



# Intensifying insulin therapy in patients with type 2 diabetes mellitus

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U-500 insulin

The current paradigm for pharmacologic management of type 2 diabetes mellitus (DM) is to progress with oral agents until severe insulin deficiency develops, at which time insulin can be initiated. Reexamination of data from the Diabetes Control and Complications Trial (DCCT) suggests that glycemic variability may be an important factor involved in the pathogenesis of microvascular complications. It is now appreciated that oxidative stress from overproduction of reactive oxygen species may be the result of this glycemic variability, suggesting that an overemphasis of basal insulin may not be the ideal strategy for insulin replacement, even though basal insulin is often the only insulin used initially. Although finding the best insulin program for treatment of type 2 DM is an important area of research, almost all patients with severe insulin deficiency will require both basal and prandial replacement. Use of adequate lag times (time between injecting the prandial insulin and eating), U-500 insulin (500 U/mL human regular insulin), and home blood glucose monitoring to determine “glycemic trend” are important tools that are readily available to all patients.

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The paradigm for the pharmacologic management of type 2 diabetes mellitus (DM) has not changed in decades. After the diagnosis is made, lifestyle modifications are attempted and, on occasion, can have profound effects on glycemia. However, even if these attempts are successful, the natural progression to greater  $\beta$ -cell deficiency over time will necessitate pharmacologic therapy.

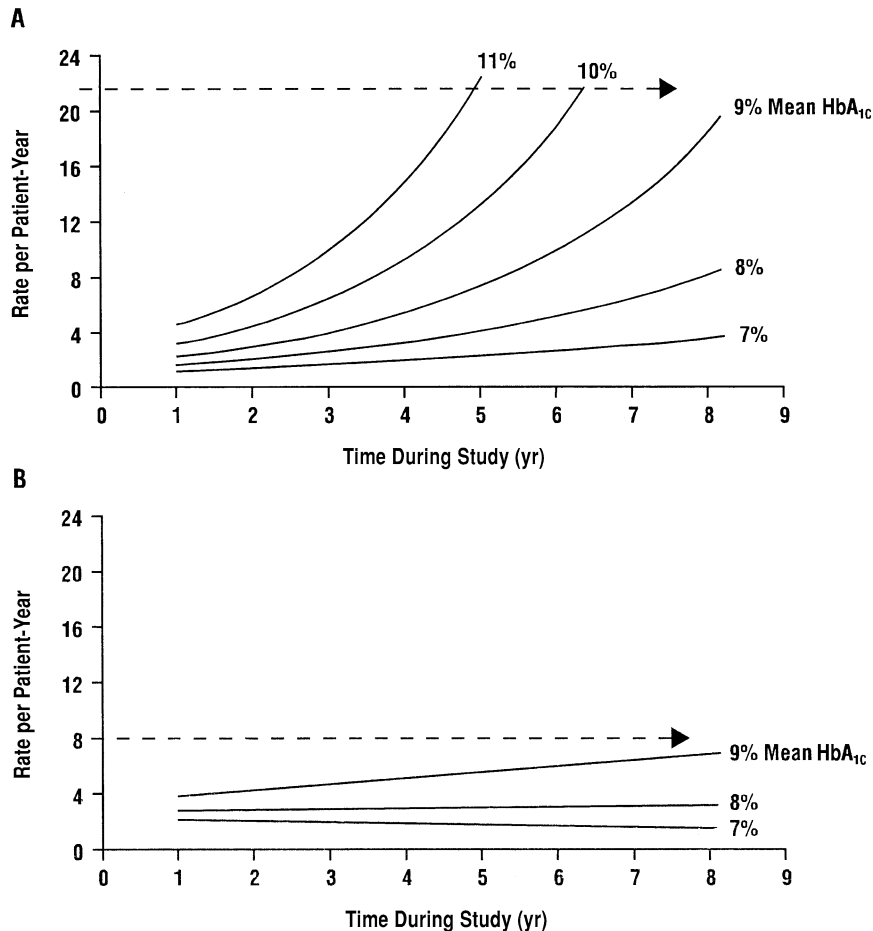
Traditionally, sulfonylureas have been used as first-line therapy, but the introduction of metformin in the United States in 1995 gave physicians the option of initially prescribing a biguanide. The landmark UK Prospective Diabetes Study (UKPDS) reported that in overweight newly diagnosed patients with type 2 DM, initial therapy with metformin confers a 32% risk reduction for any DM-related

end point and a 42% risk reduction for DM-related death compared with conventional therapy of mostly dietary modification alone.<sup>1</sup> Despite these results, there is still no agreement about which agent should be used as initial treatment.<sup>2</sup> Combination therapy with metformin and a sulfonylurea has been noted to be more effective than one agent alone, either as initial therapy<sup>3</sup> or after one agent has failed.<sup>4</sup> The introduction of  $\alpha$ -glucosidase inhibitors and thiazolidinediones has resulted in greater pharmacologic options. Although there is also no consensus on the appropriate sequence for use of all these agents (including for specific subpopulations of patients), “triple therapy” has already been prescribed, even before clinical trials have reported on its effectiveness.<sup>5</sup>

Current treatment paradigms are based on the primary treatment goal of achieving target glycosylated hemoglobin (Hb) A<sub>1c</sub> levels. Unfortunately, the lack of specific consensus on HbA<sub>1c</sub> goals has created confusion and frustration among primary care physicians and endocri-

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**Figure 1** Absolute risk of sustained retinopathy progression as a function of updated mean hemoglobin (Hb) A<sub>1c</sub> during the Diabetes Control and Complications Trial (DCCT) plotted against the time of follow-up during the study. Estimates were made using absolute (Poisson) regression models. (A) Conventional treatment group; (B) intensive treatment group. (Reprinted with permission from *Diabetes*.<sup>10</sup>)

nologists alike. As of this writing, the primary HbA<sub>1c</sub> target published by the American Diabetes Association (ADA) is <7.0%,<sup>6</sup> whereas the American Association of Clinical Endocrinologists (AACE) has proposed a target HbA<sub>1c</sub> of <6.5%.<sup>7</sup> Considering the recent National Health and Nutrition Examination Survey (NHANES) data on how poorly we are achieving any HbA<sub>1c</sub> target,<sup>8</sup> perhaps the disagreement about it is moot. Our arguments may be misguided: Is it possible that our current paradigm is flawed?

### Thinking about a new paradigm

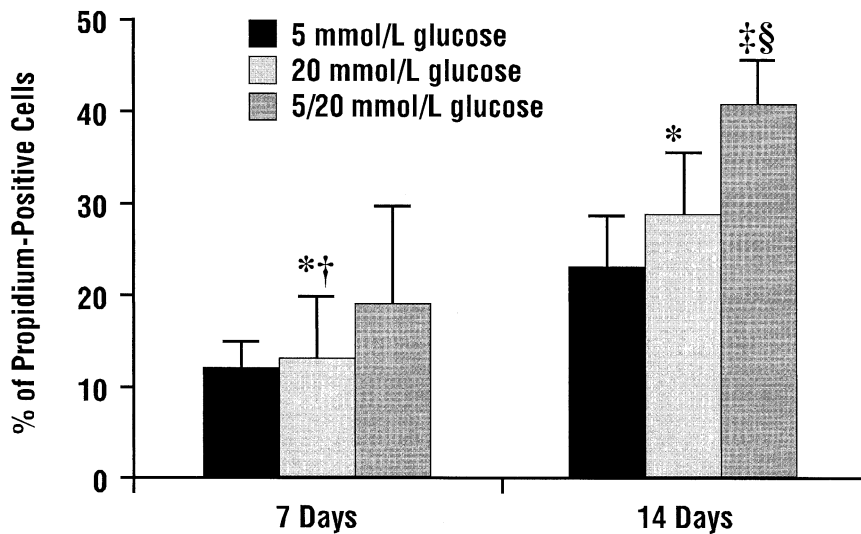
The Diabetes Control and Complications Trial (DCCT) conclusively found that in type 1 DM, an intensive therapy regimen with frequent home blood glucose monitoring, multiple injections or insulin pump therapy, psychological support, and frequent contact with healthcare professionals could reduce both the development and progression of microvascular complications and diabetic neuropathy.<sup>9</sup> The widely accepted interpretation of the study was that the

improvement in mean glycemia—from an HbA<sub>1c</sub> of ~9.0% to an HbA<sub>1c</sub> of ~7.0%—was responsible for the study outcomes.

However, 2 years after the initial DCCT publication, the same group reported a subanalysis noting that the risk for progression of diabetic retinopathy was markedly reduced for the intensive therapy group at each level of HbA<sub>1c</sub> (**Figure 1**).<sup>10</sup> How could this be? If microvascular complications are solely related to mean glycemia, why would the risk of these same outcomes appear to be related to the randomization of a study subject to one group or another? The authors of the second report concluded that mean HbA<sub>1c</sub> is “not the most complete expression of the degree of glycemia” and that “the risk of complications may be more highly dependent on other factors.”<sup>10</sup>

For this reason, it is important to look at possible etiologies other than simple mean glycemia for the development of microvascular complications. For example, what are some differences in the means by which a given HbA<sub>1c</sub> is achieved compared with the number itself?

In the DCCT, patients who were randomized to conventional therapy rarely measured blood glucose concentra-



**Figure 2** Cell death from human umbilical vein endothelial cells at low, high, and intermittent glucose concentrations. \* $P < 0.05$  vs. glucose 5 mmol/L; † $P < 0.05$  vs. glucose 20 mmol/L; ‡ $P < 0.01$  vs. glucose 5 mmol/L; § $P < 0.01$  vs. glucose 20 mmol/L. (Reprinted with permission from *Am J Physiol Endocrinol Metab.*<sup>13</sup>)

tions, received 1 or 2 injections of insulin daily, and achieved a median HbA<sub>1c</sub> of 8.7% to 9.2% over the course of the study.<sup>11</sup> The intensive therapy group, who measured home blood glucose levels frequently and received multiple injections replacing prandial insulin with each meal in addition to basal insulin either with injections or continuous subcutaneous insulin infusion (CSII), achieved a median HbA<sub>1c</sub> of 6.7% to 7.2% during the study protocol.<sup>11</sup> Nevertheless, the fact that there were fewer complications at any level of HbA<sub>1c</sub> for those in the intensive therapy group suggests that HbA<sub>1c</sub>, or mean glycemia, is not the only factor involved in the pathogenesis of complications.

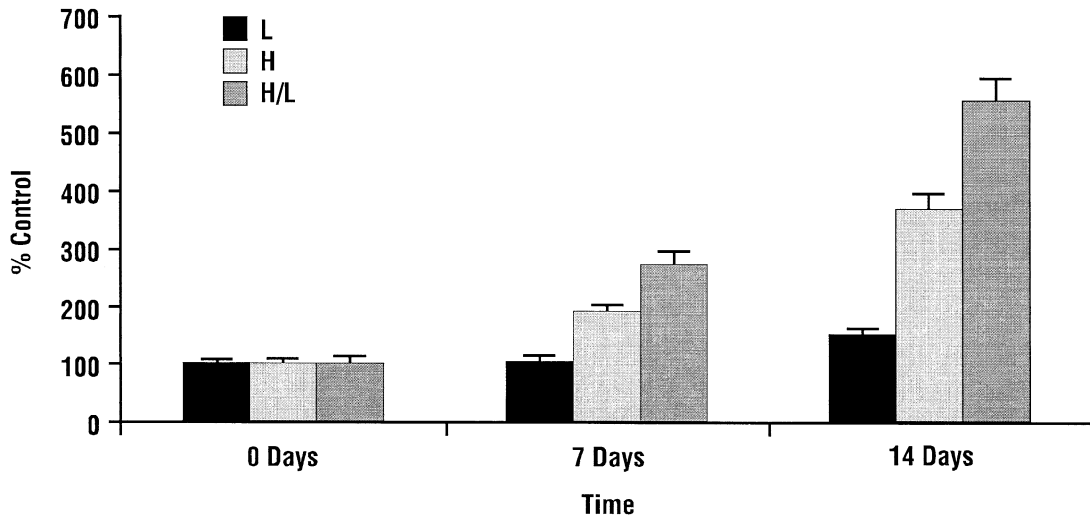
An alternative hypothesis is that increased magnitude of glycemic variability would generate more reactive oxygen species (ROS) in cells prone to complications, because hyperglycemia-induced oxidative stress—from overproduction of ROS by the mitochondrial electron-transport chain—is the chief underlying mechanism of glucose-mediated vascular damage.<sup>12</sup> This is a somewhat radical departure from the current guidelines, in which the primary end point is to safely reach target HbA<sub>1c</sub> without regard to class of drug used or how to best use prandial versus basal insulin. However, despite a lack of definitive proof that glycemic variability generating more ROS resulted in more diabetic retinopathy than was observed in the DCCT conventional therapy group, current data suggest this is so, and it is now possible to clarify the significance of glycemic variability.

Although they cannot be measured directly, ROS interact with various other macromolecules to generate oxidative products. Of these, nitrotyrosine and 8-hydroxydeoxyguanosine (8-OHdG) have been evaluated to determine the extent of vascular damage induced by periodic versus continuous exposure to high levels of glucose. The examination of cell apoptosis, a downstream marker of ROS, is another strategy by which glucose variability can be studied in vitro.

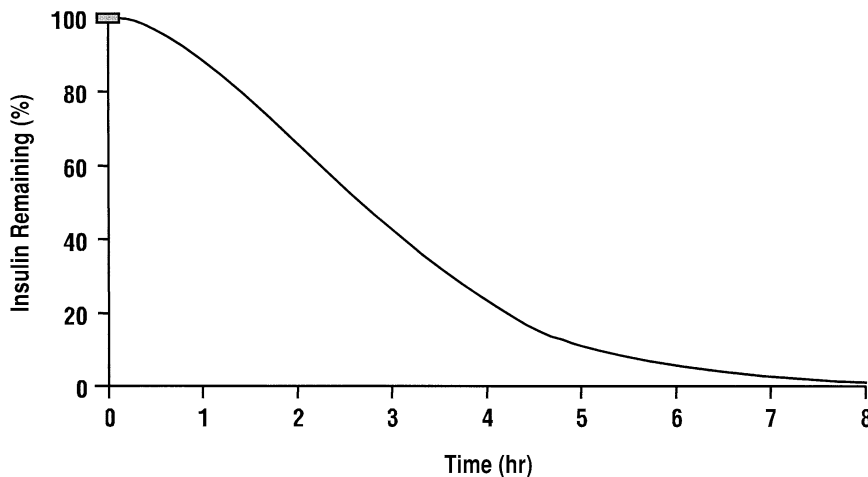
Risso and coworkers<sup>13</sup> reported that in human umbilical vein endothelial cells in culture with either a low (5 mmol/L), high (10 mmol/L), or intermittent low and high glucose concentration, cell apoptosis was most enhanced by variable glucose levels (**Figure 2**). The authors concluded that “variability in glycemic control could be more deleterious to endothelial cells than a constant high concentration of glucose.”<sup>13</sup>

In another study, Quagliaro and colleagues<sup>14</sup> investigated the differential effect of variable glucose concentrations versus stable high glucose on high glucose-induced ROS generation measured by nitrotyrosine and 8-OHdG levels. Cells cultured in an intermittent glucose condition, simulating “real-life” glycemic fluctuations typical of patients with DM, produced larger amounts of both nitrotyrosine and 8-OHdG when compared with constant high and normal glucose conditions. Not surprisingly, fluctuating glucose concentrations were found to induce a greater increase in the activity of protein kinase C—a known consequence of hyperglycemia-induced ROS formation—than did stable high glucose (**Figure 3**).<sup>14</sup>

What these and other studies suggest is that HbA<sub>1c</sub> by itself may not provide all of the prognostic significance for microvascular complications. This hypothesis also explains why the prevalence of proliferative diabetic retinopathy and end-stage renal disease is more common in type 1 DM.<sup>15,16</sup> To help clarify these questions, the markers of ROS could be measured from the stored sera of DCCT subjects. In the meantime, the argument to support the current ADA and AACE recommendations to maintain postprandial hyperglycemia at <180 mg/dL<sup>6</sup> and 140 mg/dL,<sup>7</sup> respectively, could potentially be strengthened by further research into the impact of glycemic variability on the pathogenesis of DM-related complications.



**Figure 3** Protein kinase C (PKC) activity at low (L), high (H), and intermittent (H/L) glucose concentrations. (Reprinted with permission from *Diabetes*.<sup>14</sup>)



**Figure 4** Representation of timing of insulin action for insulin aspart given by euglycemic clamp (0.2 U/kg into the abdomen). (Adapted with permission from *Diabetes Care*.<sup>21</sup>)

## Practical considerations

As insulin deficiency becomes more severe, a more physiologic multicomponent insulin regimen will be required.<sup>17</sup> With rare exception, this regimen would include a separate basal and prandial component for individuals with type 1 DM.<sup>18</sup> Neutral protamine Hagedorn (NPH) and human regular insulin, respectively, are considered the standard basal and prandial insulins. However, owing to their pharmacodynamics, NPH and regular insulin have both basal and prandial components.<sup>17</sup> With rare exception, both preparations have been replaced by insulin analogues for patients with type 1 DM. As of this writing, there is little disagreement that the standard of care for this population is either basal insulin glargine with prandial administration of insulin lispro, aspart, or glulisine, or CSII with 1 of the 3 rapid-acting analogues. The major advantage with the newer analogues is a consistent reduction of hypoglycemia.

No consensus, however, has been reached with regard to ideal insulin regimens for individuals with type 2 DM. Data exist in support of initiating treatment with either basal insulin<sup>19</sup> or prandial insulin<sup>20</sup> without the other component. For the sake of convenience, the overwhelming majority of patients would prefer a once-daily basal injection of insulin glargine. However, if insulin is initiated when HbA<sub>1c</sub> is >10.0% and the maximum dose of oral agents has been reached, both basal and prandial insulins may be required.

Clinicians can consider several practical “pearls” when managing patients with type 2 DM. First, adequate lag times (the time between injecting the prandial insulin and eating) are necessary for the prandial insulin components.<sup>17</sup> The insulin action (pharmacodynamic, not to be confused with the insulin appearance in the blood, or pharmacokinetic) of the rapid-acting analogues is quite slow compared with carbohydrate absorption (**Figure 4**).<sup>21</sup> For example, if an 80-g bagel is eaten for breakfast,

blood glucose will begin to increase almost immediately, and insulin-deficient patients usually can note blood glucose spikes  $>150$  mg/dL above baseline within the first hour. Considering that 1 hour after the injection only 10% of the insulin has had its blood glucose-lowering effect (and about half of the effect from the insulin is still present 2.5 hours after injection), it is easy to appreciate how slow our currently available insulins are compared with the much quicker carbohydrate absorption. The advice to “inject and eat” is inappropriate, especially in patients with premeal hyperglycemia.<sup>22</sup> At the very least, the blood glucose level should be decreasing when the food is consumed. The lag time and blood glucose level appropriate for eating have not been studied at the recommended levels for postprandial hyperglycemia of  $\leq 180$  mg/dL<sup>6</sup> or 140 mg/dL.<sup>7</sup> Certainly, from continuous subcutaneous blood glucose monitoring we have learned that our current strategies for insulin use are far from perfect.<sup>23</sup> Part of the problem with traditional home blood glucose monitoring is that these cross-sectional data points do not reveal the “glycemic trend” (upward or downward movement) at the time of glucose measurement. If the glucose level is decreasing, then less insulin should be injected; however, this trend is not presently under consideration. This will likely change in the future as home continuous monitoring is further developed.

One conclusion from the available data examining the mismatching of insulin action with food absorption is that clinicians underemphasize the timing of food consumption in relation to prandial insulin injection when we counsel patients. As larger doses of insulin are required to dispose of larger quantities of carbohydrate, the delay in insulin absorption will result in greater postprandial peaks. A reduction in carbohydrate content will reduce the postprandial surge, but most of these spikes now go unnoticed. This will become much clearer when continuous glucose sensing becomes available.

## Other tools

Insulin pump therapy for the treatment of DM has been used for  $\sim 25$  years, and interest from patients with type 2 DM continues. However, only 1 randomized clinical trial assessed the effectiveness of CSII in patients with insulin-requiring type 2 DM. A total of 132 patients were randomized to receive multiple injections or CSII; after 24 weeks, no differences were observed in HbA<sub>1c</sub> or 8-point blood glucose levels.<sup>24</sup> However, patient satisfaction subscores were significantly improved ( $P < 0.001$ ) with those randomized to CSII. Although it seems logical to conclude that CSII for those with type 2 DM will never reach the popularity it has with type 1 DM, it is clear that individual patients can benefit from pump therapy.

There also has been increased interest in the use of insulin pen therapy in the United States. Insulin adminis-

tration with a pen device has been available for  $>20$  years, but it has been much more popular in Europe than in the United States. Although more expensive than vial insulin,<sup>25</sup> insulin therapy with a pen has been shown to be better accepted by patients.<sup>26</sup> Common reasons include greater convenience, especially when away from home, and improved accuracy of administration, especially for those with visual impairment. It is important to point out that, when used in a pen, premixed insulin (typically 70% or 75% protamine insulin and 25% to 30% prandial insulin) cannot provide supplemental insulin for premeal hyperglycemia without also giving the longer-acting insulin.<sup>25</sup> For this reason, many clinicians would not recommend the use of pen insulin with premixed insulins.

Although there is a difference of opinion as to why there has been such a surge in the use of insulin glargine compared with prandial insulin analogues, the truth is that it is easier to replace basal insulin. Knowing exactly how much insulin to provide for a given amount of food is a challenge, particularly if food intake is not consistent from day to day. There have been several strategies to help resolve this problem for patients who use a basal/bolus regimen in which an injection of prandial insulin is administered before each meal. Carbohydrate counting is among the most frequent strategies used to estimate prandial insulin dosage. With the improved use of food labels and a variety of other sources to identify carbohydrate contents of different foods, patients are able to better adjust their insulin dose for a specific quantity of food. This is best accomplished with the assistance of a nutritionist. Some patients find this too burdensome or complicated, and actually manage to do well using ranges of insulin doses for a given meal. For example, a dose between 8 U and 12 U may be given for lunch, with the higher dose used in case of a larger meal. Additional insulin can then be given to correct premeal hyperglycemia.

Perhaps the most important underused tool for the type 2 DM population is the use of U-500 insulin, a highly concentrated form available only as 500 U/mL human regular insulin. This insulin is 5-fold more concentrated than U-100 insulin (100 U/mL), which is the only other concentration of insulin sold in the United States. Thus, 10 U of U-500 insulin in a U-100 insulin syringe would actually be equivalent to  $10 \times 5$ , or 50 U of insulin. The need to be extremely cautious with this insulin is obvious, particularly if it is used in an in-patient situation where there is potential to confuse it with U-100 regular insulin.

The premise for its use is that for those patients who are severely insulin resistant, administering smaller doses of insulin would result in more consistent absorption compared with the erratic absorption that occurs with large doses of insulin. Few reports on the use of U-500 insulin are found in the literature. Knee and colleagues<sup>27</sup> described 4 patients using CSII who converted to U-500 insulin from insulin lispro. After 6 months, the mean HbA<sub>1c</sub> was reduced from 10.8% to 7.6%,

leading to a 4-fold reduction in insulin dose. Moreover, this resulted in a potential cost savings of \$3,400 per patient per year. More recently, Garg and associates<sup>28</sup> described 16 patients who had a mean decrease in HbA<sub>1c</sub> from 11.3% to 9.0% over 23 months. We have had a similar experience with 8 patients taking U-500 insulin during a 24-month period. Levels of HbA<sub>1c</sub> decreased by >1.0% in all patients, and 6 of the 8 patients had HbA<sub>1c</sub> levels <8.0% at the end of the observation period. We are now considering the use of U-500 insulin in all patients requiring >30 to 40 U per injection with each meal. Except for our patients receiving CSII, we use insulin glargine as the basal insulin for these individuals.

## Summary

Contemporary management of type 2 DM uses insulin therapy only after the failure of oral agents. The current paradigm is to use HbA<sub>1c</sub> level as the primary marker of glycemic control, and to initiate insulin therapy after marked hyperglycemia occurs. Unfortunately, this often results in initiating insulin therapy quite late in the natural history of  $\beta$ -cell exhaustion. How to best initiate insulin therapy for the patient whose DM is not controlled by oral agents likely depends on the initial level of HbA<sub>1c</sub>. For example, starting basal insulin alone when HbA<sub>1c</sub> is 8.0% will likely be effective, whereas it will not be effective when HbA<sub>1c</sub> is 11.0%. In the latter situation, both basal and prandial insulins will be required. Provocative data suggest that the “quality” of HbA<sub>1c</sub> may be a separate but important measurement to consider. Large glycemic variability resulting in an HbA<sub>1c</sub> of 7.0% may prove to have different prognostic relevance than an identical level with little glycemic variability. To reduce this glycemic variability, prandial insulin can best be matched by using appropriate lag times, especially with premeal hyperglycemia. Some tools already available, such as CSII and U-500 insulin, are likely underutilized. More clinical trials would be welcome.<sup>9,24,27,28</sup>

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