

# Editorials

## *Controversies in Family Medicine*

### Should Adults with Prediabetes Be Prescribed Metformin to Prevent Diabetes Mellitus?

#### **Yes: High-Quality Evidence Supports Metformin Use in Persons at High Risk**

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A surge in the prevalence of prediabetes<sup>1</sup> highlights the importance of improving prediabetes awareness and engaging in strategies to lower the risk of type 2 diabetes mellitus. Based on evidence from randomized controlled trials and observational studies, U.S. and international guidelines advocate for the use of medications in addition to intensive lifestyle interventions to prevent diabetes.<sup>2,3</sup> Metformin, alpha-glucosidase inhibitors, orlistat (Xenical), glucagon-like peptide-1 receptor agonists, and thiazolidinediones can all lower diabetes risk.<sup>4</sup> Among these, metformin has the strongest evidence of safety and effectiveness, making it the preferred pharmacologic option for diabetes prevention.<sup>4</sup>

#### **High-Quality Evidence Supports Metformin for Diabetes Prevention in Higher-Risk Patients**

Several randomized controlled trials, including the Diabetes Prevention Program (DPP) study, have shown that metformin can significantly lower incident diabetes risk among overweight and obese patients with prediabetes.<sup>3</sup> When compared with placebo, metformin had a relative risk reduction of 31% over three years,<sup>2</sup> with a number needed to treat of 14.<sup>2,5</sup> Three randomized controlled trials (including the DPP study) reported absolute risk reductions ranging from 4% to 14%.<sup>5</sup> However, rates of diabetes progression vary significantly among individuals.

Although prevention is the ideal outcome, even delaying the onset of diabetes has several potential advantages. Compared with those who have prediabetes, individuals with diabetes require additional tests, procedures, and closer monitoring (i.e., retinal and foot examinations,

more rigorous monitoring of blood pressure control); are at greater risk of diabetes-related complications; and may be more likely to face stigmas or discrimination.<sup>6</sup> Currently, there is no U.S. Food and Drug Administration indication for metformin use in prediabetes, in part because longitudinal follow-up data have yet to demonstrate whether metformin use can improve cardiovascular outcomes.<sup>7</sup> Longer-term follow-up in the DPP Outcomes Study may help determine whether treatment with metformin can lower the risk of microvascular and macrovascular complications,<sup>7</sup> and a large randomized clinical trial is underway to assess the effect of metformin use on cardiovascular outcomes among individuals with prediabetes and coronary artery disease.<sup>8</sup>

Clinicians should consider prescribing metformin for diabetes prevention in adults at higher risk of incident diabetes, in whom the benefits are strongest. In clinical trials, metformin was more effective in those who were younger than 60 years or more obese (body mass index greater than 35 kg per m<sup>2</sup>) and in women with a history of gestational diabetes.<sup>4,7</sup> When A1C level was used to define DPP eligibility and diagnosis of diabetes, metformin and intensive lifestyle intervention showed similar degrees of risk reduction.<sup>9</sup> Thus, higher A1C (i.e., 6.0% to 6.4%), but also other important risk factors, such as family history of diabetes, higher fasting plasma glucose levels, and higher triglyceride levels, may predict greater risk of progression to diabetes.<sup>10</sup> All of these risk factors should also be assessed when metformin is being considered for individual patients.<sup>10</sup>

#### **Benefits of Metformin Use for Diabetes Prevention Outweigh the Risks**

Metformin is a safe, tolerable, cost-effective, and possibly cost-saving treatment for prediabetes.<sup>11,12</sup> In general, the biggest concern regarding metformin has been the potential risk of lactic acidosis. However, a Cochrane review of more than 300 studies found no increased risk of lactic acidosis.<sup>13</sup> Adverse effects of metformin include mild gastrointestinal symptoms and B<sub>12</sub> deficiency.<sup>14</sup> From an individual perspective, even mild adverse effects may deter patients from using metformin, whereas the delay and/or prevention of diabetes may signify overwhelming benefit for others. From a societal perspective, the high prevalence of prediabetes underscores the importance of recommending metformin

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for higher-risk patients given its established safety and cost-effectiveness.

## Metformin Use for Diabetes Prevention Is Aligned with Patient-Centered Principles of Care

To provide patient-centered care for any condition, it is critical to help patients understand management options, weigh relative risks and benefits, and make choices that are aligned with their values and preferences. Initiating intensive lifestyle interventions is the first-line treatment for prediabetes, but metformin should also be presented as a safe and effective option for higher-risk patients. Studies have shown that most patients consider both metformin and intensive lifestyle intervention as acceptable treatment options.<sup>15</sup>

In summary, high-quality evidence supports metformin use for diabetes prevention among younger or more obese individuals or for women with a history of gestational diabetes. In these groups, the benefits of metformin likely outweigh the risks; therefore, clinicians should consider prescribing metformin, in addition to intensive lifestyle interventions, in accordance with patients' values and preferences. Family physicians have the opportunity to provide more patient-centered care and reduce the burden of type 2 diabetes, one patient at a time.

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