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## Q / How can we keep impaired glucose tolerance and impaired fasting glucose from progressing to diabetes?

### EVIDENCE-BASED ANSWER

**> Lifestyle modification (weight loss plus exercise) is the best way to prevent impaired fasting glucose or impaired glucose tolerance from progressing to diabetes.**

**A / LIFESTYLE CHANGES AND SOME DRUGS CAN HELP.** Lifestyle interventions aimed at weight loss of 5% to 10% of body weight along with moderate aerobic exercise such as brisk walking for 150 minutes a week are the most effective means to prevent impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) from progressing to diabetes (strength of recommendation [SOR]: **A**, several meta-analyses, including a recent Cochrane review).

Effective pharmacologic interventions include metformin (SOR: **A**, meta-

analysis), acarbose (SOR: **A**, meta-analysis), and orlistat (SOR: **B**, meta-analysis).

Although thiazolidinediones, such as rosiglitazone, can decrease the rate of progression to diabetes (SOR: **B**, randomized controlled trial [RCT]), they pose a significant risk of fluid overload and heart failure. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers aren't recommended for the express purpose of preventing diabetes in patients with IGT or IFG (SOR: **B**, RCTs with inconsistent results).

### Evidence summary

Patients with either IFG or IGT have a significant risk of progressing to diabetes. A recent Cochrane review evaluated studies that randomized patients to intensive exercise and diet counseling or standard advice with follow-up for 1 to 6 years.<sup>1</sup> Although treatment arms varied from study to study, exercise recommendations averaged at least 150 minutes a week and diet recommendations included counseling by dietitians. These lifestyle interventions reduced progression to diabetes by 37%. Another meta-analysis showed a relative risk reduction of 49% for lifestyle changes.<sup>2</sup>

### Metformin is the most effective drug; acarbose and orlistat also help

This meta-analysis also encompassed 10 RCTs that evaluated the effectiveness of pharmacologic interventions, including oral diabetes

drugs (metformin, phenformin, acarbose, glipizide, flumamine) and an antiobesity drug (orlistat).<sup>2</sup> Metformin was the most effective drug, with a 31% to 35% relative risk reduction (number needed to treat [NNT]=7-14), although acarbose and orlistat also produced significant reductions. In a small study, glipizide didn't prevent development of diabetes.

A 2006 Cochrane review of acarbose encompassed 5 RCTs, including the Study to Prevent Non-Insulin-Dependent Diabetes (STOP-NIDDM), which showed a relative risk reduction of 22%.<sup>3</sup>

### Rosiglitazone offers benefit, but also hazard

The Diabetes Reduction Assessment with ramipril and rosiglitazone Medication (DREAM) Trial of 5269 participants with IGT or IFG compared treatment with rosiglitazone

and placebo.<sup>4</sup> Rosiglitazone reduced development of diabetes for participants (hazard ratio=0.40; 95% confidence interval [CI], 0.35-0.46;  $P<.0001$ ; NNT=5).

However, the risk of heart failure was higher in the rosiglitazone arm, with a risk ratio of 7.00 (95% CI, 1.59-30.76) and a number needed to harm of 250. No statistically significant difference was noted in cardiovascular-related deaths. This trial is consistent with recent evidence showing an increased risk of fluid overload and heart failure in patients with diabetes who take thiazolidinediones.<sup>5</sup>

### ACE inhibitors aren't routinely recommended

Early evidence suggested that blockade of the renin-angiotensin system might delay the onset of diabetes.<sup>6</sup> The DREAM trial included a ramipril arm to evaluate for this effect in IGT and IFG.<sup>7</sup> After 3 years of follow-up, no significant decrease in the incidence of diabetes was found among participants taking ramipril compared with placebo.

However, a significant regression to normoglycemia was observed in participants taking ramipril, which suggests that ACE inhibitors may have a modest favorable effect on glucose metabolism. Routine use of ACE inhibitors for the express purpose of preventing diabetes isn't indicated at this time.

### Recommendations

The American Diabetes Association's (ADA) 2009 position statement recommends starting treatment for IGT or IFG with intensive lifestyle modifications, including referral to an effective ongoing support program for loss of 5% to 10% of body weight and increasing exercise to at least 150 minutes a week of moderate aerobic activity (50%-70% of maximum heart rate).<sup>8</sup> Follow-up counseling is important for success.

Metformin can be considered in addition to lifestyle interventions for patients at high risk for progression to diabetes, defined as:

- both IGT and IFG plus 1 other risk factor, such as hemoglobin A1C >6%, hypertension, low levels of high-density lipoprotein, elevated triglycerides, or diabetes in a first-degree relative
- obesity
- <60 years of age.

The ADA recommends against using other drugs for diabetes prevention because of issues of cost, side effects, and failure to produce a persistent pharmacologic effect. Patients with prediabetes should be monitored annually for progression to diabetes, using either fasting glucose or a 2-hour oral glucose tolerance test. **JFP**

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