensive lifestyle intervention (which focused on achieving  $\geq 150$  min/wk of exercise and  $\geq 7\%$  body weight loss), metformin 850 mg twice daily, or placebo twice daily; the latter 2 groups also received standard exercise and diet recommendations. Mean age was 51 years, mean BMI was 34, and 68% of participants were female.

At the conclusion of the initial 5-year trial, treatment was unmasked and 86% of the patients continued to be followed for long-term outcomes. Patients in the lifestyle group were offered semiannual lifestyle reinforcement, while the metformin group continued to receive the twice-daily 850-mg dose unless a contraindication developed. If FPG levels increased to  $\geq 140$  mg/dL in the DPP study, or A1C increased to  $\geq 7\%$  in the DPPOS, study metformin was discontinued and management of the patient's diabetes was transferred to their health care provider. By the end of the DPPOS, 53% of patients in the lifestyle group and 55% in the metformin group had progressed to T2D, compared with 60% in the placebo group ( $P = 0.003$ ).

After a median 21-year follow-up interval, the investigators collected data on cause of death for patients and evaluated hazard ratios (HRs) for overall and cause-specific mortality. In total, 14% of the participants died, with no statistically significant difference in rates between the 3 groups. Cancer (37%) was the leading cause of death in all groups, followed by cardiovascular disease (CVD; 29%).

Compared with the placebo group, patients taking metformin did not have a decreased rate of overall mortality (HR = 0.99; 95% CI, 0.79-1.25), mortality from cancer (HR = 1.04; 95% CI, 0.72-1.52), or mortality due to CVD (HR = 1.08; 95% CI, 0.70-1.66). Similarly, compared with the placebo group, lifestyle intervention did not decrease overall mortality (HR = 1.02; 95% CI, 0.81-1.28), mortality from cancer (HR = 1.07; 95% CI, 0.74-1.55), or mortality due to CVD (HR = 1.18; 95% CI, 0.77-1.81). Results were similar when adjusted for other factors, including out-of-study metformin use, T2D status and duration, BMI change, and other cardiovascular risk factors.

#### WHAT'S NEW

##### **Long-term data clarify limits to interventions' utility**

This study looked at long-term follow-up data on mortality outcomes for patients with prediabetes treated with metformin or lifestyle intervention. Although these interventions did support weight loss, reduce the incidence of T2D, and lower cardiovascular risk factors (eg, hypertension, dyslipidemia), the comorbidity benefits did not affect risk for all-cause or cause-specific mortality, which were similar between the treatment and placebo groups.

#### CAVEATS

##### **Exclusion criteria, residual confounding may limit the findings**

Patients with significant cardiovascular or renal disease were excluded, so results may not apply to patients with these comorbidities. Additionally, there was a high amount of "drop-in" use of metformin prescribed by physicians once patients developed T2D, which may not have been controlled for completely. And

while the intensive lifestyle intervention group had specific goals, the metformin and placebo groups also were encouraged to follow standard diet and lifestyle recommendations—and during a bridge period, all participants were offered a modified group lifestyle intervention. However, multivariable adjustment did not change the study conclusion.

### CHALLENGES TO IMPLEMENTATION

#### Physicians may be unwilling to change their current prescribing habits

Physicians may not be willing to change their practice of prescribing metformin in prediabetes based on a singular study (with residual confounding) that showed no long-term mortality differences between the study groups. However, there may be long-term morbidity differences of interest to patients that were not specifically evaluated in this study—such as quality-of-life benefits from weight loss that may outweigh the risks (eg, gastrointestinal adverse effects such as diarrhea, nausea, and abdominal pain) of metformin for some patients. Therefore, a discussion of the risks and benefits of treatment for prediabetes should be had with patients at high risk who would prefer a pharmacologic intervention. **JFP**

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