

# Medicinal prevention of pre-diabetes – no purpose?

Non-medicinal interventions involving weight loss prevent the development of type 2 diabetes in people with glucose intolerance. Whether medicinal interventions can prevent type 2 diabetes is more controversial, however. In the NAVIGATOR study, published in 2010, it was attempted to prevent type 2 diabetes and cardiovascular incidents with the aid of nateglinide, alternatively valsartan. The authors who participated in the Norwegian branch of the study here discuss the findings in light of previous literature.

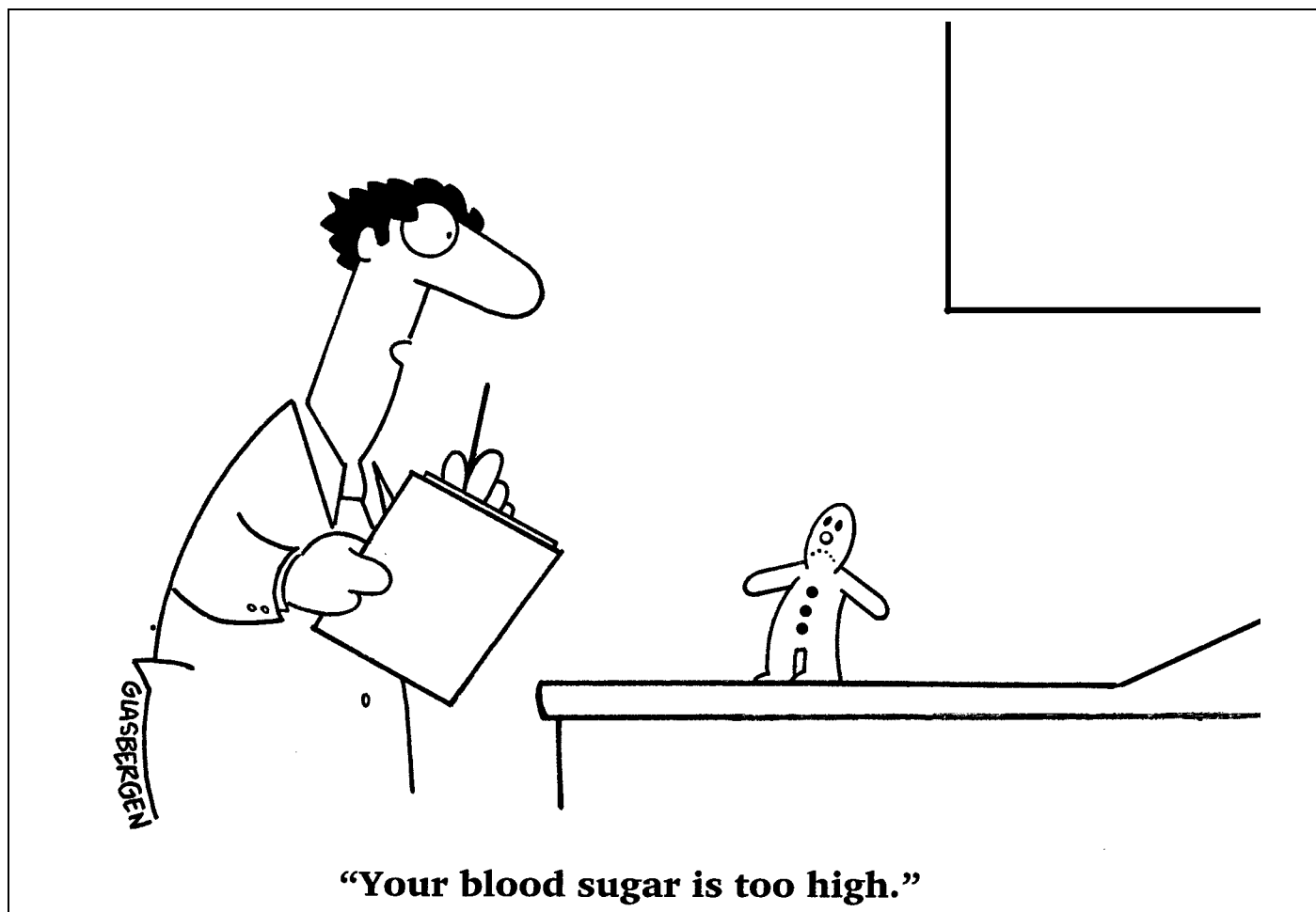


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The NAVIGATOR study (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research) was published in two articles in the *New England Journal of Medicine* in 2010 (1, 2). It was attempted to prevent diabetes and cardiovascular incidents medicinally in more than 9,000 individuals with pre-diabetes (glucose intolerance) in 40 countries.

In previous studies, treatment with metformin (3), acarbose (4) and rosiglitazone (5) appears to reduce the development of type 2 diabetes. Angiotensin-converting enzyme inhibitors (ACE inhibitors) and AII blockers are associated with fewer cases of diabetes in association studies. In a recently

published intervention study this does not appear to apply to ramipril (5).

### What can the NAVIGATOR study tell us?

The NAVIGATOR study investigated the drug nateglinide, which lowers blood glucose, and the AII blocker valsartan against a placebo. In addition, all participants were subject to a lifestyle intervention programme aiming to achieve a five per cent weight loss and 150 minutes of physical activity per week. Ten per cent of the participants reached the weight-loss goal. A total of 9,306 individuals were followed for as long as seven years.

There was no difference between nate-

glinide and placebo with regard to development of diabetes or cardiovascular incidents. Valsartan, on the other hand, reduced the incidence of diabetes by 14 per cent compared to the placebo, but had no effect on cardiovascular incidents.

### Did we learn anything?

NAVIGATOR is an important study, because it involved testing of key hypotheses from epidemiological research. The rapidly acting insulin release agent nateglinide does not reduce the development of diabetes in the long term. In fact, at the end of the study the two-hour glucose level was higher in the group treated with nateglinide than in the

placebo group, most likely because the oral glucose load was implemented in the absence of morning drugs. HbA<sub>1c</sub> was in fact 0.2 percentage points lower in the nateglinide group compared to the placebo group (6.1 per cent as opposed to 6.3 per cent). On the other hand, it may appear that a reduction in more serious forms of hyperglycaemia, such as diabetes, can have a beneficial effect after more than 10–15 years (6), i.e. a much longer time than is covered by normal intervention studies.

It remains uncertain why metformin, acarbose or rosiglitazone should be able to prevent diabetes, while nateglinide is not. We do not know whether this can be ascribed to differences in the effects profile, differences in the studied populations, or both. Two studies of tolbutamide (7, 8) and one study of sulfonylurea drugs (9), both with an effects profile not unlike that of nateglinide, likewise failed to demonstrate any preventive effect for diabetes.

Valsartan was proven to have a moderate preventive effect on diabetes, which was greater than that observed for ramipril in the DREAM study, in which ramipril reduced the incidence of diabetes by nine per cent, although not to a statistically significant degree (5). Why interventions targeting the renin-angiotensin system should be able to prevent diabetes remains unclear.

In the NAVIGATOR study valsartan did not prevent cardiovascular incidents, unlike the results of previous studies of valsartan and other drugs in the same class. However, the previous studies only included persons with a higher risk profile. In the NAVIGATOR study only 24 per cent of the participants suffered from cardiovascular disease at the time of inclusion, only three of four persons had hypertension, and the participants completed a lifestyle programme that must have been at least partly successful. There was also an extensive use of other drugs for prevention of cardiovascular disease. In addition, the daily dosage of valsartan in the NAVIGATOR study was only half of that used in previous studies.

In conclusion, nateglinide, like sulfonylurea, does not protect against the development of type 2 diabetes. Nor does the treatment appear to reduce the cardiovascular risk in individuals with glucose intolerance. Valsartan may act to prevent diabetes among persons with glucose intolerance and hypertension, but is unlikely to have an impact on cardiovascular risk.

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*The authors do not necessarily represent the views of the international group of researchers in the NAVIGATOR study.*

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