Navigating the Choices for Diabetes Prevention
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The global epidemic of type 2 diabetes has prompted a large number of clinical trials aimed at reducing its incidence. Not surprisingly, addressing the underlying lifestyle behaviors — overeating and inactivity — that result in obesity, the primary cause of the epidemic, has had a major and consistent effect in reducing the cumulative incidence of diabetes. In addition, lifestyle interventions have reduced the cardiovascular risk factors that typically accompany the prediabetic and diabetic states. Several drugs that are used to treat diabetes have also been studied as a means of reducing the incidence of the development of diabetes. Metformin, the alpha-glucosidase inhibitor acarbose, and the thiazolidinedione rosiglitazone have been shown to reduce the incidence of diabetes to variable degrees. The Diabetes Prevention Program (ClinicalTrials.gov number, NCT00004992) and its long-term outcome study (NCT00038727), which are the only studies that can address comparative effectiveness since they included random assignment to lifestyle modification, a medication, and placebo, showed that lifestyle intervention had a substantially more powerful effect than did metformin when each was compared with placebo (a reduction in incident diabetes with lifestyle intervention of 58% at 3 years and 34% after 10 years vs. a reduction with metformin of 31% at 3 years and 18% after 10 years).

Although a reduction in the incidence of diabetes is important, the major public health impact of prevention studies will be determined by whether the prevention of diabetes — or a delay in the development of the disease — will translate into a reduction in the diabetes-specific long-term complications affecting the eye, kidney, and nervous system and will ameliorate the less specific cardiovascular disease that is the major cause of death in patients with type 2 diabetes. Safe, inexpensive, and acceptable interventions that lower glycemia, halt or delay the progression to diabetes, and reduce cardiovascular disease are highly desirable.

In this issue of the Journal, the investigators of the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVI GATOR) study report the results of their international trial that examined the effects of the approved diabetes medication nateglinide, a relatively weak, rapid-acting, sulfonylurea-like drug, and the angiotensin-receptor blocker valsartan on the development of diabetes and cardiovascular disease in a high-risk population. Although the study had an efficient factorial design, the results with respect to nateglinide and valsartan are reported separately in the Journal, as if there were two parallel trials, since the authors report no interactions between the treatments. This presentation belies one of the stated goals of NAVIGATOR — specifically, to study the combined effects of the two study drugs. These effects are reported only briefly in Supplementary Appendix 1 for each article.

The rationale for studying nateglinide is that the meglitinide class of hypoglycemic medications, of which nateglinide is a member, has been shown to lower postprandial glycemia, a putative treatment target, since rising postprandial glucose is the most common route to the development of diabetes. Moreover, postprandial hyperglycemia (or hyperglycemia after an oral glucose-tolerance test) has been shown to be more closely associated with the risk of cardiovascular disease than are fasting glucose levels. There has been widespread interest in determining whether a causal relationship exists between el-
evated postprandial glycemia and cardiovascular disease, and it has been recommended that trials be performed to test this hypothesis.9 Finally, owing to its rapid-action profile, nateglinide has a relatively low risk of causing hypoglycemia. The rationale behind the choice of valsartan to inhibit the renin–angiotensin axis is less clear, other than the fact that both nateglinide and valsartan are manufactured by the pharmaceutical sponsor, which also designed the study. Secondary analyses of clinical trials have suggested that angiotensin-converting–enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) are associated with a reduced incidence of diabetes; however, the development of diabetes was not measured uniformly, and the only clinical trial that directly examined whether ACE inhibition would prevent diabetes failed to show that diabetes was prevented or that there were any beneficial effects on insulin resistance or beta-cell function.10,11

The results of the NAVIGATOR study are largely negative. Neither drug (nor the combination, keeping in mind that one quarter of the study cohort took both drugs) reduced the two coprimary cardiovascular-disease outcomes. The only positive result was a weak, albeit statistically significant, reduction in the incidence of diabetes with valsartan.5 The relative reduction of 14% and the absolute reduction of 3.7 percentage points in incident diabetes with valsartan, as compared with placebo, over a mean follow-up of 5 years make valsartan the weakest of the drugs studied to date.1

Unfortunately, the NAVIGATOR study has not definitively answered whether lowering postprandial glycemia reduces the incidence of cardiovascular disease or diabetes, since the mean glucose levels 2 hours after a glucose challenge in the annual oral glucose-tolerance tests were higher in the nateglinide group than in the placebo group. The authors describe this paradoxical finding as a rebound effect, since nateglinide was not administered on the mornings that the oral glucose-tolerance tests were performed, suggesting that on the 364 other days of the year, when the administration of nateglinide was not delayed, postprandial glucose levels were lower in the nateglinide group. However, there are no direct data to support this contention, and no data on glycated hemoglobin are presented, other than in the subgroup that progressed to diabetes, to support a substantial lowering of overall glycemic levels with nateglinide. The other factor that might have mitigated any putative salutary effect of nateglinide on the development of diabetes or cardiovascular disease was the provision of a lifestyle intervention program for all participants. Considering the powerful effects of lifestyle interventions in other trials,1 this design feature may have reduced the magnitude of the potential benefit from nateglinide. This explanation is not persuasive. The lifestyle intervention program was not effectively implemented, as evidenced by the trivial weight loss over the course of the study and the 8% annual incidence of diabetes in the placebo group, which was close to the rates found in control groups from other studies.

The finding that valsartan failed to have an effect on either of the cardiovascular-disease outcomes but had a positive effect on the incidence of diabetes is surprising. Previous studies of ACE inhibitors and ARBs have suggested that these drugs have a beneficial effect on cardiovascular disease in patients with diabetes, and the lower blood pressure achieved would be expected to result in a reduction in cardiovascular disease. In the NAVIGATOR study, the high rates of loss to follow-up (13%), use of off-study ACE inhibitors or ARBs among participants assigned to placebo (24%), and nonadherence to valsartan (34% by study end) could explain the absence of an effect on cardiovascular disease.

The results from the NAVIGATOR study do not support the contention that reducing postprandial hyperglycemia has a specific role in preventing diabetes or reducing cardiovascular disease. Other than increasing the rate of hypoglycemia by a factor of two, nateglinide had little effect. Although the authors suggest that the prevention of diabetes with valsartan might make it a preferred drug as compared with antihypertensive drugs that potentially worsen glycemia, valsartan was relatively weak in preventing diabetes, and it did not lower the rates of cardiovascular disease. The prevention of diabetes remains a critical public health priority, but for now we should steer away from these two drugs and use effective lifestyle interventions and, in selected persons, metformin to combat the epidemic.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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This article (10.1056/NEJMe1002322) was published on March 14, 2010, at NEJM.org.


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