

**CLINICAL UPDATE**

# Practical strategies for introducing Insulin Therapy in 2006

Satish K. Garg, MD ■ George Dailey, MD ■ Irl B. Hirsch, MD

An estimated 20.8 million persons in the United States (approximately 7% of the population) have diabetes; the vast majority (90%-95%) has type 2 diabetes. Although more than 14.6 million persons have received a diabetes diagnosis, 6.2 million remain undiagnosed and thus remain untreated. An additional 41 million persons have prediabetes (that is, impaired glucose tolerance [IGT] and/or impaired fasting glucose [IFG]) and may convert to type 2 diabetes. The cumulative 5- to 6-year incidence of type 2 diabetes among patients with either IFG or IGT is 20% to 34%.<sup>1</sup>

**Satish K. Garg, MD**

Professor of Medicine and Pediatrics  
Director of Adult Program, University of Colorado Health Sciences Center  
Barbara Davis Center for Diabetes  
Denver, Colorado

**George Dailey, MD**

Senior Consultant in Diabetes and Endocrinology  
Head, Diabetes Research, Scripps Clinic  
Clinical Professor of Medicine, University of California, San Diego,  
School of Medicine  
La Jolla, California

**Irl B. Hirsch, MD**

Professor of Medicine, University of Washington School of Medicine  
Seattle, Washington

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## Key points and recommendations

- Patients with type 2 diabetes who are currently taking 2 or more oral antidiabetic drugs (OADs) and have glycosylated hemoglobin (A1C) values between 7% and 10% are the best candidates for good control with basal insulin and OADs.
- Compared with insulin alone, treatment with insulin plus OADs produces comparable (or better) reductions in A1C, as well as less weight gain, and may be associated with fewer hypoglycemic events.
- When initiating basal insulin, continue metformin, if possible. Metformin added to an established insulin regimen can result in greater reductions in A1C, a decrease in insulin dose, and less weight gain than insulin alone.
- Reduce the sulfonylurea (eg, glimepiride) dosage when fasting plasma glucose nears 100 mg/dL. Lower sulfonylurea doses will enable titration of insulin doses up to optimal levels. Weight gain and hypoglycemia are dose dependent.
- Continue thiazolidinediones to take advantage of insulin-sparing and possible cardioprotective effects.
- If postprandial plasma glucose concentrations consistently exceed 180 mg/dL, discontinue sulfonylureas and prescribe a rapid-acting insulin analog at an initial dose of 0.1 mg/kg (5-10 U) to be administered before the largest meal of the day. This may be the only premeal injection needed for some period of time.
- Physicians and caregivers should adopt a treat-to-target approach to prevent the development and/or progression of microvascular and macrovascular complications.

TABLE 1

**Glycemic goals for adults with diabetes**

Glycemic Parameter	American College of Endocrinology	American Diabetes Association
A1C	≤6.5%	<7%*
Preprandial plasma glucose	<110 mg/dL	90-130 mg/dL
Postprandial glucose	<140 mg/dL <sup>†</sup>	<180 mg/dL <sup>‡</sup>

\*The A1C goal for the individual patient is an A1C as close to normal (<6%) as possible without significant hypoglycemia. The A1C goal for patients in general is <7%.  
<sup>†</sup>12-hour postprandial blood glucose  
<sup>‡</sup>1- to 2-hour peak postprandial capillary plasma glucose  
 Data from American College of Endocrinology. *Endocr Pract.* 2002;8(suppl 1):5-11; American Diabetes Association. *Diabetes Care.* 2006;29(suppl 1):S3.<sup>5,6</sup>

Evidence from the Diabetes Control and Complications Trial (DCCT)<sup>2</sup> and the United Kingdom Prospective Diabetes Study (UKPDS)<sup>3</sup> indicates that improving glycemic control in patients with either type 1 or type 2 diabetes prevents or delays the development of microvascular complications and may have a beneficial effect on macrovascular complications. An epidemiologic analysis of data from the UKPDS patient population found that each 1% reduction in mean A1C was associated with a 37% reduction in risk for microvascular complications ( $P<.0001$ ) and a 14% reduction in macrovascular complications ( $P<.0001$ ), regardless of other factors, such as sex, age, ethnic group, and duration of diabetes. Notably, this relation was observed over a range of A1C values ranging from <6% to ≥10%, with no threshold for any diabetes-related complication, suggesting that achievement and maintenance of near normoglycemia is an important goal of treatment (TABLE 1).<sup>4,6</sup>

The DCCT found that long-term (approximately 6.5 years) intensive insulin therapy in patients with type 1 diabetes reduced development of retinopathy by 76% (95% confidence interval [CI], 62%-85%). Similarly, occurrence of other microvascular complications was dramatically reduced with intensive insulin therapy in this study.<sup>2</sup> Following 93% of the original cohort until February 2005, a recent analysis of long-term incidence of cardiovascular disease (CVD) demonstrated that

intensive treatment reduced the risk for any CVD event by 42% (95% CI, 9%-63%;  $P = .02$ ) and the risk for nonfatal myocardial infarction (MI), stroke, or death due to CVD by 57% (95% CI, 12%-79%;  $P = .02$ ). Thus, long-term beneficial effects that reduce the risk for CVD in

patients with type 1 diabetes can be achieved with intensive diabetes therapy.<sup>7</sup>

Recent data also indicate that progression of macrovascular complications can be decreased with the thiazolidinedione (TZD) pioglitazone when added to current regimens (oral agents, insulin, or combination therapy).<sup>8</sup> In the PROspective pioglitAZone Clinical Trial In macroVascular Events (also known as the PROactive study), patients at high risk for macrovascular events were randomized either to pioglitazone, titrated from 15 mg to 45 mg ( $n = 2605$ ), or to matching placebo ( $n = 2633$ ), taken in addition to their current diabetes medication(s). Significantly fewer patients in the pioglitazone group reached the composite endpoint of all-cause mortality, nonfatal MI, or stroke ( $P = .027$ ). Thus, addition of pioglitazone to patients' diabetes treatment regimens can be an effective method of improving diabetes-related cardiovascular outcomes.<sup>8</sup> More studies are needed to confirm these findings and to further assess the safety of such regimens.

The clinical significance of such reductions in microvascular and macrovascular complications has been demonstrated in an analysis of data regarding men aged 45 to 79 years who were part of the Norfolk cohort of the European Prospective Investigation into Cancer and Nutrition. This analysis, which examined the relation between A1C, dia-

betes, and mortality, found that A1C independently predicted mortality in men with or without diabetes. A 1% increase in A1C was associated with a 30% increase in all-cause mortality and a 40% increase in cardiovascular or ischemic heart disease mortality. As in the UKPDS, the increased mortality risk was present throughout the range of A1C values with no evidence of a threshold.<sup>9</sup>

Data collected during the Third National Health and Nutrition Examination Survey indicate that US patients are not meeting glycemic goals. More than 50% of adults with type 2 diabetes have A1C levels above 7%, and 18% of those adults have A1C levels above 9.5%.<sup>10,11</sup> In a medical outcomes study comparing A1C values of patients with type 2 diabetes by specialty of the treating physician, the mean A1C value of patients treated by general internists was 9.7%, compared with 9.3% for those treated by family physicians and endocrinologists. At baseline, the percentages of patients with A1C values at or above 12% in each practice type were 21.9%, 18.5%, and 24.1%, respectively.<sup>12</sup> Notably, glycemic control was similar across treatment specialties. Less than 10% of patients with diabetes are treated by diabetes specialists or endocrinologists; most patients are cared for by internists and general or family physicians.<sup>13</sup> Accordingly, we suggest that primary care physicians revisit the traditional approach to diabetes treatment.

### **Outpatient treatment of type 2 diabetes: a stepwise approach**

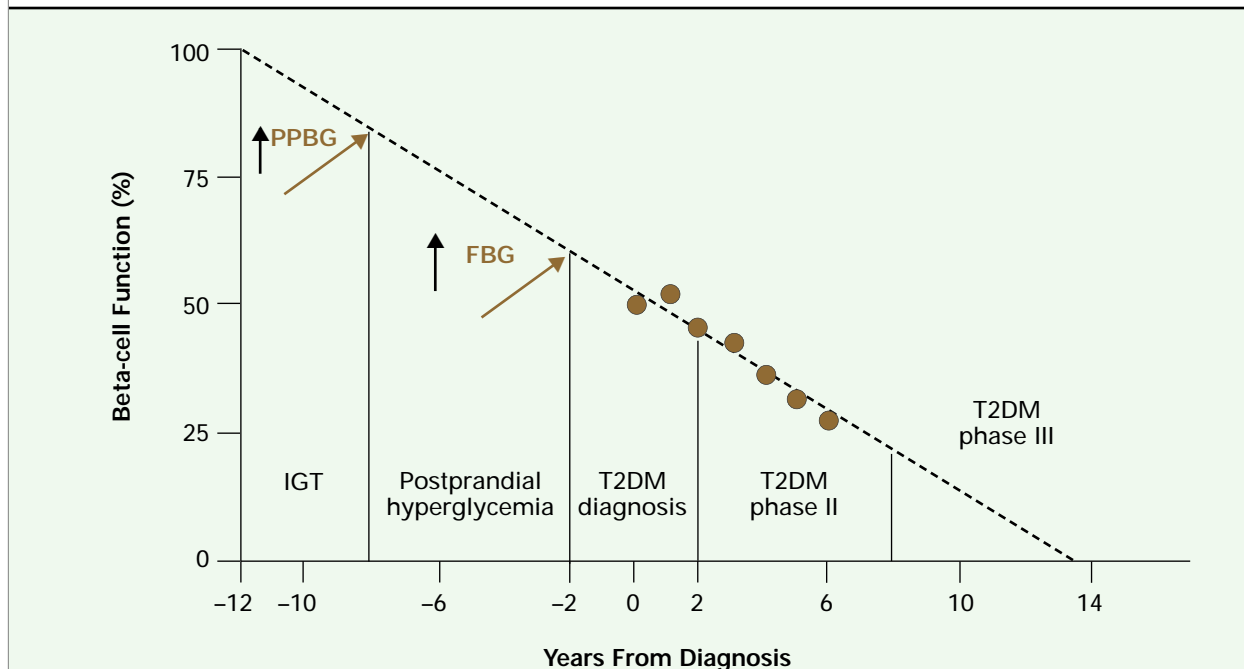
Appropriate nutrition and exercise are important components of any therapeutic regimen for type 2 diabetes, and providing patients with education in these areas should be the first step in managing newly diagnosed type 2 diabetes.<sup>14,15</sup> These interventions should be initiated as early as possible to prevent or delay the conversion from prediabetes to diabetes. In the Diabetes Prevention Program Research Group study, intensive lifestyle inter-

ventions (that is, a healthy, low-calorie, low-fat diet designed to achieve and maintain a weight loss of at least 7% of total body weight plus 150 minutes per week of moderate-intensity physical activity) reduced the incidence of diabetes in at-risk subjects (mean values at baseline: body mass index, 34 kg/m<sup>2</sup>; fasting plasma glucose [FPG], 106.5 mg/dL; 2-hour postprandial plasma glucose [PPG], 164.6 mg/dL; A1C, 5.91%) by 58%, compared with subjects who received placebo, and by 39%, compared with subjects who received metformin.<sup>16</sup>

However, diet as monotherapy has not proved to be effective in the majority of patients with type 2 diabetes and, over time, fewer patients are able to maintain glycemic control without pharmacotherapy. Less than 20% of the 4075 patients with newly diagnosed type 2 diabetes who entered the UKPDS had FPG concentrations below 108 mg/dL after 3 months on a low-fat, high-carbohydrate, high-fiber diet.<sup>17</sup> Following the initial 3-month diet phase and randomization to treatment with diet alone or with insulin, sulfonylurea, or metformin (overweight patients only), the majority of patients with FPG concentrations of 108 mg/dL to 270 mg/dL were unable to meet glycemic goals with monotherapy. Only 25% in the diet group had an A1C value below 7% after 3 years, and only 9% were able to maintain that goal at 9 years. Although a greater proportion of patients treated with insulin, sulfonylurea, or metformin monotherapy had A1C levels below 7% at 3 years (47%, 50%, and 44%, respectively), by year 9 the percentages had decreased to 28%, 24%, and 13%, respectively. Ultimately, most patients needed multiple therapies to maintain A1C and FPG values in the target range, reflecting the progressive deterioration of beta-cell function that is characteristic of type 2 diabetes.<sup>17,18</sup> In the UKPDS, when maximal doses of sulfonylurea failed to maintain glycemic control, the early addition of insulin to oral antidiabetic drug (OAD) therapy resulted in significantly lower A1C values (6.6% vs 7.1%;  $P < .0066$ ) and in a higher proportion of patients whose A1C values

**FIGURE 1**

**Time to deterioration of beta-cell function**



Progressive beta-cell failure from 0 to 6 years from diagnosis represents data from the United Kingdom Prospective Diabetes Study Group population<sup>18</sup> and was determined by the homeostatic assessment model. These data were extrapolated both forward and backward in time.

PPBG = postprandial blood glucose; FBG = fasting blood glucose; T2DM = type 2 diabetes mellitus; IGT = impaired glucose tolerance  
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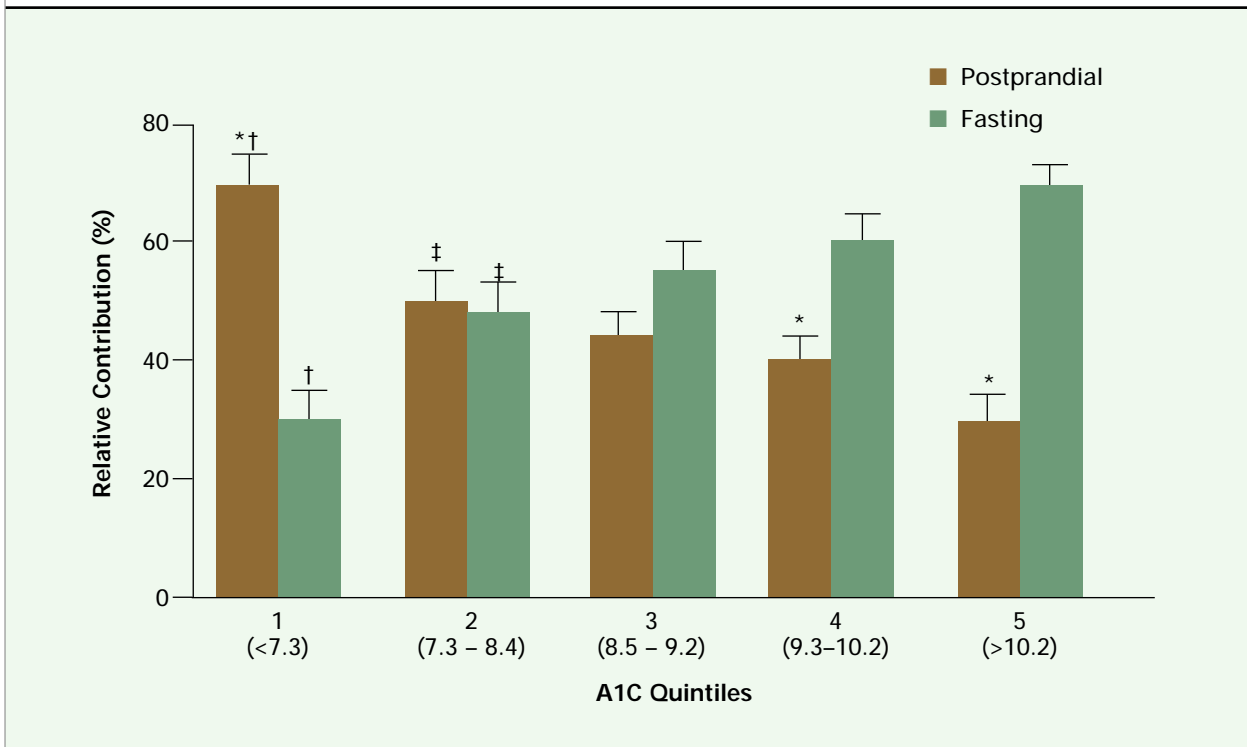
exceeded 7% (47% vs 35%;  $P = .011$ ) with no increase in weight gain or hypoglycemia compared with insulin alone.<sup>19</sup>

The addition of insulin to OADs may have several advantages over treatment with either combination oral therapy or insulin alone. During clinical trials, combination therapy with various OADs resulted in reductions in A1C that ranged from 0.9% to 1.7%, whereas the possible reduction in A1C with insulin plus OADs is open, depending on baseline and target A1C values.<sup>20</sup> Compared with insulin alone, treatment with insulin plus OADs results in improved glycemic control (an insulin-sparing effect), less weight gain, reduced insulin resistance, reduced risk for hypoglycemia, and an improved car-

diovascular profile.<sup>21-24</sup> By the time a diagnosis of type 2 diabetes is made, patients have lost nearly 50% of beta-cell function and may already have evidence of diabetes-related complications. An epidemiologic study found that approximately 20% of white patients in the United States have retinopathy at the time of diabetes diagnosis. Based on the degree of retinopathy present and the role of hyperglycemia in the pathophysiology of retinopathy, the study results suggest that detectable retinopathy may occur 4 to 7 years prior to diagnosis and that IGT may actually occur as early as 9 to 12 years prior to diagnosis.<sup>25</sup> These findings are consistent with observations from the UKPDS that demonstrated a large loss of beta-cell function in study participants at diagnosis and further

**FIGURE 2**

**Relative contribution of FPG and PPG to overall hyperglycemia**



FPG = fasting plasma glucose; PPG = postprandial plasma glucose; A1C = glycosylated hemoglobin; ANOVA = analysis of variance  
 \*Significant difference between fasting and postprandial (paired t test) glucose.  
 †Significant difference from all other quintiles (ANOVA)  
 ‡Significant difference from quintile 5 (ANOVA)  
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deterioration over a 6-year period despite treatment with diet or OADs. The UKPDS data, which were determined by the homeostatic assessment model, were extrapolated back to a point in time when 100% beta-cell function would have existed, suggesting that deterioration of beta-cell function may have taken place during a prediabetic phase 10 to 12 years prior to diagnosis (FIGURE 1).<sup>18,26</sup> Thus, it may be necessary to add insulin therapy to existing oral regimens at an earlier stage in the course of type 2 diabetes.

**Initiating basal insulin therapy**

Both FPG and PPG contribute to overall hyperglycemia in patients with type 2 diabetes. However,

in patients who have poor glycemic control (that is, A1C values at or above 8.5%) with either nutrition therapy or OADs, the relative contribution of FPG is significantly greater than that of PPG (FIGURE 2).<sup>27</sup> Therefore, it appears prudent to concentrate efforts on addressing fasting hyperglycemia first by initiating basal insulin therapy in patients whose disease has been inadequately controlled with OADs.<sup>28</sup> However, postprandial glucose excursions do contribute to overall hyperglycemia at all A1C values and need to be addressed with either OADs or exogenous insulin in any management plan.

Two studies have demonstrated the efficacy of adding basal insulin (either insulin glargine or neutral protamine Hagedorn [NPH] insulin) to oral

**TABLE 2**

**Practical guidelines  
for starting basal insulin**

- Continue oral agent(s) at same dosage (eventually reduce sulfonylurea when nearing FBG target)
- Add single dose of insulin (10-20 U)
  - Neutral protamine Hagedorn insulin (bedtime)
  - Insulin glargine (bedtime or morning)
- Adjust dose according to self-monitored FBG
- Increase insulin dose weekly as needed
  - Increase 8 U if FBG >180 mg/dL
  - Increase 4 U if FBG >140 mg/dL
  - Increase 2 U if FBG = 120-140 mg/dL
- Treat to target (FBG usually 100 mg/dL)
- Alternative titration: Increase basal insulin by 2 units every 3-4 days until FBG ≤100 mg/dL

FBG = fasting blood glucose  
 Data from Riddle MC, et al. *Diabetes Care*. 2003;26:3080-3086;  
 Davies M, et al. *Diabetes Care*. 2005;28:1282-1288; Chan JL,  
 Abrahamson MJ. *Mayo Clin Proc*. 2003;78:459-467.<sup>29,31,32</sup>

therapy in patients with poorly controlled type 2 diabetes. In the Treat-to-Target Trial, once-daily insulin glargine or NPH was added to existing oral regimens, and the insulin dose was titrated based on a target FPG value at or below 100 mg/dL. Although both types of insulin were effective in reducing A1C values from baseline (glargine, 8.61% to 6.96%; NPH, 8.56% to 6.97%; between-group difference, .03%; *P* value not significant), more subjects in the insulin glargine group than in the NPH group achieved an A1C value at or below 7% without documented nocturnal hypoglycemia (33.2% vs 26.7%, respectively; *P*<.05).<sup>29</sup> This beneficial effect of insulin glargine vs NPH was confirmed in a meta-analysis of data from 3 clinical studies of 1786 subjects with type 2 diabetes who were treated with 1 injection of insulin glargine or NPH. The analysis revealed that at any given rate of hypoglycemia, lower A1C values could be achieved with insulin glargine than with NPH.<sup>30</sup> In addition, results of A Trial comparing Lantus Algorithms to achieve Normal blood glucose Targets in patients

with Uncontrolled blood Sugar (also known as AT.LANTUS) indicated that reductions in A1C values similar to those observed in the Treat-to-Target Trial could be achieved in subjects with inadequately controlled type 2 diabetes whether the titration of insulin glargine was managed by the physician or by the subject. Patients who titrated their own insulin glargine dose every 3 days experienced a reduction of -1.22% from baseline A1C values, compared with a decrease of -1.08% in those patients whose physicians had titrated their insulin dose once weekly (*P*<.001).<sup>31</sup> Thus, a reasonable approach to the management of type 2 diabetes in patients who are not achieving goals in line with American Diabetes Association or American College of Endocrinology (ACE) guidelines (TABLE 1)<sup>5,6</sup> is the addition of basal insulin. Basal insulin may be initiated at 10 U once daily and adjusted weekly using a simple forced titration algorithm based on a target FPG at or below 100 mg/dL (TABLE 2).<sup>29,31,32</sup>

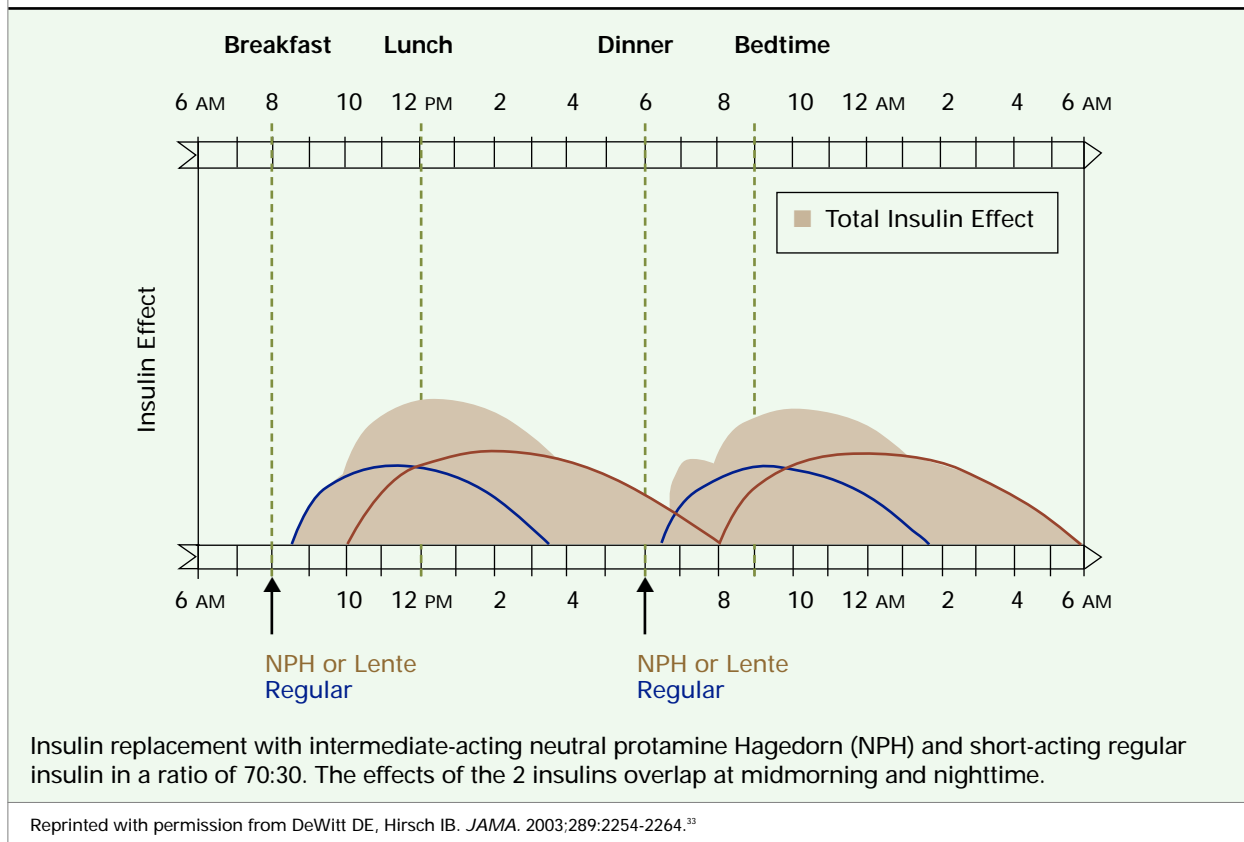
**Basal insulin vs premixed formulations**

One of the challenges facing patients with type 2 diabetes and their physicians is the decision of when to move from a basal insulin-plus-OAD regimen to a basal-prandial insulin regimen that involves multiple injections per day. Some physicians try to make this transition by using premixed insulin formulations that contain an intermediate- or long-acting insulin plus a short-acting insulin. This type of formulation does not mimic physiologic beta-cell function since each insulin component acts as both basal and prandial insulin replacement at different times during the day (FIGURE 3).<sup>33</sup>

Two recent studies compared the effects of using insulin glargine plus OADs with the effects of using insulin regimens in subjects who have inadequately controlled type 2 diabetes. Janka et al<sup>21</sup> studied insulin-naive subjects who were failing to maintain glycemic goals (A1C values between 7.5% and 10.5%) while on combination therapy with metformin and a sulfonylurea. Subjects were randomly assigned to treatment with morning

**FIGURE 3**

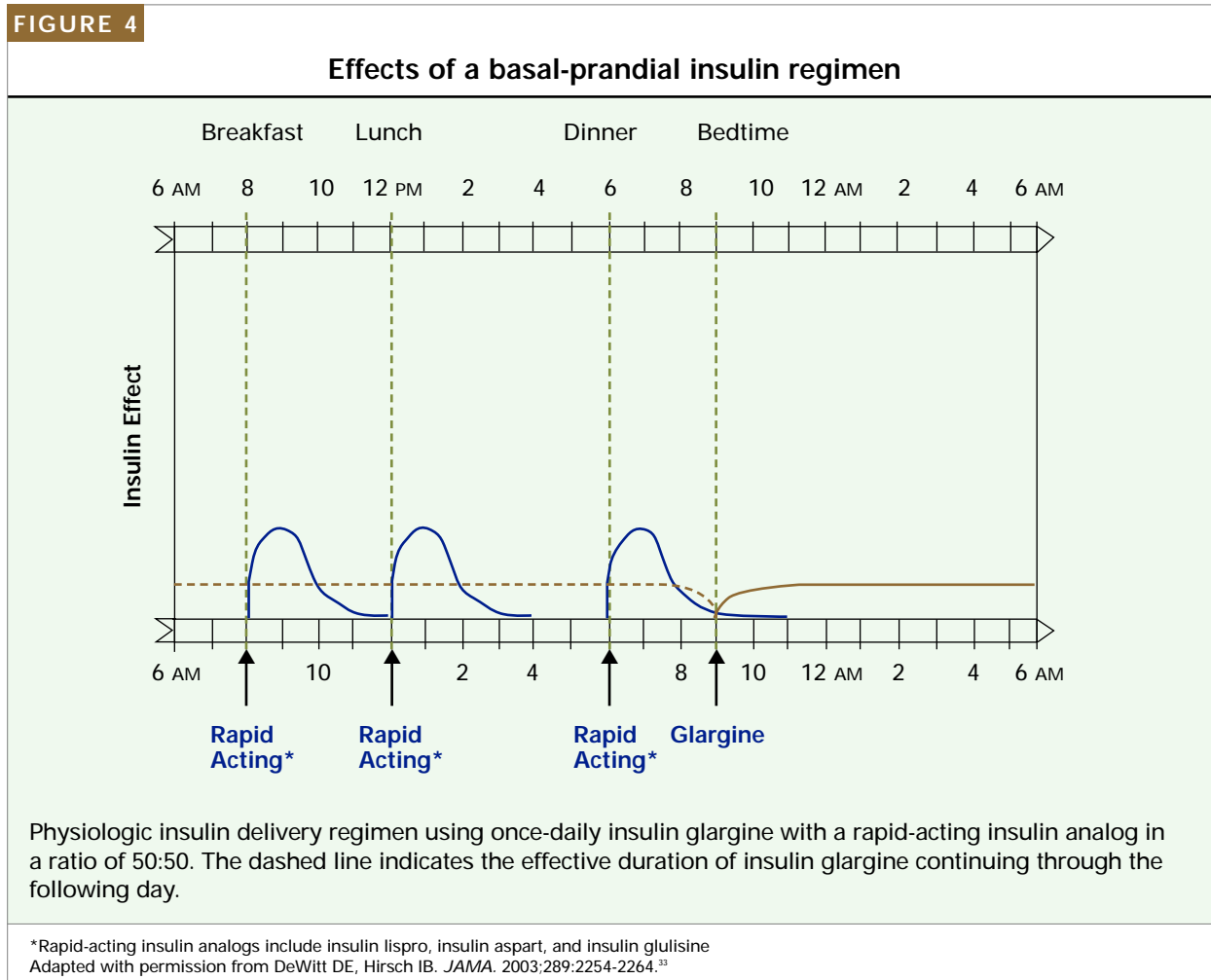
**Effects of a premixed insulin formulation**



insulin glargine plus stable doses of glimepiride and metformin or twice-daily premixed insulin (30% regular insulin, 70% NPH) without OADs. Subjects treated with insulin glargine plus OADs had a greater decrease from baseline of A1C than those treated with premixed insulin alone (-1.64% vs -1.31%, respectively;  $P = .0003$ ) and fewer confirmed hyperglycemic episodes (4.07 vs 9.87 per patient year;  $P < .0001$ ). The insulin glargine group also had a higher percentage of subjects reaching A1C levels at or below 7% without nocturnal hypoglycemia (45.5% vs 28.6%;  $P = .0013$ ).

Raskin et al<sup>34</sup> compared the initiation of insulin therapy in insulin-naïve subjects with either twice-daily injections of a biphasic insulin analog formulation consisting of 30% soluble insulin aspart and 70% insulin aspart crystallized with protamine

(BIAsp 70/30) or once-daily insulin glargine at bedtime. Subjects were entered into the study if they had an A1C value at or above 8% during previous treatment with metformin (at or above 1000 mg/d) alone or in combination with a TZD and/or secretagogues and alpha-glucosidase inhibitors. Treatment with metformin was optimized to 1500 to 2550 mg/d and the secretagogues and alpha-glucosidase inhibitors were discontinued in all subjects during a 4-week run-in phase; TZDs were continued (approximately one third of patients were on a pioglitazone regimen). At the end of the 28-week study, subjects treated with BIAsp 70/30 experienced a significantly greater reduction in A1C compared with the insulin glargine group (-2.79 vs -2.36, respectively;  $P < .01$ ). This difference in response was most notable in subjects with baseline A1C values above 8.5% and may



reflect the greater degree of beta-cell dysfunction usually found in patients with higher A1C values and the discontinuation of secretagogues in both treatment groups, which would have left subjects in the basal insulin glargine group with diminished postprandial insulin coverage. Consistent with this hypothesis is the fact that no difference in reduction from baseline values was observed between treatment groups in subjects with baseline A1C at or below 8.5%. Notable as well, however, was the finding that the mean daily dose of insulin glargine at study end was substantially lower than that of BIAsp 70/30. This may indicate that insulin glargine was not sufficiently titrated to achieve maximal reduction of hyperglycemia, a conclusion supported by the sig-

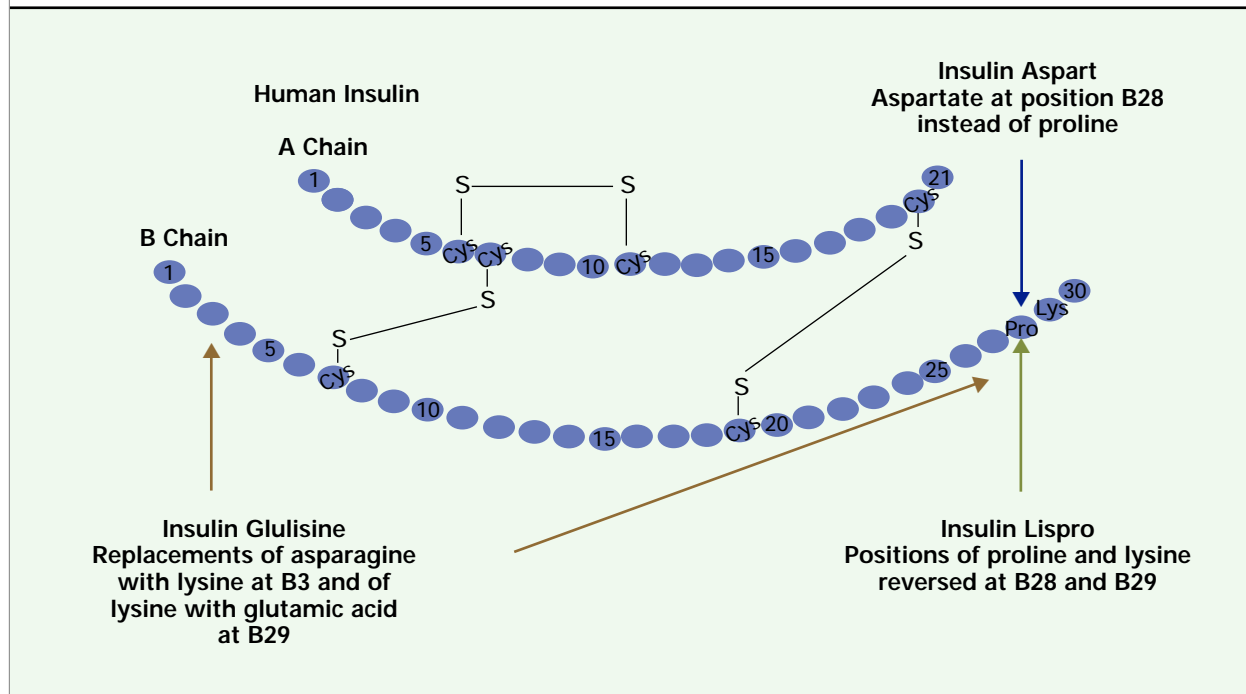
nificantly lower incidence of minor hypoglycemia in the insulin glargine group relative to the BIAsp 70/30 group ( $P < .05$ ).<sup>34</sup>

### Basal-prandial insulin regimens

As beta-cell function continues to deteriorate, a physiologic basal-prandial insulin regimen that allows mealtime flexibility may be more effective for patients with type 2 diabetes (FIGURE 4).<sup>33</sup> Prior to the advent of rapid-acting insulin analogs, regular insulin was the only available prandial insulin. However, the use of regular insulin is associated with several limitations, including the need to administer it 30 to 45 minutes prior to a meal and the occurrence of episodes of premeal hypoglycemia because of its long

**FIGURE 5**

**Similar IGF-1 activity**



Fast-acting insulin analogs: Insulin lispro, insulin aspart, and insulin glulisine differ from human insulin by small alterations in molecular structure. (Amino acid substitutions are noted in the graphic representation.) These molecular modifications in the respective analogs reduce the analogs' tendency to aggregate into dimeric or hexameric molecules, thus speeding absorption after subcutaneous injection.

Adapted with permission from Garg SK, et al. *Expert Opin Pharmacother.* 2005;6:643-651.<sup>38</sup>

duration of action (ie, 3-6 h).<sup>15,35</sup> It is the hexameric form that leads to a slower absorption and onset, as only insulin monomers are biologically active.<sup>36</sup> In addition, compliance with respect to the recommended interval between injection and meal is poor: the majority of patients inject their regular insulin 15 minutes or less before their next meal.<sup>36</sup>

The impact of the first rapid-acting insulin analog, insulin lispro, on glycemic control in patients with type 1 diabetes was assessed in a retrospective analysis of patient records. The records of patients (N = 884) who were entered into the database at one diabetes clinic from January 1, 1993, through December 31, 1998, were reviewed to identify possible changes in A1C following the publication of results from the DCCT in 1993 and

the introduction of insulin lispro in 1996.<sup>37</sup> The study found that a significant decrease ( $P < .001$ ) in A1C values and a significant increase ( $P < .001$ ) in the number of severe hypoglycemic episodes occurred between 1993 and 1996. A further decrease in A1C values ( $P < .001$ ) between the years 1996 and 1998 was noted in 676 subjects who switched from regular insulin to insulin lispro in 1996, but no significant decrease in A1C was observed in the 208 subjects who continued using regular insulin. Despite the decrease in A1C associated with the use of insulin lispro, subjects did not experience a corresponding increase in the number of severe hypoglycemic episodes ( $P = .26$ ).

Currently, 3 rapid-acting insulin analogs are available in the United States: insulin lispro, insulin

aspart, and insulin glulisine. FIGURE 5 depicts the amino acid substitutions to the B chain of the insulin protein that give those insulin analogs their rapid onset of action.<sup>38</sup> This rapid onset of action enables administration 5 to 15 minutes before a meal. Insulin glulisine, however, may be injected within 20 minutes after the patient begins to eat a meal.<sup>39-41</sup> Using a basal-prandial regimen with insulin glargine, insulin glulisine administered either postmeal or premeal has been found to be as effective as premeal regular insulin in reducing A1C in subjects with type 1 diabetes (N = 860), with no increase in hypoglycemic episodes. Postmeal insulin glulisine also was associated with a decrease in weight ( $P = .03$ , compared with premeal insulin glulisine and premeal regular insulin).<sup>42</sup>

In addition, insulin glulisine has been shown to be comparable to insulin lispro both in reducing A1C values in patients with type 1 diabetes and in the associated incidence of hypoglycemia when used as part of a basal-prandial regimen with insulin glargine.<sup>43</sup> Similar results were obtained in patients with type 2 diabetes (N = 876) treated with NPH plus either insulin glulisine or regular insulin before breakfast and dinner. Patients treated with insulin glulisine experienced a greater reduction in A1C from baseline than patients in the regular insulin group ( $-0.46\%$  vs  $-0.30\%$ , respectively;  $P = .0029$ ), with a similar occurrence of symptomatic hypoglycemia and weight gain.<sup>44</sup>

### In-hospital management of diabetes

In-hospital management of hyperglycemia in patients with diabetes is critically important for preventing increases in morbidity and mortality that have been observed in such patients following ischemic stroke, MI, and surgery.<sup>45-47</sup> In recent years, it has become clear that these poor outcomes are associated with the presence of hyperglycemia at admission, irrespective

of an existing diagnosis of diabetes.<sup>46,48-50</sup> In addition, prospective studies have demonstrated that control of hyperglycemia reduces mortality, organ dysfunction, and length of stay in the intensive care unit in critically ill patients<sup>51,52</sup> and also decreases mortality following MI in patients with diabetes.<sup>53</sup> Given that nearly 40% of patients admitted to the hospital have hyperglycemia,<sup>50</sup> physicians must be vigilant in monitoring the glycemic control of hospitalized patients who do or do not have diabetes.

The ACE position statement on inpatient diabetes and metabolic control urges strict glycemic targets for hospitalized patients.<sup>54</sup> For patients in intensive care units, maximum glucose concentrations should be maintained at 110 mg/dL. In non-critical care units, preprandial glucose should be 110 mg/dL and 180 mg/dL should be the maximal glucose concentration.

The ACE guidelines indicate that insulin is the only viable option for treatment of hyperglycemia in hospitalized patients.<sup>54</sup> The use of sliding-scale regimens, in which short-acting regular insulin is used with no basal component, is discouraged because of the association with high rates of hyperglycemia, hypoglycemia, and diabetic ketoacidosis.<sup>54,55</sup> Continuous intravenous insulin infusion (CII) is recommended during the perioperative period, as well as in patients with critical illnesses and those who are unable to take adequate nutrition by mouth. Patients who do not require CII should be managed using individualized subcutaneous insulin regimens that cover both basal and nutritional needs (that is, meals and/or intravenous glucose). In addition, correction or supplemental doses should be provided based on bedside capillary glucose readings to optimize control.

### Conclusion

Near euglycemia can be safely pursued with insulin therapy in patients with type 2 diabetes. However, such patients most likely will need a combination of insulin plus OADs for optimal glycemic control. In

general, although treatment should be individualized for each patient when the use of insulin is initiated, metformin and TZD should be continued; the sulfonylurea dose can be reduced. The priority is to stabilize FPG first, by adding a basal insulin. If PPG remains excessively high (that is, above 180 mg/dL), a rapid-acting analog can be added for prandial insulin replacement, starting before the largest daily meal. The use of insulin to decrease hyperglycemia in critically ill hospitalized patients has been shown to decrease morbidity and mortality, which might reflect some of the nonglycemic effects of insulin, including anti-inflammatory and antiatherogenic activity.<sup>56</sup> Earlier and optimal use of insulin, whether in the outpatient or inpatient settings, is an important therapeutic strategy for achieving glycemic control and improving patient outcomes.

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