EDITORIAL (SEE RAZ ET AL., P. 381)

Postprandial Hyperglycemia and Cardiovascular Disease

Is the HEART2D study the answer?

In the recent HEART2D (Hyperglycemia and its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus) study, published in this issue of *Diabetes Care*, Raz et al. (1) try to answer a hotly debated question of the last 10 years: is postprandial hyperglycemia an independent risk factor for cardiovascular disease in diabetes? This question, highlighted recently, has arisen because of the identified linear relationship, widely confirmed in many studies, between the risk of cardiovascular disease death and 2-h oral glucose tolerance test values (2). Consistent with these past results, a recent study has confirmed postprandial hyperglycemia as an independent risk factor for cardiovascular disease in type 2 diabetes (3). At the same time, in the STOP-NIDDM Trial it has been 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 (4)—a finding confirmed in type 2 diabetes by a meta-analysis on the use of acarbose (5).

Another important issue is that prandial glucose regulation, an emerging approach to treating type 2 diabetes, emphasizes the need for moderating the acute surges in plasma glucose levels that follow meals (6). Mechanistic and epidemiological studies indicate that postprandial glucose significantly contributes to overall glycemic exposure (6). In particular, postprandial hyperglycemia is the most important contributor to A1C, particularly when it is lower than 7.5% (7). Therefore, targeting postprandial hyperglycemia is important for the achievement of A1C targets. Numerous prandial therapeutics are now available, and an ever-growing literature on their use shows that they are safe, effective, and convenient and that they may offer distinct clinical benefits not found with treatments that target basal (fasting) glycemia (8–9). The International Diabetes Federation has recently recognized, in specific guidelines, the significance of postprandial hyperglycemia and the need to measure and treat it (8–9). In these guidelines, the cutoff for postprandial hyperglycemia is indicated as 7.8 mmol/l (140 mg/dl)—a value which, as has recently been shown, normal healthy people never attain (10).

The HEART2D study does not show any beneficial effect of treating postprandial hyperglycemia in reducing cardiovascular events in diabetic patients at very high risk for more cardiovascular events. It is, however, important to take into account that the patients were enrolled within 21 days of hospital admission for a recent acute myocardial infarction. Is the result of this study surprising? Given the recent lessons from the ACCORD trial (11), ADVANCE study (12), and long-term follow-up of the UK Prospective Diabetes Study (13), I believe that the negative result of the HEART2D study is just in line with these studies: if the control of hyperglycemia (either fasting [ACCORD and ADVANCE] or postprandial [HEART2D]) is started too late, the possible beneficial effect of treating hyperglycemia (either fasting [UK Prospective Diabetes Study] or postprandial [STOP-NIDDM]) in a very early stage of the disease is lost.

It may be that several aspects of the HEART2D study can be criticized. The study is clearly underpowered, and this is confirmed by the low rate of the events. Otherwise, the patients were very well treated for cardiovascular disease. As reported by the authors, "the frequency of concomitant cardiovascular drug use was high and similar between groups (prandial vs. basal: 95.0 vs. 95.9%; $P = 0.478$)." This means that, as learned from the ACCORD and ADVANCE studies, if on one hand we can be happy because the patients seem to be very well treated today, on the other hand this also implies that the calculation of sample size for the studies in the field of cardiovascular disease and diabetes must be revised in order to get real information. Another important issue is the failure of the study to reach the predetermined difference in postprandial hyperglycemia of 2.5 mmol/l: the mean difference at the end of the study was only 0.8 mmol/l, which, though a significant difference between the two groups, is less than one-third of the goal. Some interesting points emerge from consideration of these data. The difference seems to be too small to influence so hard an outcome, particularly in a very short period. This point of view is sustained by recent evidence suggesting why the benefits of reducing blood glucose levels on macrovascular outcomes take so much longer to appear in type 2 versus type 1 diabetes. Additional evidence from an earlier study conducted over 18 years ago shows that the contribution of hyperglycemia to CVD risk is much greater in type 1 than in type 2 diabetes, due to other risk factors present in these patients. A 1% increase in A1C was associated with a >50% increase in CVD risk for patients with type 1 diabetes compared with a 7.5% increase for patients with type 2 diabetes (14,15). This, in my opinion, implies that the control of hyperglycemia is important for the prevention of cardiovascular complications in diabetes, but to show this effect takes time and, of course, it would be more evident if there were a larger difference between the values of glycemia over time.

However, the real source of worry is the evidence that controlling postprandial hyperglycemia is difficult. I think we can say that control of hyperglycemia—any kind of hyperglycemia, be it fasting or postprandial—is still a difficult task, as learned from the recent trials, particularly from the Steno-2 (16), and also from the HEART2D. In this study, at the end point, the mean A1C was 7.7% in the prandial group and 7.8% in the basal, and only 28% of the patients in the prandial group and 31% in the basal group achieved an A1C <7.0%. The situation for fasting glycemia seems no different: 8.1 ± 0.2 mmol/l prandial vs. 7.0 ± 0.2 mmol/l basal.

In my opinion, we have learned another lesson consistent with evidence from the recent trials: starting the control of hyperglycemia when established cardiovascular disease is already present cannot have a beneficial effect on the progression of this kind of complication of diabetes. At the same time, we have again learned how difficult optimal control of hyperglycemia is—a goal that seems to be mandatory at a very early stage of diabetes.

In conclusion, the HEART2D study has just confirmed these two aspects of the management of diabetes but certainly has not answered the key question: whether postprandial hyperglycemia is an independent risk factor for cardiovascular complications in diabetes. Surely, I wonder whether the results would have been different if the study had used other postprandial drugs in addition to insulin to achieve goal (e.g., acarbose or pramlintide, which are approved with insulin) and whether the study will be repeated with newer drugs that more effectively lower postprandial glucose, such as GLP-1 agonists or DPP-4 inhibitors (8). Finally, maybe we will receive more information from two studies that are still ongoing: *1*) the NAVIGATOR (Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research) trial (17), which uses nateglinide and has already been prolonged because of a low rate of events, and *2*) the ACE (Acarbose Cardiovascular Evaluation) trial, which is a large study being performed in China. However, both of these studies are, again, in people with impaired glucose tolerance and at high risk for cardiovascular disease.

Nevertheless, although the key question of whether postprandial hyperglycemia is really a risk factor for cardiovascular disease is still open, I believe that implementing strategies aiming to lower postprandial hyperglycemia in clinical practice remains a good therapeutic choice because it seems the best approach to reach recommended A1C targets (8–9). And this is always very good for our patients.

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