Postprandial Hyperglycemia and Glycemic Variability

Should we care?

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The aim of this article is to evaluate the pros and cons of a specific impact of postprandial hyperglycemia and glycemic variability on the—mainly cardiovascular (CV)—complications of diabetes, above and beyond the average blood glucose (BG) as measured by HbA_{1c} or fasting plasma glucose (FPG). The strongest arguments in favor of this hypothesis come from impressive pathophysiological studies, also in the human situation. Measures of oxidative stress and endothelial dysfunction seem to be especially closely related to glucose peaks and even more so to fluctuating high and low glucose concentrations and can be restored to normal by preventing those glucose peaks or wide glucose excursions. The epidemiological evidence, which is more or less confined to postprandial hyperglycemia and postglucose load glycemia, is also rather compelling in favor of the hypothesis, although certainly not fully conclusive as there are also a number of conflicting results. The strongest cons are seen in the missing evidence as derived from randomized prospective intervention studies targeting postprandial hyperglycemia longer term, i.e., over several years, and seeking to reduce hard CV end points. In fact, several such intervention studies in men have recently failed to produce the intended beneficial outcome results. As this evidence by intervention is, however, key for the ultimate approval of a treatment concept in patients with diabetes, the current net balance of attained evidence is not in favor of the hypothesis here under debate, i.e., that we should care about postprandial hyperglycemia and glycemic variability. The absence of a uniformly accepted standard of how to estimate these parameters adds a further challenge to this whole debate.

Although undoubtedly diabetes, i.e., hyperglycemia, is associated with an increased risk of microvascular and macrovascular complications, how exactly the various parameters of hyperglycemia exert their influence on the vascular system is still under debate (1). Fasting plasma glucose (FPG), postprandial hyperglycemia, and glucose variability all contribute to the net balance of the long-term glycemic parameter HbA_{1c} (not to forget that hypoglycemia has recently re-emerged as an independent risk predictor of major cardiovascular (CV) and other negative events in its own right, but that is not the focus of this article). Does it not suffice to concentrate on HbA_{1c} values, because they have been shown by several meta-analyses in 2009 based on all available data from randomized intervention trials on blood glucose (BG)-lowering therapies to be clearly independent determinants of major CV events, especially myocardial infarction (2,3)? This article, therefore, aims to evaluate the pros and cons of a specific impact of postprandial hyperglycemia and glycemic variability on the vascular complications in diabetes, and whether they matter. Three areas of evidence mainly are to be considered: the epidemiology, the pathophysiology, and randomized prospective intervention trials. As a basis, methods of assessing postprandial hyperglycemia and glycemic variability are briefly discussed.

METHODS OF ASSESSMENT—Table 1 gives an overview of the glucose-related measures used in studying the relationship with CV parameters, both short- and longer-term. So far, no uniformly accepted standard of measurement has emerged, which poses a challenge in its own when comparing or planning studies. The postprandial parameters are self-explanatory.

Numerous measures of glycemic variability have been proposed in the literature (4). Some of these tools are easy to use; others are very complex or difficult to apply in clinical practice, even when using new methods such as continuous glucose self-monitoring. Table 1 focuses on only a few of the most important methods.

Average glucose value and SD

The calculation of the glycemic average was thought to provide better insight into glycemic variability because several study groups could demonstrate that people with diabetes—and therefore a higher mean glycemic value—produced larger amounts of compounds related to oxidative stress (i.e., nitrotyrosine, 8-hydroxy-deoxyguanosine, or 8-iso-prostaglandin $F_{2\alpha}$) than did patients without diabetes (5,6):

$$\frac{\sum_{t=t_1}^{t_k} GV_t}{k}$$

Table 1—*Measures of postprandial glucose and glycemic variability*

Postprandial hyperglycemia
2 h, 1 h, 90 min after meal
Meal, however, often undefined
In trials mainly 2 h after an oral glucose load (75 g)
Glycemic variability
Average glucose + SD
Hyperglycemic index (self-monitoring of BG)
MAGE (CGMS glucose excursions)
CONGA (CGMS intraday variability)
ADRR (log transformation)

CGMS, continuous glucose monitoring system.

where k is the number of glucose values (GVs) in a given individual.

But, the mere average turned out to be inadequate in evaluating glycemic oscillations. Therefore, the SD is considered to be the simplest tool for describing glycemic variability.

In order to overcome these shortcomings, Wójcicki (7) proposed the J-index for the assessment of glycemic variability, which is given by the formula $J = 0.324 \times (MBG + SD)^2$ where mean BG (MBG) is the MBG level measured in mmol/L, and SD is the SD of glucose levels. (The corresponding factor for calculations in mg/dL is 0.001 instead of 0.324.)

In fact, the software incorporated in most of modern measuring devices provides information on the number of measurements per day, average glucose value, and SD. Unfortunately, this SD is calculated over the total number of measurements taken by the meter and includes all oscillations without a weighting of the minor or major variations.

Hyperglycemic index
The calculation of the hyperglycemic index is based on self-monitored BG measurements and is defined as the area under the glucose curve above the normal range divided by the total time of the observation period. The cutoff for the normal glucose range is set at 6.0 mmol/L.

Mean amplitude of glycemic excursions
Mean amplitude of glycemic excursions (MAGE) (8) was designed to take into account the glycemic peaks and nadirs encountered during a day, beyond average glucose values, according to the formula:

$$\sum \frac{\lambda}{x} \quad \text{if } \lambda > y$$

where λ is the difference from peak to nadir, x is the number of valid observations, and y is 1 SD of mean glucose in a 24-h period.

The objective of this parameter is to more heavily consider the major variations of glucose levels and to give less weight to the minor ones. Only the variations exceeding 1 SD of the average glycemic value during the observation period are considered.

MAGE is a popular measure especially in studies based on continuous glucose monitoring systems. A study by Monnier et al. (5) demonstrated a good

correlation of MAGE values with oxidative stress indicators; this could not be seen for other, traditional biomarkers like HbA_{1c}, MBG, or postprandial glucose (PPG) levels. However, MAGE has some inherent limitations. Firstly, it does not discern the total number of oscillations of BG levels because the selection of 1 SD (or multiple or fraction of 1 SD) as the cut-off point is completely arbitrary. Secondly, it is a relative measure because it is relative to the mean. Thirdly, the MAGE value can be biased: if only one major decline or increase occurs during the observation period, this nevertheless yields a high result. Other problems with MAGE may occur, such as potential dependence on sampling frequency and the ambiguity as to where a peak or nadir begins and ends.

Continuous overlapping net glycemic action
The concept of the continuous overlapping net glycemic action (CONGA) was first described by McDonnell et al. (9) in 2005 and is designed as a tool for the analysis of continuous glucose monitoring system data. Contrary to methods that illustrate the interday variation of glucose levels, CONGA is designed to analyze intraday glycemic variability. For each observation after the first n hours of observations, the difference between the current observation and the observation n hours prior is calculated. CONGAn is defined as the SD of the differences. Mathematically, CONGAn can be described by the formula:

$$\sqrt{\frac{\sum_{t=t_1}^{t_k}(D_t - \bar{D})^2}{k-1}}$$

where Dt = GVt – GVt – m and

$$\bar{D} = \frac{\sum_{t=t_1}^{t_k} D_t}{k}$$

where κ is the number of observations in which there is an observation n × 60 min ago (m = n × 60).

Average daily risk range
The most recently proposed measure of glycemic variability is the approach of Kovatchev et al. (10), the average daily risk range (ADRR). The basic underlying idea of this concept is the asymmetry of the BG scale, i.e., the hyperglycemic range

(BG >10 mmol/L, potentially up to 33 mmol/L) is much broader than the hypoglycemic range (BG <3.9 mmol/L), and the target BG range (3.9–10.0 mmol/L) is not centered along the entire possible scale of BG values. This leads to a skewed distribution of glucose readings. Consequently, classical statistical measures like the mean of glucose values and the SD will describe the underlying data only poorly because these measures require a normal distribution. Thus a logarithmic transformation of the glucose scale has been proposed that is symmetrical about 0 and defines 6.25 mmol/L as a clinical and numerical center. This results in the transformed BG readings exhibiting a normal distribution.

The ADRR is calculated from 2–4 weeks of routine self-monitoring of BG readings with a frequency of three or more readings per day, applying the aforementioned data transformation to "normalize" the BG scale. The resulting values are then converted into risk values, using the formula r(BG) = f(BG). The procedure is analog to the low BG index/high BG index calculation mentioned before.

The ADRR is than calculated using the formula:

$$ADRR = \frac{1}{M}\sum_{i=1}^{M} LR^i + HR^i$$

where LRi and HRi represent the maxima of, respectively, the left and the right branch of the resulting parabola of the formula r(BG) = f(BG).

ADRR values <20 represent a low risk, 20–40 corresponds to a moderate risk, and values >40 indicate a high risk for BG excursions.

EPIDEMIOLOGICAL EVIDENCE—
Since 1997, over 15 observational studies have been published showing that elevated postprandial glucose values, even in the high nondiabetic impaired glucose tolerance (IGT) range, contribute to an approximately threefold increase in the risk of developing coronary heart disease or a CV event. Table 2 contains an overview of these studies in greater detail. This trend is confirmed in the meta-analysis by Coutinho et al. (11) that analyzed 20 studies published between 1966 and 1996. Controversy, however, exists whether elevated FPG and postload glucose contribute differently to all-cause mortality or CV outcomes, respectively,

Table 2—*Epidemiological studies on the effect of postprandial hyperglycemia on CV risk*

Study	Reference	Year of publication	Setting	Duration of follow-up	Risk measure
Cardiovascular Health Study	Smith et al.[16]	2002	4,014 American men and women from four U.S. communities, ≥65 years of age	8.5 years	HR for CV event = 1.29 for 2-h PG >8.5 mmol/L
Chicago Peoples Gas Company Study	Vaccaro et al.[17]	1992	873 American men, 34–65 years of age	19 years	CVD/CHD mortality; OR = 2.3–2.7 for 2-h PG >11.2 mmol/L vs. normoglycemic patients
Chicago Heart Association Detection Project in Industry Study	Lowe et al.[18]; Orencia et al.[19]	1997	12,220 white and black American men, 35–64 years of age	22 years	CVD mortality: RR = 1.18 for 2-h PG >8.9 mmol/L vs. normoglycemic patients
DECODA	Nakagami[20]	2004	6,817 subjects of Japanese and Asian Indian origin; 30–89 years of age	5 years (median)	RR all-cause mortality for 2-h PG >11.1 mmol/L = 2.80; RR of CVD mortality for 2-h PG >11.1 mmol/L = 3.42
DECODE	Decode Study Group[12]	2001	22,514 men and women in several European countries, 30–89 years of age	8.8 years (median)	HR for all-cause mortality = 1.73 for 2-h PG >11.2 mmol/L; HR for CVD mortality = 1.40; HR for CHD mortality = 1.56; HR for stroke mortality = 1.29
Framingham Offspring Study	Meigs et al.[21]	2002	3,370 American men and women, 26–82 years of age	4 years	RR for CVD in patients with 2-h PG >11.1 mmol/L = 1.42 per 2.1 mmol/L increase
Funagata Diabetes Study	Tominaga et al.[13]	1999	2,534 men and women from Funagata, Japan	6 years	OR for CVD mortality in patients with diabetes vs. normoglycemic subjects = 3.54
Honolulu Heart Program	Rodriguez et al.[22]	1999	8,006 Japanese-American men from Oahu, Hawaii, 45–68 years of age	23 years	RR for CHD mortality in patients with 1-h PG >12.5 mmol/L vs. normoglycemic subjects = 3.49
Hoorn Study	de Vegt et al.[23]	1999	2,363 Dutch men and woman in Hoorn, the Netherlands, 50–75 years of age	8 years	RR for CVD mortality in patients with 2-h PG >11.1 mmol/L = 3.31 vs. normoglycemic subjects
Mauritius-Fiji-Nauru Study	Shaw et al.[24]	1999	9,179 men and women from Mauritius, Fiji, and Nauru, >20 years of age	5–12 years	HR for CVD mortality in patients with 2-h PG >11.1 mmol/L vs. normoglycemic subjects = 2.3 in men, 2.6 in women
Paris Prospective and Helsinki Policemen Studies	Balkau et al.[25]	1998	7,260 subjects: 6,629 men from the Paris Prospective Study (mean age 48.5 years) and 631 subjects of the Helsinki Policemen Study	20 years	HR for CVD and CHD mortality in patients in the upper 20% (2.5%) of the 2-h PG distribution vs. those in the lower 80% of these distributions = 1.8 (2.7)

Table 2—*Continued*

Study	Reference	Year of publication	Setting	Duration of follow-up	Risk measure
	Qiao et al.[26]	2002	6,766 subjects from five Finnish cohorts	7–10 years	HR for 1 SD increase in 2-h PG = 1.22 for CVD mortality
Rancho Bernardo Study	Barrett-Connor and Ferrara[27]	1998	1,858 Caucasian adults of European ancestry in California, 50–85 years of age	7 years	HR for CVD and CHD mortality in patients with 2-h PG >11.1 mmol/L = 2.6 (CVD) and 2.9 (CHD) vs. normoglycemic control subjects
San Luigi Gonzaga Study	Cavalot et al.[28]	2006	529 men and women in a suburban area of Turin, Italy, mean age 60.4 years for men and 63.3 years for women	5 years	HR for CV event in patients with PPG in the third vs. first and second tertile = 5.54 for women and 2.12 for men
	Saydah et al.[29]	2001	3,092 American adults from the NHANES II cohort, 30–74 years of age	16 years	Relative hazard for CVD mortality in patients with 2-h PG >11.1 mmol/L = 2.3 vs. normoglycemic subjects
Whitehall Study	Brunner et al.[30]	2006	17,869 male civil servants in the U.K., 40–64 years of age	33 years	HR in patients with 2-h PG >11.1 mml/L for CVD mortality = 3.2, CHD mortality = 3.7, and stroke mortality = 1.16 vs. normoglycemic control subjects

CHD, coronary heart disease; CVD, CV disease; HR, hazard ratio; NHANES II, Second National Health and Nutrition Examination Survey; OR, odds ratio; PG, plasma glucose; RR, relative risk.

as the meta-analysis by Coutinho et al. suggests that both parameters contribute more or less equally, in contrast to publications, e.g., from the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) (12) or the Funagata Diabetes Study (13). The still ongoing prospective Australian Diabetes, Obesity and Lifestyle (AusDiab) Study, which follows a representative cohort (14) of more than 10,000 people across Australia after an initial glucose tolerance test, has indicated a dose-effect relationship between glucose exposure and CV mortality after some 5 years of follow-up in the rank order from low to high risk of normal glucose tolerance, prediabetes, newly diagnosed diabetes by screening, and known diabetes, with no difference, however, between the two prediabetic states of impaired fasting glucose (IFG) and IGT. So the jury still seems to be out in epidemiological terms whether there is a unique specific impact of postprandial hyperglycemia in the range below the current threshold of overt diabetes compared with IFG and/or HbA$_{1c}$. In a more recent

follow-up, the AusDiab Study reports that after 6 years there is a strikingly similar continuous relationship between all three glycemic parameters—FPG, PPG, and HbA$_{1c}$—and all-cause and CV mortality, with the exception that very low FPG values were also associated with a higher mortality risk (15).

The relationship between glucose peaks and increased risk for stroke is analyzed less explicitly, albeit most of the studies described in Table 2 included stroke as a form of CV disease in the outcome parameters.

Furthermore, the Oslo study (*n* = 16,209) (31) analyzed this relationship in a more detailed way. It was determined that the relative risk increased by 1.13 (95% CI 1.03–1.25) per 1 mmol/L increase of the serum glucose value.

Only a few prospective studies have analyzed the relationship between PPG and CV risk in overt diabetes. One of the first studies of this kind, the Diabetes Intervention Study (32), investigated the effect of PPG values 1 h after a meal in more than 1,000 subjects with newly

diagnosed type 2 diabetes who were followed for 11 years. They found that patients with a mean PPG >10 mmol/L had a 40% greater risk of myocardial infarction than those with a mean PPG <8 mmol/L. More recently, Cavalot et al. (28), in an ad hoc designed 5-year prospective study, were able to confirm PPG as an independent risk factor for CV disease in type 2 diabetes, particularly in women.

Some prospective studies have also analyzed the effect of glycemic variability on patient-relevant outcomes. Recently, Krinsley (33) reported a strong and independent relationship between glycemic variability and mortality in a large cohort of patients with a variety of medical, surgical, and trauma diagnoses in an intensive care unit. The mortality rate in patients with the lowest quartile of glycemic variability, as assessed by the SD of the MBG values, was 12.1% and increased to 19.9, 27.7, and 37.8% in the second, third, and fourth quartiles, respectively. Also, the length of stay was shorter among patients in the first quartile compared with those in the other three quartiles.

The strong association between glycemic variability and intensive care unit mortality was also described by Egi et al. (34) in a cohort of patients admitted to several Australian hospitals.

Japanese studies have shown a relationship between PPG and nephropathy (35). But, the impact of short-term glucose toxicity seems less clear than it is in macrovascular complications because contradictory results have also been published (36).

In a study of the Diabetes Control and Complications Trial (DCCT) population, Service and O'Brien (37) determined a higher risk for retinopathy with average glucose values of 8.3 mmol/L. However, as mentioned previously, contradictory results are available (36).

So, in all, although the accumulated data looks impressive that PPG seems to be important, especially for glucose variability, the evidence is still inconclusive in terms of a unique role for long-term prediction of CV and even microvascular sequelae of diabetes and its prestates, above and beyond other glycemic parameters like FPG and HbA$_{1c}$.

PATHOPHYSIOLOGICAL LINKS—
Acute increases of plasma glucose levels have significant hemodynamic effects, even in nondiabetic subjects. In one study (38), the maintenance of plasma glucose at 15 mmol/L for 2 h in healthy subjects significantly increased the mean heart rate (+9 bpm; $P < 0.01$), systolic (+20 mmHg; $P < 0.01$) and diastolic blood pressure (+14 mmHg; $P < 0.001$), and plasma catecholamine levels. These hemodynamic effects were abolished by infusion of glutathione, suggesting that they were mediated by an oxidative pathway. If this is so, one would expect glucose levels to affect endothelial function as well. Indeed, a study of flow-mediated endothelium-dependent vasodilation of the brachial artery among 52 subjects during an oral glucose tolerance test found significant decreases at 1 and 2 h among those with IGT or diabetes, but not among the control subjects. In fact, plasma glucose levels were negatively correlated with endothelium-dependent vasodilation. Endothelial function also normalized after 2 h in the control subjects but not in the group with IGT or diabetes (39). This evidence is also in line with the finding that modulating postprandial hyperglycemia, e.g., with insulin aspart (40) or acarbose (41), will prevent its deleterious effects on endothelial function. Postprandial hyperglycemia also has been found to cause myocardial perfusion defects. In a recent prospective study (42), 20 patients with well-controlled diabetes and 20 healthy control subjects were given a standard mixed meal, and a myocardial contrast echocardiography was used to assess myocardial perfusion. Before the meal, the two groups had similar myocardial flow velocity, blood volume, and blood flow. In the postchallenge state, all these parameters increased significantly in the healthy control subjects, but flow velocity and flow decreased significantly among the patients with diabetes. There was a significant correlation between changes in blood volume and the degree of postprandial hyperglycemia in the diabetic patients. These data suggest that postprandial myocardial perfusion defects are related to impaired coronary microvascular circulation and represent an early marker of diabetic CV damage. A follow-up study showed that treatment with a short-acting insulin analog significantly decreased postprandial hyperglycemia and partly restored the postprandial myocardial perfusion defects to normal (43). So, there seems to be a consistent proof of principle that endothelial dysfunction can be normalized by intervening postprandial hyperglycemia.

Several laboratory studies have also approached the issue of glucose variability. A deleterious effect of glucose fluctuations on renal mesangial, renal tubulointerstitial, umbilical endothelial, and pancreatic β-cells has been reported. Specifically, mesangial and tubulointerstitial cells cultured in periodic high glucose concentration increase matrix production more than cells cultured in high stable glucose. Increased apoptotic cell death was observed in both β- and endothelial cells in response to fluctuating as compared with continuous high glucose. Interestingly, it has been shown that the increased expression of fibrogenesis markers in human renal cortical fibroblasts is dependent on high glucose "peaks" but is independent of the total amount of glucose to which cells are exposed.

Oxidative stress, in particular the increased superoxide production at the mitochondrial level, has been suggested as the key link between hyperglycemia and diabetes complications. Evidence suggests that the same phenomenon underlines the deleterious effect of oscillating glucose, leading to a more enhanced deleterious effect of fluctuating glucose compared with constant high glucose (44–46).

Experiments in animals also support the hypothesis of a deleterious effect of fluctuating glucose. Recently, Azuma et al. (47) have established a method that allows for the observation of the entire surface of the endothelium of a rat aorta to quantitate the number of attached monocytes, a marker of vascular inflammation (47). Using this method, the investigators have demonstrated that repetitive fluctuation of hyperglycemia resulted in significantly induced monocyte-endothelial adhesion as compared with sustained hyperglycemia (48). Furthermore, to assess the role of glucose fluctuations on atherogenesis, they used atherogenic-prone mice fed maltose twice daily to model repetitive glucose spikes (49). The results show that fluctuations in BG concentrations accelerated macrophage adhesion to endothelial cells and the formation of fibrotic arteriosclerotic lesions. The same group was also able to show that reducing glucose "swings" is accompanied by a significant decrease of monocyte-endothelial adhesion (50).

All the above laboratory data are consistent with clinical data. Specifically, repeated fluctuations of glucose produce increased circulating levels of inflammatory cytokines as compared with stable high glucose in healthy subjects, as well as endothelial dysfunction in both healthy and type 2 diabetic patients (51). The role of oxidative stress also seems to be a key causative factor clinically because the use of an antioxidant reduced the phenomenon in both the studies (51). Consistent with the hypothesis of an involvement of oxidative stress is the evidence that daily glucose fluctuations in type 2 diabetes are strongly predictive of increased generation of oxidative stress (5). However, the same results have not been confirmed in type 1 diabetes (52).

Even if oxidative stress generation appears to be the key player of all the phenomena reported above, the precise mechanism through which oscillating glucose may be worse than constant high glucose still remains to be fully elucidated. Although further studies are certainly warranted, these would be quite difficult to accomplish in humans. A possible explanation is that the cells are not able to sufficiently increase their own intracellular antioxidant defenses in oscillating glucose conditions (53), a condition that has been suggested to favor the development of diabetes complications (54). In this regard, a recent study showed that during acute hyperglycemia in healthy

subjects, several genes involved in free radical detoxification were downregulated (55).

Table 3 summarizes potential mechanisms involved in linking especially postprandial hyperglycemia and CV risk. Overall, the pathophysiological evidence looks highly suggestive for PPG, IGT, and glucose variability being important key determinants of vascular damage.

EVIDENCE FROM RANDOMIZED CONTROLLED TRIALS

—The ultimate proof for pathophysiological concepts has to come from interventional trials attempting to target and abolish a given risk constellation and, by doing so, improving clinically relevant outcomes. Several controlled, prospective, and randomized clinical studies, e.g., the Stop-NIDDM Trial (56), the HEART2D Trial (57), the NAVIGATOR Trial (58), and the ongoing Acarbose Cardiovascular Evaluation (ACE) Trial have set out to target postprandial hyperglycemia in patients with IGT or overt diabetes and have looked or are looking into the related CV outcomes. It is important to emphasize that although surrogate markers for CV damage are of interest, such as intima-media thickening at the carotid artery level or biomarkers such as high-sensitivity C-reactive protein, they are not good enough to substantiate final proof for the effectiveness of an intervention as has been seen in the context with the BG-lowering thiazolidinedione rosiglitazone. In this case, a wealth of potentially beneficial effects had been established on intima-media thickening, in-stent stenosis, and a number of biomarkers, but the

randomized clinical outcome studies with that drug were rather disappointing and—at best—showed no CV harm (with the exception of heart failure), but certainly no CV benefit, e.g., in terms of reducing myocardial infarctions (59,60).

By targeting PPG with use of the α-glucosidase inhibitor acarbose in subjects with IGT, the Stop-NIDDM Trial (56) provided evidence that this approach not only was highly effective to prevent the manifestation of overt type 2 diabetes, but also to prevent the occurrence of myocardial infarction and overall CV events. CV outcomes, however, had been prespecified as secondary outcomes only, so these results are seen as hypothesis generating, but no final proof. In addition, it is somewhat disturbing that measurements of PPG yielded only a very small, barely significant difference, whereas a marked difference in blood pressure (some −10/5 mmHg) was associated with the use of acarbose. So it is of great importance that the ongoing ACE Trial is seeking to confirm the results of the Stop-NIDDM Trial (56) in IGT patients with a prior myocardial infarction where CV outcomes are predefined as primary outcomes and independently adjudicated.

Earlier in 2010, the NAVIGATOR Trial (58) produced negative results in this regard. Postprandial hyperglycemia was targeted by randomized administration of the short-acting sulfonylurea analog nateglinide in IGT patients, but this type of blinded intervention neither reduced the manifestation of overt type 2 diabetes nor did it reduce hard CV composite outcomes such as myocardial infarction, stroke, and others over a 6-year follow-up. Postload glucose values, however, were not lower in the nateglinide arm, where the drug was withheld on the day of the oral glucose tolerance test, as compared with the control arm.

Finally, the HEART2D Trial (57) was also a negative trial in terms of the effectiveness of targeting postprandial hyperglycemia by a specific insulin regimen in diabetic patients after myocardial infarction. On the other hand, the study also failed to achieve the intended difference for postprandial hyperglycemia by far, so the negative result over a 4-year follow-up may not be a total surprise.

If the four intervention studies are taken together, there certainly is no definite proof that targeting postprandial hyperglycemia results in a more beneficial outcome of CV complications in IGT

patients or overt type 2 diabetic subjects. No intervention trials are available in studying the benefits of minimizing glucose variability.

CONCLUSIONS: SHOULD WE CARE?

—The concept of postprandial hyperglycemia as well as high glucose variability as important independent risk determinants of vascular and especially CV complications in subjects with IGT or type 2 diabetes is highly intriguing. It is best supported by impressive pathophysiological studies, also in the human situation. The epidemiological evidence that is more or less confined to postprandial hyperglycemia and postload glycemia is likewise rather compelling, although certainly not fully conclusive. The biggest gap still is the missing evidence as derived from randomized prospective intervention studies targeting postprandial hyperglycemia and seeking to reduce hard CV end points. In fact, there has been some stark disappointment recently in this context. As this evidence by intervention is, however, key for the ultimate approval of a treatment concept that it is mandatory to care for postprandial hyperglycemia and glucose variability beyond achieving appropriate glycemic control as assessed by HbA$_{1c}$, the current net balance of attained evidence is not favorable that we should care. The absence of a uniformly accepted standard of how to estimate postprandial hyperglycemia and glucose variability adds a further challenge to this whole debate.

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Table 3—*Mechanisms involving postprandial hyperglycmeia and CV risk*

Excessive postprandial hyperglycemia: some pathogenetic links with CV disease
Glucose auto-oxidation increased (oxidative stress)
Endothelial function disordered (reduced NO release)
Low-grade inflammation increased
Blood coagulation increased
Fibrinolysis reduced
Plaque stability decreased
Triglyceride-rich lipoproteins and LDL removal reduced
HDL cholesterol catabolism increased
Free fatty acid decrease and early phase insulin secretion reduced and insulin resistance increased

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