Point: Postprandial Glucose Levels Are a Clinically Important Treatment Target

The results of the Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial have been recently reported (1–2). Nateglinide, a member of the meglitinide class, which has been shown to lower postprandial hyperglycemia by increasing the first phase of insulin secretion, was not effective in decreasing both the new cases of diabetes and the new cardiovascular events in a population at high risk (1). Valsartan, an angiotensin (AT-1) blocker, was ineffective on cardiovascular events but significantly—even marginally—reduced the onset of new diabetes (2). The negative results of nateglinide immediately raised the concern about the possibility that postprandial hyperglycemia could be considered an independent risk factor for cardiovascular disease (CVD) and whether its treatment may give any advantage in the management of diabetes (3).

Diabetologists have long debated whether the lack of insulin action (insulin resistance) or impaired insulin secretion represents the primary pathological mechanism underlying type 2 diabetes. Recent analyses confirm that impaired pancreatic β-cell glucose sensitivity and whole-body insulin sensitivity are strong predictors of a progression to hyperglycemia (4). Conversely, numerous studies have shown that acute insulin secretion defects represent a powerful early predictor of diabetes progression.

During the progression from normal glucose tolerance to increasingly severe type 2 diabetes, first-phase insulin secretion (FPIS) is an early casualty. Prior to the diagnosis of diabetes, insulin response to mealtime glucose becomes delayed and blunted; eventually, it is lost (5). In a landmark study, Polonsky et al. (5) showed that FPIS responses were more sluggish and less dramatic in diabetic individuals. In another analysis, a marked and increasing loss of the early-phase β-cell secretory response to a meal challenge correlated with increasing postprandial hyperglycemia in a group of individuals recently diagnosed with diabetes (6). Together these data indicate that declining FPIS and postprandial hyperglycemia are key features of type 2 diabetes.

The relative contribution of fasting versus postprandial glucose (PPG) to overall glycemic exposure was a matter of considerable controversy until recently when influential analyses from Monnier et al. (7,8) appeared showing that the contribution of postprandial hyperglycemia varies depending on an individual's degree of glycemic control. This fundamental insight—that postprandial glycemia excursions make an ever greater contribution to A1C as glycemic control improves—has been confirmed in other settings (9) and has been extended to subjects whose A1C values lie well within the normal range (10). Based on this information, one would predict that attempts to treat patients to target, especially when aiming for ambitious A1C targets, will generally fail unless PPG is controlled. Many studies directly support this hypothesis (11), including the recent data of the Treating to Target in Type 2 diabetes (4-T) trial (12) and in particular the data after 1 year (13), where even the conclusions of the authors were, surprisingly, different.

The link between postprandial hyperglycemia and the risk for CVD has been recently highlighted due to the identified linear relationship, widely confirmed in many studies, between the risk of CVD death and the glucose value at 2 h during an oral glucose tolerance test (OGTT) (11). A recent study (14) consistently confirmed postprandial hyperglycemia as an independent risk factor for CVD in type 2 diabetes. However, most of the epidemiological data supporting this concept were available from studies using the OGTT (11). This approach raised the concern that because the OGTT could not be considered a meal, the existing relationship between the 2-h glucose values during an OGTT did not necessarily mean that these subjects could have increased postprandial hyperglycemia after a meal. This concern has now been clarified. A strong relationship between the level of glycemia after an OGTT and after a meal has been demonstrated (15), particularly in terms of peak values, thereby suggesting that this issue is now over.

However, even epidemiological data support the concept that postprandial hyperglycemia is a risk factor for CVDs, the main concern regards the need for evidence that lowering postprandial hyperglycemia CVD can be prevented. The Study To Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial has shown, as a predefined secondary end point, that treating postprandial hyperglycemia may reduce the incidence of new cardiovascular events in people with impaired glucose tolerance (16), a finding confirmed in type 2 diabetes by a meta-analysis on the use of acarbose (17). However, the Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus (HEART2D) study (18) last year and the NAVIGATOR (1) study now, have failed to confirm this finding.

What has the NAVIGATOR study demonstrated? In my opinion, it has only demonstrated that nateglinide does not reduce cardiovascular events. That is all. Unfortunately, NAVIGATOR is another study, as is the HEART2D study (18), that does not help to answer whether lowering postprandial hyperglycemia reduces the incidence of CVD.

The HEART2D study failed to reach the predetermined difference in postprandial hyperglycemia of 2.5 mmol/l, the mean difference at the end of the study being only 0.8 mmol/l, less than one-third of the goal, even if significantly different between the two groups (18). In the NAVIGATOR trial, nateglinide not only did not improve postprandial hyperglycemia, but the glucose levels 2 h after a glucose challenge in the annual OGTTs were higher in the nateglinide group than in the placebo group (1). Furthermore, the incidence of new diabetes was also higher in the treated group than in the placebo group (1).

As already suggested (19), we have to pay attention to the level of risk in the patients included in the studies. We have learned that the control of hyperglycemia may have a different impact in the pri-

mary and secondary prevention of CVD in type 2 diabetes (19), influencing the sample size of the study. Looking at the recent lessons from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (20), the Action in Diabetes and Vascular Disease–Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial (21), the Veterans Affairs Diabetes Trial (VADT) (22), and the long-term follow-up of the UK Prospective Diabetes Study (UKPDS) (23), it has been suggested that if the control of hyperglycemia, both fasting (ACCORD, ADVANCE, and VADT) or postprandial (HEART2D), is started too late, the possible beneficial effect of treating hyperglycemia, both fasting (UKPDS) or postprandial (STOP-NIDDM), in a very early stage of the disease is lost.

In NAVIGATOR, people in the primary prevention and who already suffered a cardiovascular event were pooled and evaluated together (1). This may introduce another bias in the evaluation of the results. This concept is strengthened during the study by the need to change the primary outcome, including a third coprimary core cardiovascular outcome, previously designated as a secondary outcome (1). To this, we have to add the very high rate of dropouts (1).

The authors of NAVIGATOR claim that the paradox increase of glucose during the OGTT in the nateglinide arm would be a rebound effect since nateglinide was not administered on the morning that the OGTT was performed, therefore suggesting that postprandial hyperglycemia was lower during the other days of the study (1). However, as already outlined by Nathan (3), "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."

As reported above, the impact of postprandial hyperglycemia on CVD is still a matter of debate, and perhaps we will obtain an answer from the Acarbose Cardiovascular Evaluation (ACE), a huge trial performed in China. However, in my opinion, what we have learned again (19) is how complex the management of postprandial hyperglycemia truly is.

This is certainly an important issue because prandial glucose regulation is an emerging approach to treating type 2 diabetes (11). Mechanistic and epidemiological studies indicate that PPG significantly contributes to overall glycemic exposure (7–8). In particular, postprandial hyperglycemia is the most important contributor to A1C, particularly when it is lower than 7.5% (7–8). Targeting postprandial hyperglycemia has been largely confirmed as important for the achievement of A1C targets (24). Paradoxically, it has been published (25) that in type 2 diabetic patients with good glycemic control (A1C $<$ 6.5%), further strict glycemic control by nateglinide (A1C of 6.1%) resulted in the regression of carotid intima-media thickness, a useful marker of cardiovascular risk.

Oxidative stress, in particular the increased superoxide production at the mitochondrial level, has been suggested as the key link between hyperglycemia and diabetic complications (26). Evidence suggests that the same phenomenon underscores the deleterious effect of oscillating glucose, leading to a more enhanced deleterious effect of fluctuating glucose compared with constant high glucose (27).

Postprandial hyperglycemia, which can be considered just an aspect of the glucose variability, produces oxidative stress, which, in turn, induces endothelial dysfunction and inflammation (28), all well recognized risk factors for CVD. Considering that the specific management of postprandial hyperglycemia is so difficult, one can wonder whether treating oxidative stress (in the right, modern way [29]) while managing postprandial hyperglycemia would be a good strategy. For instance, an AT-1 blocker, irbesartan, has been demonstrated to reduce oxidative stress, endothelial dysfunction, and inflammation induced by postprandial hyperglycemia (30), evidence which might explain the positive effect of valsartan in preventing the new onset of diabetes (1).

Accumulating evidence suggests that glucose "variability" in terms of widely fluctuating glucose may have a deleterious effect in worsening the prognosis, not only for diabetic complications, but also for several critical care situations (27). The hypothesis that maintaining the level of glycemia under very strict control would be relevant in any clinical setting is, in my opinion, stressed by the recent evidence that glycemia in normoglycemic people is always maintained in very narrow range, particularly after a meal (31,32). One can argue that if the human body spends so much energy to maintain the blood glucose level under so strict a range, it is because otherwise it could be deleterious.

Finally, I wonder if the acronym "NAVIGATOR" was chosen because in the past the concept of postprandial hyperglycemia as a damaging factor was represented with a "wave" (28). If this is the case, this NAVIGATOR (nateglinide) would have been good for lakes and rivers, certainly not for a stormy sea (postprandial hyperglycemia).

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