COMMENTS AND RESPONSES

Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy: A Consensus Statement From the American Diabetes Association and the European Association for the Study of Diabetes

Response to Jellinger, Lebovitz, and Davidson

Jellinger, Lebovitz, and Davidson (1), writing on behalf of the American College of Endocrinology/American Association of Clinical Endocrinologists (ACE/AACE) Outpatient Glycemic Control Implementation Task Force, challenge the consensus treatment algorithm of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (2). I will attempt to answer each of their objections.

First, I will address the statement that the therapeutic A1C target should be <6.5% rather than <7.0%. The discussion of this point needs to be separated into microvascular and macrovascular outcomes. Regarding microvascular disease, there have been five studies in over 2,000 type 1 (3–5) and type 2 (6,7) diabetic patients demonstrating that there was virtually no development or progression of retinopathy and nephropathy over 6–9 years if mean A1C levels are maintained at <7.0%. In two of these studies (3,6), an intervention that lowered glycemia resulted in much less retinopathy and neuropathy, proving a causative relationship between control and improved outcomes.

Regarding macrovascular disease, there is an association with glycemia defined by oral glucose tolerance testing that extends down into the midnormal range (8). Regarding glycemia at more than one point in time, there are significant ~2.5-fold increases in clinical cardiac events in individuals with A1C levels >5.0% in one study (9) or 4.6% in another (10) over 4 or 8–10 years, respectively. However, in addition to the impossibility of reducing A1C levels to these values, association must not be confused with causation. One of the only things I remember from the biostatistics course in the first year of medical school was the nearly perfect correlation between the subsequent development of lung cancer and the sale of radios in Britain after the second world war. The culprit, of course, was the increased availability of cigarettes, not radios.

There are at least five studies that individually (11) or in a meta-analysis (12) did not show that lowering glycemia was beneficial for macrovascular outcomes in type 2 diabetic patients. A recent publication from the Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group (an observational continuation of the Diabetes Control and Complications Trial [DCCT]) revealed that myocardial infarctions occurred significantly less often in the intensely controlled group (13). However, the mean follow-up time was 17 years after tight control was instituted. The fact that one-third of individuals already have a history of myocardial infarction, intermittent claudication, stroke, or transient ischemic attacks when type 2 diabetes is diagnosed (14) may compromise any clinical effect of lowering glycemia in type 2 diabetic patients.

Given the totality of evidence currently available, there does not seem to be any clinical benefit of lowering the A1C target to 6.5%, possibly exposing patients to the risks of excessive hypoglycemia. I should point out that the consensus algorithm (2) and the ADA Standards of Care (15) consider the A1C goal to be <7.0% for patients in general but to be as close to normal as possible without significant hypoglycemia for the individual patient.

In addition, Jellinger, Lebovitz, and Davidson argue that our algorithm fails to recognize the importance of achieving postprandial glucose control. However, the most important determinant of the postprandial glucose concentration is the preprandial one. It is true that in early diabetes, and in some patients under treatment, A1C levels are >7.0% due to high postprandial values even though preprandial values are in the target range. In that situation, specific treatment of postprandial glycemia seems appropriate. However, the objection above goes beyond this circumstance and implies that targeting postprandial glucose levels per se would be beneficial. It seems to rest on two possibly related sets of data and one assumption. The first is the association between the 2-h value on an oral glucose tolerance test and the subsequent risk of mortality (16). The second is a number of in vitro studies showing that glycemic variability increased indexes of oxidative stress, which is postulated to be an important mechanism of glucose-mediated vascular damage (17). The assumption is that, because decreases in fasting plasma glucose (FPG) and A1C levels did not improve macrovascular outcomes in studies in which postprandial glucose concentrations were not specifically targeted, then lowering the latter would benefit cardiovascular disease (8).

Are there any clinical data to support (or refute) this hypothesis? In 2001, an ADA consensus conference concluded that there was not enough evidence to recommend targeting postprandial glucose concentrations per se (18). Since then there have been several clinical studies evaluating the effects of postprandial glucose excursions. Urinary excretion of 8-iso prostaglandin $F_{2\alpha}$ (a marker of oxidative stress) significantly correlated with the mean amplititude of glycemic excursions measured by a continuous glucose monitoring system but not with FPG or A1C levels in type 2 diabetic patients (19). In a randomized clinical trial, drug-naïve type 2 diabetic patients were treated with either repaglinide or glyburide for 6–8 weeks for drug titration and followed for another 12 months (20). Although there was no significant difference in A1C response between the two groups, the decrease in FPG concentrations was significantly greater in the glyburide group and the postprandial glucose rise significantly less in those receiving repaglinide. The carotid intima media thickness significantly decreased by 0.03 mm in the repaglinide group and remained stable with glyburide. At 3 years after adding an α-glucosidase inhibitor to type 2 diabetic patients treated with diet alone, a sulfonylurea agent, or insulin, maximal carotid intima media thickness showed no progression, whereas it significantly increased in a group treated similarly but without the addition of the inhibitor (21).

Although perhaps not pertinent to diabetic patients, in the Study to Prevent Non-Insulin-Dependent Diabetes Melli-

tus [STOP-NIDDM] research trial, individuals with impaired glucose tolerance who were given an α-glucosidase inhibitor for a mean of 3.3 years had significantly fewer cardiovascular events (22). However, the STOP-NIDDM research trial has been severely criticized as seriously flawed (23). Finally, A1C levels in type 1 diabetic patients and insulin-requiring type 2 patients were related to mean glycemia and not affected by glucose variability (the latter reflecting, at least indirectly, postprandial glucose excursions) (24). Likewise, pre- and postprandial glucose values were equally predictive of the microvascular complications of patients enrolled in the Diabetes Control and Complications Trial (25). Given this current body of evidence, it seems premature to recommend the specific targeting of postprandial glucose to improve clinical outcomes (unless preprandial glucose values are at target and the A1C level is not, as discussed above).

As for our algorithm's rejection of newer treatments because they lack multiyear trials, the issue here is not one of efficacy, but of potential safety concerns. The rofecoxib (Vioxx) (26) and celecoxib (Celebrex) (27) stories are a cautionary tale. If newer treatments were shown to be clearly superior to older therapies, one could perhaps make a case for their early recommendation. However, that is not the situation here; newer treatments for diabetic patients have not been shown to be more effective than established medications.

In spite of the contention otherwise by Jellinger, Lebovitz, and Davidson, cost was not a criterion used to make the recommendations. Note that the expensive thiazolidinediones are recommended as possible second- or third-line drugs.

The ADA maintains a flexible approach to its recommendations and guidelines. The situation concerning LDL-cholesterol concentrations is a case in point. As the evidence accumulated, the guidelines changed from <130 to <100 to <70 mg/dl for patients with coronary artery disease to recommending a statin for all people with diabetes over the age of 40 years regardless of their baseline LDL-cholesterol concentrations (15). When (if) specific targeting of postprandial glucose levels can be shown to improve clinical outcomes, I am confident that the ADA will seriously consider the evidence and make appropriate recommendations if warranted.

Acknowledgments— M.B.D. was supported by National Institutes of Health Grant U54-RR014616.

MAYER B. DAVIDSON, MD

From the Clinical Center for Research Excellence, Charles R. Drew University, Los Angeles, California.

Address correspondence to Mayer B. Davidson, MD, Clinical Center for Research Excellence, Charles R. Drew University, 1731 East 120th St., Los Angeles, CA 90059. E-mail: mayerdavidson@cdrewu.edu.

The views expressed here are the personal ones of the author and not those of the American Diabetes Association.

DOI: 10.2337/dc06-2482

References

1. Jellinger PS, Lebovitz HE, Davidson JA: Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes (Letter). *Diabetes Care* 30:e16–e17, 2007. DOI: 10.2337/dc06-2373
2. Nathan DM, Buse JB, Davidson MB, Heine RJ, Holman RR, Sherwin R, Zinman B: Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 29:1963–1972, 2006
3. The Diabetes Control and Complications Trial Research Group: The relationship of glycemic exposure (HbA_{1c}) to the risk of development and progression of retinopathy in the Diabetes Control and Complications Trial. *Diabetes* 44:968–983, 1995
4. Krolewski AS, Laffel LMB, Krolewski M, Quinn M, Warram JH: Glycosylated hemoglobin and the risk of microalbuminuria in patients with insulin-dependent diabetes mellitus. *N Engl J Med* 332:1251–1255, 1995
5. Warram JH, Scott LJ, Hanna LS, Wantman M, Cohen SE, Laffel LMB, Ryan L, Krolewski A: Progression of microalbuminuria to proteinuria in type 1 diabetes: nonlinear relationship with hyperglycemia. *Diabetes* 49:94–100, 2000
6. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motooyoshi S, Kojima Y, Furuyoshi N, Shichiri M: Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract* 28:103–117, 1995
7. Tanaka Y, Atsumi Y, Matsuoka K, Onuma T, Tohjima T, Kawamori R: Role of glycemic control and blood pressure in the development and progression of nephropathy in elderly Japanese NIDDM patients. *Diabetes Care* 21:116–120, 1998
8. Bonora E, Muggeo M: Postprandial blood glucose as a risk factor for cardiovascular disease in type II diabetes: the epidemiological evidence. *Diabetologia* 44:2107–2114, 2001
9. Khaw K-T, Wareham N, Luben R, Bingham S, Oakes S, Welch A, Day N: Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of European prospective investigation of cancer and nutrition (EPIC-Norfolk). *BMJ* 322:15–18, 2001
10. Selvin E, Coresh J, Golden SH, Brancati FL, Folsom AR, Steffes MW: Glycemic control and coronary heart disease risk in persons with and without diabetes: the atherosclerosis risk in communities study. *Arch Int Med* 165:1910–1916, 2005
11. Wild SH, Dunn CJ, McKeigue PM, Comte S: Glycemic control and cardiovascular disease in type 2 diabetes: a review. *Diabete Metab Res Rev* 15:197–204, 1999
12. Huang ES, Meigs JB, Singer DE: The effect of interventions to prevent cardiovascular disease in patients with type 2 diabetes mellitus. *Am J Med* 111:633–642, 2001
13. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group: Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 353:2643–2653, 2005
14. UKPDS Group: UK prospective diabetes study 6: complications in newly diagnosed type 2 diabetic patients and their association with different clinical and biochemical risk factors. *Diabetes Res* 13:1–11, 1990
15. American Diabetes Association: Standards of medical care of diabetes:2006 (Position Statement). *Diabetes Care* 29 (Suppl. 1):S4–S42, 2006
16. The DECODE study group on behalf of the European Diabetes Epidemiology Group: Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. *Lancet* 354:617–621, 1999
17. Hirsch IB, Brownlee M: Should minimal glucose variability become the gold standard of glycemic control? *J Diabetes Complications* 19:178–181, 2005
18. American Diabetes Association (Consensus Statement): Postprandial blood glucose. *Diabetes Care* 24:775–778, 2001
19. Monnier L, Mas E, Ginet C, Michel F, Villon L, Cristol J-P, Colette C: Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *JAMA* 295:1681–1687, 2006
20. Esposito K, Giugliano D, Nappo F, Marfella R, the Campanian Postprandial Hyperglycemia Study Group: Regression of carotid

atherosclerosis by control of postprandial hyperglycemia in type 2 diabetes mellitus. *Circulation* 110:214–219, 2004
21. Yanasaki Y, Katakami N, Hayaishi-Okano R, Matsuhisa M, Kajumoto Y, Kosugi K, Hatano M, Hori M: α-Glucosidase inhibitor reduces the progression of carotid intima-media thickness. *Diabetes Res Clin Pract* 67:202–210, 2005
22. Chiasson J-L, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M the STOP-NIDDM Trial Research Group: Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. *JAMA* 290:486–494, 2003
23. Kaiser T, Sawicki PT: Acarbose for prevention of diabetes, hypertension and cardiovascular events? A critical analysis of the STOP-NIDDM data. *Diabetologia* 47: 575–580, 2004
24. Derr R, Garrett E, Stacy GA, Saudek CD: Is HbA_{1c} affected by glycemic instability? *Diabetes Care* 26:2728–2733, 2003
25. Kilpatrick ES, Rigby AS, Atkin SL: The effect of glucose variability on the risk of microvascular complications in type 1 diabetes. *Diabetes Care* 29:1486–1490, 2006
26. Bresalier RS, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K, Lines C, Riddell R, Morton D, Lanas A, Konstam MA, Baron JA, the Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial Investigators: Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 352:1092–1102, 2005
27. Solomon SD, McMurray JJV, Pfeffer MA, Wittes J, Fowler RF, Finn P, Anderson WF, Zauber A, Hawk E, Bertagnolli M, the Adenoma Prevention with Celecoxib (APC) Study Investigators: Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med* 352:1071–1080, 2005