

FPIN's Clinical Inquiries

Metformin vs. Lifestyle Changes for Prevention of Type 2 Diabetes Mellitus

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Clinical Question

Is metformin therapy more effective than therapeutic lifestyle changes in preventing progression to type 2 diabetes mellitus in patients with prediabetes?

Evidence-Based Answer

Metformin is more effective than standard lifestyle changes at preventing progression to type 2 diabetes. (Strength of Recommendation [SOR]: A, systematic review and meta-analysis of randomized controlled trials [RCTs] and RCT of disease-oriented outcomes.) However, intensive lifestyle interventions are as effective as metformin. The effects of these interventions are enduring, with a continued benefit of intensive lifestyle interventions and metformin at 15 years of follow-up. (SOR: B, RCT of disease-oriented outcomes.) Patients with a body mass index (BMI) greater than 35 kg per m², age younger than 60 years, higher fasting glucose or A1C, or a history of gestational diabetes benefit the most from using metformin to prevent the progression from prediabetes to type 2 diabetes. (SOR: B, RCT of disease-oriented outcomes.)

Evidence Summary

A 2019 Cochrane review of 20 RCTs studied metformin for diabetes prevention for a follow-up

period of one to three years.¹ The metformin dosage varied drastically in these trials, from 38 mg per day to 3,000 mg per day. A total of 12 RCTs (n = 3,632) evaluated the incidence of type 2 diabetes in patients randomized to metformin therapy compared with those randomized to placebo or standard care (i.e., physician recommendations about healthy diet and exercise). These trials found that metformin was more effective (relative risk [RR] = 0.50; 95% CI, 0.38 to 0.65; *P* < .001). Seven RCTs (n = 2,960) compared the incidence of type 2 diabetes in patients randomized to metformin vs. intensive diet and lifestyle modification (defined differently among studies, but often including at least 30 minutes of exercise per day and structured visits with a dietitian). There was no significant difference between the two groups (RR = 0.80; 95% CI, 0.47 to 1.37; *P* = .42).

The largest and most comprehensive trial in this Cochrane review was the Diabetes Prevention Program, a multicenter RCT of 3,234 people in the United States recruited from different socioeconomic and ethnic backgrounds.² All participants had risk factors for type 2 diabetes, such as impaired glucose tolerance (elevated fasting glucose greater than 95 mg per dL [5.27 mmol per L], post-75-g glucose load greater than 140 to 199 mg per dL [7.8 to 11.0 mmol per L]), and a BMI of greater than 24 kg per m²). Participants were

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randomized to intensive lifestyle interventions (150 minutes of exercise per week and dedicated in-person and telephone visits to assess compliance) with a goal of losing 7% of their body weight or to standard lifestyle changes combined with either 850 mg of metformin or placebo twice per day. The average follow-up was three years. In the metformin-only group, there was a 31% relative reduction in the incidence of type 2 diabetes (95% CI, 17% to 43%; number needed to treat [NNT] = 14). In the intensive lifestyle intervention group, there was a 58% relative reduction in the incidence of type 2 diabetes (95% CI, 48% to 66%; NNT = 7).

A subanalysis of the Diabetes Prevention Program published in 2015 looked at which patient groups were at the highest risk of progression to type 2 diabetes and would benefit the most from metformin.³ The subanalysis used a diabetes prediction risk model, which considered 17 factors, including fasting glucose, age, A1C, and BMI. The benefit of metformin was greatest in the highest-risk quartile of patients, with an NNT of 5 and a 21.4% absolute risk reduction (ARR) in the progression to diabetes over three years. No benefits were noted for metformin therapy in the lowest-risk group. Lifestyle intervention was beneficial across all four risk groups, with an NNT of 4 and ARR of 28.3% in the highest-risk group and an NNT of 21 and ARR of 4.9% in the lowest-risk group.

Among the surviving members of the original Diabetes Prevention Program, 88% were included in an analysis at 15 years of follow-up.⁴ After the initial three-year study had ended, participants in the metformin and placebo groups were eligible to receive lifestyle intervention in a group format for one year. The original lifestyle intervention group continued to receive additional support, including individual check-ins twice per year. The metformin group was unblinded and continued taking metformin. The incidence of type 2

diabetes was reduced by 27% in the intensive lifestyle intervention group compared with placebo (hazard ratio [HR] = 0.73; 95% CI, 0.65 to 0.82; $P < .0001$) and by 18% in the metformin group compared with placebo (HR = 0.82; 95% CI, 0.72 to 0.93; $P < .001$). The difference between the lifestyle and metformin groups was not statistically significant.

Recommendations From Others

The American Diabetes Association recommends that individuals with prediabetes enroll in intensive lifestyle programs.⁵ Metformin therapy should also be considered, particularly in patients younger than 60 years with risk factors, including a BMI of 35 kg per m² or greater, fasting glucose of 110 mg per dL (6.11 mmol per L) or greater, and an A1C of 6% or greater.

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References

1. Madsen KS, Chi Y, Metzendorf MI, et al. Metformin for prevention or delay of type 2 diabetes mellitus and its associated complications in persons at increased risk for the development of type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2019;(12):CD008558.
2. Knowler WC, Barrett-Connor E, Fowler SE, et al.; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346(6):393-403.
3. Sussman JB, Kent DM, Nelson JP, et al. Improving diabetes prevention with benefit based tailored treatment: risk based reanalysis of Diabetes Prevention Program. *BMJ*. 2015;350:h454.
4. Diabetes Prevention Program Research Group. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study. *Lancet Diabetes Endocrinol*. 2015;3(11):866-875.
5. American Diabetes Association. Standards of medical care in diabetes-2022 abridged for primary care providers. *Clin Diabetes*. 2022;40(1):10-38. ■