

EDITORIAL



Angiotensin-Converting–Enzyme Inhibitors for Impaired Glucose Tolerance — Is There Still Hope?

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In our increasingly sedentary society, the rates of overnutrition, the metabolic syndrome, and frank diabetes mellitus are rising at an alarming rate.¹ Once diabetes has developed, the risks of cardiovascular and renal disease are markedly increased.² Given the immense costs of diabetes — both personal and economic — considerable attention has been focused on identifying effective strategies to prevent or delay its onset in people at high risk.

The benefits of diet and exercise in reducing the risk of diabetes are well accepted. Numerous observational studies have documented that both adiposity and physical inactivity are strong independent risk factors for diabetes. The Diabetes Prevention Program, a randomized trial of lifestyle changes and metformin in people with impaired glucose tolerance, showed a 58% reduction in the progression to diabetes in the group that underwent caloric reduction and regular exercise³; the group receiving metformin also had a reduced risk of diabetes (by 31%), but this reduction was significantly less than that resulting from the lifestyle changes. Another multicenter randomized trial, the Finnish Diabetes Prevention Study,⁴ reported a reduction in the incidence of diabetes as a result of lifestyle changes that was similar to the reduction in the Diabetes Prevention Program. Lifestyle changes are currently the standard recommendation for patients recognized to be at high risk for diabetes, especially obese patients. Yet maintaining adherence to these nonpharmacologic strategies is notoriously challenging. Thus, the possible use of pharmacologic interventions to prevent diabetes in people at high risk remains of keen interest.

The concept that an angiotensin-converting–

enzyme (ACE) inhibitor might reduce the risk of diabetes emerged from secondary findings of several trials. The Captopril Prevention Project,⁵ designed to assess complications and death from cardiovascular disease among patients with hypertension who were randomly assigned to receive either captopril or diuretics or beta-blockers, showed a 14% lower incidence of diabetes in the captopril group. However, it was unclear whether this finding might be attributable to adverse metabolic effects of the non-ACE inhibitor medications. Data from the Heart Outcomes Prevention Evaluation (HOPE) trial, designed primarily to test the hypothesis that an ACE inhibitor (ramipril) or vitamin E would reduce the risk of cardiovascular events among patients at high risk, provided more persuasive support for a possibly beneficial effect of ACE inhibitors on the risk of diabetes.⁶ Subjects in the HOPE trial had known vascular disease or diabetes plus at least one other risk factor for cardiovascular disease. As compared with placebo, the use of ramipril significantly reduced the rates of death, myocardial infarction, and stroke; it also reduced the risk of newly diagnosed diabetes by 34%. A subsequent meta-analysis of 12 randomized trials also showed reductions in the risk of diabetes in subjects receiving ACE inhibitors, as well as in those receiving angiotensin-receptor blockers (27% and 23%, respectively),⁷ suggesting that this effect might be related generally to inhibition of the renin-angiotensin system. However, none of these trials were designed with a reduction in the incidence of diabetes as the primary end point, and glucose tolerance was not assessed routinely, leaving open the possibility of ascertainment bias.

In this issue of the *Journal*, the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) Investigators⁸ report the effects of ramipril on the risk of diabetes in a randomized trial designed with diabetes as a primary outcome. Subjects had impaired plasma glucose levels after an overnight fast (at least 110 mg per deciliter [6.1 mmol per liter] but less than 126 mg per deciliter [7.0 mmol per liter]) or impaired glucose tolerance (a 2-hour post-load plasma glucose level greater than 140 mg per deciliter [7.8 mmol per liter] but less than 200 mg per deciliter [11.1 mmol per liter]) and did not have prior cardiovascular disease. They were randomly assigned, according to a 2-by-2 factorial design, to receive either ramipril (up to 15 mg daily) or placebo and either the thiazolidinedione rosiglitazone or placebo and were followed for a median of 3 years. Rates of the primary end point — diabetes or death — were not significantly lower in the ramipril group (18.1%) than in the placebo group (19.5%; hazard ratio, 0.91; 95% confidence interval [CI], 0.81 to 1.03). This end point largely reflected a diagnosis of diabetes, since deaths were uncommon. However, regression to normoglycemia, a secondary outcome, was significantly more frequent in the ramipril group than in the placebo group (42.6% vs. 38.3%), although the absolute difference between the groups was small. In addition, glucose levels measured 2 hours after a glucose challenge were significantly lower in the ramipril group (although fasting glucose levels were not).

There was no significant interaction between the two therapies; the results for rosiglitazone are reported separately.⁹ In contrast to ramipril, the use of rosiglitazone resulted in a significant and substantial reduction in diabetes or death (11.4%, vs. 26.2% in the placebo group; hazard ratio, 0.40; 95% CI, 0.35 to 0.46).⁹ Thiazolidinediones are peroxisome-proliferator-activated receptor γ (PPAR γ) agonists, which are known to improve insulin sensitivity, and the concept that they would prevent or delay progression from abnormal glucose metabolism to diabetes is not new. The Troglitazone in Prevention of Diabetes (TRIPOD) study,¹⁰ for example, showed that troglitazone significantly reduced the incidence of diabetes among women at high risk, although reports of hepatotoxicity led to the withdrawal of that medication. Follow-up studies will assess

whether the effect of rosiglitazone on the rate of diabetes will persist after drug washout.

The observations that ramipril increased the likelihood of regression to normoglycemia and significantly reduced post-challenge glucose levels suggest that an ACE inhibitor may improve glucose metabolism. How? ACE inhibitors block the conversion of angiotensin I to angiotensin II, decreasing the angiotensin II that is available both in the circulation and, locally, in various organs and tissues.^{11,12} Angiotensin II may adversely affect glucose metabolism by increasing reactive oxygen species and inducing inflammation, decreasing blood flow in many tissue beds, and stimulating the sympathetic nervous system. It may also impair insulin-signaling pathways and pancreatic function. Angiotensin II inhibits the differentiation of adipocytes through the angiotensin II type 1 receptor, and low adiponectin levels are associated with insulin resistance. Inhibiting the renin-angiotensin system may improve blood flow to muscles, decrease the activity of the sympathetic nervous system, enhance insulin signaling, lower levels of free fatty acids, increase plasma adiponectin levels, and improve glucose disposal. Another putative mechanism by which the inhibition of the renin-angiotensin system may improve insulin sensitivity is through effects on PPAR γ , which is inhibited by angiotensin II.^{11,12}

How can the absence of a significant effect of ramipril on the incidence of diabetes in the DREAM trial be reconciled with prior findings that this drug and other inhibitors of the renin-angiotensin system reduce the risk of diabetes? As the DREAM Investigators note, previous trials included subjects with hypertension and subjects with, or at high risk for, cardiovascular disease, populations that differed from those in the DREAM trial — and did not include standard assessments of glucose levels. It is possible that observed reductions in the incidence of diabetes with the use of inhibitors of the renin-angiotensin system may, in some cases, have reflected improvement in unrecognized hyperglycemia at baseline or reduced detection of diabetes (owing to fewer hospitalizations for cardiovascular events). The 95% CI for the hazard ratio for diabetes in the present trial (0.80 to 1.03) means that the findings are compatible with the absence of an effect of ramipril on the risk of

diabetes but do not exclude the possibility of some benefit. In addition, the 3-year study duration may have been insufficient to demonstrate a benefit, although the duration of the Diabetes Prevention Program (in which interventions significantly reduced the risk of diabetes) was similar.

Given the primary findings of the DREAM trial, ramipril cannot be recommended for the prevention of type 2 diabetes. For patients who take ACE inhibitors for another indication (such as hypertension, congestive heart failure, or a high risk of cardiovascular events), improvement in glycemia may turn out to be yet another benefit. For now, ongoing attention to diet and exercise remains our best hope for reducing the rising rate of diabetes.

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