Physicians' Corner

Sunshine on a Rainy Day: Good News for Diabetes

Commentary provided by Charles F. Shaefer, Jr., MD, FACP, FCCP
University Primary Care Physicians, Augusta, Georgia

As I write this, I am sitting in Oregon on a cold, rainy night. Gas here is more than $3.25 per gallon. My flights were delayed. Avalanches are occurring at an unusually high rate. The stock market is down. The presidential candidates are saying that we are all in trouble. You can't help but hope for a little good news. And yet, a little good news is exactly what we received over the past few weeks. It may not change the weather or the price of gas or the political outlook, but good news it is for the diabetes community!

An article published in January 2008[1] reported a decrease in the average glycosylated hemoglobin (A1C) level in America for the first time in more than a decade! This is wonderful news, indeed! The decrease itself is noteworthy, but the news gets even better. It seems that aggressive treatment of our patients with type 2 diabetes mellitus (DM) is paying off in lasting ways. The extended results from the Steno-2 study[2] reported a few weeks ago indicate that careful attention to overall control of multiple risk factors in patients with type 2 DM produces long-term benefits by reducing the risk of stroke and heart attack, the major complications of the disease.

Are we really lowering A1C levels in America today? It is unclear from the results of the latest National Health and Nutrition Evaluation Survey (NHANES)[1] whether our current treatment efforts are paying off. Certain limitations must be considered in the interpretation of the NHANES data. This is a self-reported study. Respondents are called; they inform the questioners whether or not they are diabetic and, if so, report their A1C level. Obviously, it is impossible to determine from this information whether our diabetes treatment efforts are succeeding. However, it is also impossible to determine that they are not succeeding.

SOMETHING OTHER THAN THE MARKET IS DOWN

It may be that all we will learn from the new data is that people who identify themselves as diabetics are now doing so at lower A1C levels than they have done in the past. Even if this is the only explanation for the lower A1C levels, it still seems to be good news. It is obviously easier to achieve recommended A1C levels if one has a low A1C level initially. If we are simply recognizing diabetes at lower A1C levels, that also contributes to better care because it allows us to initiate therapy earlier in the process.

Perhaps we really are experiencing benefits from more aggressive intervention. Several advances have been made since the previous, and somewhat discouraging, NHANES data were published.[3] Use of thiazolidinediones has become widespread. More aggressive use of insulin has been touted. More physiologically consistent basal insulin analogues have been introduced, making insulin use less complicated. (Although dipeptidyl peptidase-IV inhibitors and glucagon-like peptide-1 analogues are now in use, they were not approved in time to be included in the latest NHANES report.) It is also possible that educational activities encouraging more aggressive treatment strategies are paying off. After delivering lectures to ~10,000 primary care providers during the past year, I believe that such educational efforts are indeed beneficial in changing therapeutic strategies and that the primary care community is responding.

It would be wonderful if the NHANES data allowed us to pinpoint the reason(s) for the reduction in A1C levels. Unfortunately, that information is not in the data. However, we do know that we are doing better. We should continue to work toward earlier detection of type 2 DM; currently, 30% of cases are undetected.[4] We should clearly work toward more aggressive interventions, and we should take heart that there is evidence that A1C levels are lower.

STENO-2—"THE WHOLE PATIENT APPROACH"

In my opinion, one of the most instructive studies on the overall primary care of diabetic patients came out of the Steno-2 trial published several years ago.[5] From this work we learned that aggressive control of blood pressure, cholesterol, and A1C levels (**Table**)[2] produced significant (~50%) reductions in the incidences of stroke and heart attack. Primary care providers specialize in the treatment of these 3 variables. The Steno-2 trial demonstrated that over the 8.5 years of the active study, aggressive control of these variables significantly reduced macrovascular events in patients with type 2 DM. Many of us were motivated and encouraged our patients to achieve the target levels reported in the Steno-2 trial; this became our personal "standard of care" for patients with type 2 DM.

Table. Recommendations from the Steno-2 trial for aggressive control of blood pressure (BP), cholesterol, and glycosylated hemoglobin (A1C) levels.[2]

Parameter	Intensive Goal
Systolic BP	<130 mm Hg
Diastolic BP	<80 mm Hg
Total cholesterol	<175 mg/dL
Triglycerides	<150 mg/dL
A1C	<6.5%

Cynics say that patients will not sustain aggressive control of these 3 variables for long. It is a universally recognized phenomenon that compliance declines over time. We saw from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study[6] of patients with type 1 DM that, after the study was over, A1C levels in the patients in the intensively controlled group gradually slipped back into ranges similar to those reported for the conventionally treated group. Was the benefit of all that intensive effort lost? The answer is clearly NO. When the long-term impact of intensive treatment on cardiovascular events was evaluated, it appeared that there was a type of metabolic memory. A period of good control was rewarded with a longer period of improvement in cardiovascular risk (~50% reduction in events). But what about patients with type 2 DM? The newly published data from the extension of the Steno-2 study[2] shed some important light on this question.

When the active study period of the Steno-2 trial was completed, all participants were informed of the benefits of tight control of cholesterol, blood pressure, and A1C levels. These patients were then followed up for an additional 5 years under the care of their usual physician. As one might expect, the group that had received intensive treatment started to look more like the conventionally treated group from a control standpoint, and vice versa. What benefit was derived from intensive management for 8.5 years? As in the patients with type 1 DM in the DCCT/EDIC trial, the patients with type 2 DM in the Steno-2 trial sustained a protective benefit from cardiovascular events for the additional 5 years of follow-up, reducing their cardiovascular event rates by ~50%.

These results should motivate primary care providers to control cholesterol aggressively, to achieve excellent blood pressure control, and to deliver appropriately aggressive diabetes therapy aimed at achieving target A1C levels. Comprehensive care (ie, reduction of multiple cardiovascular risk factors) provides both immediate and long-term benefits for our patients with type 2 DM by lowering the risk of cardiovascular complications.

It is interesting to note the changes in diabetes care that have taken place since the outset of the Steno-2 study. Virtually no drug therapy was used at the start of the study. By the end of the study, use of medication was almost universal. Changes in the reliance on lifestyle changes alone parallel the current recommendation of the consensus algorithm developed by the American Diabetes Association and the European Association for the Study of Diabetes (ADA/EASD) for the treatment of type 2 DM, which calls for addition of medication (metformin) at the time of diagnosis.[7] Indeed, the intensively treated group in the Steno-2 trial increased their use of metformin >5-fold during the 13.5-year period of active study and follow-up. Use of sulfonylureas decreased ~20% in the intensively treated group and >60% in the conventionally treated group during the course of the study. In the intensively treated group, insulin use increased >10-fold by the end of the active study period and then increased an additional 10% during the 5-year follow-up period.

Of particular interest, the combination of oral hypoglycemic agents plus insulin was used by almost none of the patients at the start of the Steno-2 trial; 32% of patients in the intensively treated group used the combination by the end of the 5-year active study period, and 83% of participants used the combination by the end of the 13.5-year active study and follow-up period. Clearly, the big news about the treatment regimens was a progressively greater use of insulin, particularly the combination of insulin and oral hypoglycemic agents.

These trends in therapy seem to generally reflect the treatment strategy outlined by the ADA/EASD consensus algorithm.[7] It appears that more metformin is being used, and a lot more insulin is being used, especially in combination with oral hypoglycemic agents. These strategies, coupled with intensive efforts to control blood pressure and cholesterol, clearly provide some degree of durable benefit by reducing macrovascular complications. It is estimated that 80% of our patients with type 2 DM will suffer a stroke or heart attack, 66% of whom will not survive the initial episode.[8] We should explore any intervention that can reduce that risk. Certainly, insulin is playing an increasingly important role in the tight control of A1C levels.

CONCLUSIONS

These 2 studies bring us a little good news and provide some important messages. Regardless of the reason(s) for the recent decrease in A1C levels, the decrease itself is important. Regardless of whether we are detecting cases of type 2

DM at lower initial A1C levels or delivering more effective treatment strategies, patients are self-reporting diabetes at lower A1C levels—and this must be good. Findings of the 5-year observation period of the Steno-2 trial suggest that intensive multifactorial efforts aimed at improving A1C, blood pressure, and cholesterol in patients with type 2 DM pay real and somewhat long-term dividends.

We need to continue aggressive and early detection of diabetes to allow early intervention. We need to commit to aggressive management of cardiovascular risk factors such as tight control of blood pressure, cholesterol, and A1C levels, and we need to continue to educate ourselves about the types of insulin available and their characteristics and uses. We also must understand the balance between rapid-acting mealtime and long-acting basal insulin analogues because the trends observed in the Steno-2 trial indicate that insulin will continue to play an increasingly important role in the treatment of our patients with type 2 DM.

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