

# Insulin Therapy in Patients with Type 2 Diabetes Mellitus: Treatment to Target Fasting and Postprandial Blood Glucose Levels

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## ABSTRACT

**Background:** Type 2 diabetes mellitus (DM) is a progressive disease characterized by both insulin resistance and  $\beta$ -cell failure, resulting in a decline in insulin secretion and increased blood glucose levels. Endogenous insulin replacement is eventually required to avoid the complications associated with poor glycemic control. Increasingly, evidence suggests that early introduction of insulin may slow the progression of type 2 DM, laying the foundations for long-term good glycemic control.

**Objective:** The aim of this article was to review the advantages and disadvantages of various insulin-based treatment regimens and examine the best method of initiating insulin therapy in patients with type 2 DM.

**Methods:** MEDLINE (1966–2006) was used to identify studies that reported on the use of insulin and insulin analogues for the treatment of DM. Key words used for the search included the following: *insulin glargine, insulin detemir, insulin lispro, insulin aspart, insulin glulisine, regular human insulin, postprandial blood/plasma glucose, fasting blood/plasma glucose, and oral antidiabetic agents.*

**Results:** Although it is clear that both fasting blood glucose (FBG) and postprandial blood glucose levels contribute to glycemic control, evidence reviewed in this article suggests that FBG levels should first be normalized in newly diagnosed patients with poor glycemic control. Options for introducing insulin therapy include the use of 1 of the 3 broad classes of insulin preparations: basal, prandial, and premixed. The new basal insulin analogues may be the most effective method of targeting FBG. Indeed, insulin glargine and insulin detemir offer a number of advantages over more traditional preparations such as neutral protamine Hagedorn insulin and premixed insulin, including a reduced risk of hypoglycemia and less weight gain. Reducing the risk of these adverse effects is beneficial since they can prevent the initiation and appropriate titration of insulin. As the patient's condition deteriorates, prandial insulin can be added to the basal insulin analogue in a stepwise manner, eventually resulting in the use of a full basal-bolus regimen. Unfortunately, despite evidence supporting the early initiation of insulin therapy in patients with type 2 DM, many barriers to treatment exist, including the possibility of weight gain, a fear of injections, the belief that insulin regimens are complex, and skepticism over whether patients will follow the titration algorithms needed to achieve the stringent glycemic control targets. To ensure that insulin regimens are acceptable to patients and implemented by physicians, they should be as simple and efficient as possible. Recent studies have demonstrated the effectiveness of simple titration regimens for the initiation of basal insulin.

**Conclusion:** A basal-bolus regimen can be tailored to the glycemic needs of each individual patient; the simplicity and flexibility of dosing may result in greater patient compliance and, thus, improved glycemic control. (*Insulin*. 2006;1:158–165) Copyright © 2006 Excerpta Medica, Inc.

**Key words:** type 2 diabetes mellitus, insulin glargine, insulin detemir, fasting blood glucose, glycemic control, prandial insulin.

## INTRODUCTION

In healthy individuals, insulin secretion from pancreatic  $\beta$ -cells is closely linked to blood glucose levels. In the basal state, insulin is secreted at a low, constant rate to regulate lipolysis and hepatic glucose production between meals and overnight. This basal secretion accounts for ~50% of the daily insulin output.<sup>1</sup> An amplified rate is produced in response to sharp increases in blood glucose after meals.<sup>1</sup>

Thus, normal plasma blood glucose levels are maintained within a narrow range of ~4 to 9 mmol/L (72–162 mg/dL),<sup>2</sup> thus avoiding hypo- and hyperglycemia.

Type 2 diabetes mellitus (DM) is characterized by both insulin resistance and  $\beta$ -cell failure, resulting in a decline in insulin secretion and increased blood glucose levels. The importance of tight glycemic control has been demonstrated by results of various prospective studies in which prolonged

hyperglycemia was found to be associated with an increased risk of various complications.<sup>3,4</sup> These complications include microvascular disorders such as sensory neuropathy, retinopathy, and nephropathy, as well as stroke, myocardial infarction, macrovascular mortality, and all-cause mortality. As insulin secretion declines, insulin replacement becomes the most effective method of attaining good glycemic control, often providing the basis of treatment for many patients with DM.<sup>4</sup> To this end, an ideal insulin therapy should mimic endogenous insulin secretion as closely as possible.

The goal of this article was to review the advantages and disadvantages of various insulin-based treatment regimens and examine the best method of initiating insulin therapy in patients with type 2 DM.

## MATERIALS AND METHODS

MEDLINE (1966–2006) was used to identify studies that reported on the use of insulin and insulin analogues for the treatment of DM. Key words used for the search included the following: *insulin glargine, insulin detemir, insulin lispro, insulin aspart, insulin glulisine, regular human insulin, postprandial blood/plasma glucose, fasting blood/plasma glucose, and oral antidiabetic agents.*

## RATIONALE FOR INSULIN THERAPY IN TYPE 2 DIABETES MELLITUS

Type 2 DM is a progressive disease. The decline of  $\beta$ -cell function is largely under genetic control, but environmental factors may also contribute to the glucotoxic and lipotoxic states. By the time type 2 DM is clinically diagnosed, only 50% of normal  $\beta$ -cell function remains.<sup>5</sup> A healthy diet and exercise are initially recommended to control blood glucose levels, followed by the use of oral antidiabetic drugs (OADs) as the disease progresses. However, the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that in patients with type 2 DM, the continued decline of  $\beta$ -cell function is inevitable, despite the use of oral therapy.<sup>6</sup> The UKPDS investigators also showed that when oral therapy does fail, exogenous insulin successfully restores glycemic control. Evidence of the progressive nature of type 2 DM was discovered in the subsequent 6-year follow-up study.<sup>7</sup> The researchers focused on the glycemic control achieved with sulfonylurea monotherapy and found that 53% of patients had progressed to insulin therapy, in addition to oral therapy, to maintain fasting blood glucose (FBG) targets.

Although patients with type 2 DM are not initially dependent on insulin, the addition of insulin therapy can still play a vital role in achieving satisfactory glycemic control. Indeed, as our understanding of type 2 DM pathophysiology improves, earlier introduction of insulin therapy is increasingly viewed as an essential therapeutic tool to maintain good metabolic control during the time course of the disease. Prolonged hyperglycemia induces glucotoxicity, resulting in insulin resistance and impaired  $\beta$ -cell function, which in turn lead to hyperglycemia. Insulin therapy can interrupt this vicious cycle, and the early introduction of

insulin may slow the progression of type 2 DM, laying the foundations for long-term good glycemic control.<sup>4</sup>

**A**lthough patients with type 2 DM are not initially dependent on insulin, the addition of insulin therapy can still play a vital role in achieving satisfactory glycemic control.

Landmark trials such as the Diabetes Control and Complications Trial, in patients with type 1 DM, and the UKPDS, in patients with type 2 DM, have demonstrated—unequivocally—the benefits of tight glycemic control.<sup>3,4</sup> The UKPDS revealed a direct correlation between blood glucose levels and the risk of micro- and macrovascular complications.<sup>4</sup> Newly diagnosed patients treated with an intensive therapy regimen using insulin or oral agents over a 10-year period achieved mean glycosylated hemoglobin (A1C) levels of 7.0% compared with 7.9% in patients receiving conventional therapy.<sup>4</sup> This improvement was associated with a 25% decrease in the rate of microvascular complications ( $P < 0.001$ ) and a 16% reduction in macrovascular disease ( $P = 0.052$ ).

These results are supported by 2 additional major studies of patients with type 2 DM: the Kumamoto Study<sup>8</sup> and the Steno-2 Study.<sup>9</sup> In the Kumamoto Study, mean A1C levels in patients ( $n = 26$ ) treated with intensive insulin therapy were greatly reduced compared with those in patients ( $n = 25$ ) receiving conventional therapy (7.1% vs 9.4%, respectively); this corresponds to substantial reductions in nephropathy and retinopathy.<sup>8</sup> More recently, the Steno-2 Study compared intensive and conventional treatment with respect to modifiable risk factors for cardiovascular disease in patients with type 2 DM and associated microalbuminuria ( $N = 160$ ).<sup>9</sup> The intensive treatment comprised a stepwise implementation of lifestyle changes and drug therapy targeting hyperglycemia, hypertension, dyslipidemia, and microalbuminuria (along with the secondary prevention of cardiovascular disease with acetylsalicylic acid). Significant reductions (>50%) in the relative risk of the development or progression of nephropathy ( $P = 0.003$ ), retinopathy ( $P = 0.02$ ), and autonomic neuropathy ( $P = 0.002$ ) were achieved in the group receiving intensive therapy.<sup>9</sup>

In light of such evidence, the major associations for diabetes management—such as the American Diabetes Association (ADA), the American Association of Clinical Endocrinologists (AACE), and the International Diabetes Federation (IDF) in Europe—have set strict targets for glycemic control.<sup>10–12</sup> Guidelines from the ADA recommend that A1C levels should be targeted to <7.0%, while the AACE and IDF advocate levels  $\leq 6.5\%$ .

Patients with type 2 DM should also be treated to target both FBG and postprandial blood glucose (PPG) levels. The UKPDS revealed the adverse effect of increased fasting plasma glucose (FPG) levels in the progression of vascular complications associated with DM.<sup>6</sup> Evidence also suggests

that greater day-to-day variability in FPG is linked to increased mortality.<sup>13</sup> However, a study of 66 patients with type 2 DM<sup>14</sup> has demonstrated that postlunch and extended postlunch PPG levels are more sensitive and more specific predictors of glycemic control than FPG and that 2-hour PPG concentrations correlate strongly with A1C levels. Approximately two thirds of the day is spent in the postprandial condition,<sup>15</sup> and given that blood glucose levels are at their highest during this period, they may contribute considerably to blood glucose control. Therefore, PPG levels may play a disproportionate role in the development of both micro- and macrovascular complications.<sup>16,17</sup>

Monnier et al<sup>18</sup> attempted to determine the relative contributions of FPG and PPG to overall diurnal hyperglycemia in 290 patients with type 2 DM. Elevated PPG was found to be the major contributor to overall hyperglycemia in patients with mild or moderate DM (ie, A1C  $\leq$ 8.4%); however, in patients with poorly controlled disease (ie, A1C  $>$ 8.4%), FPG provided a greater contribution than PPG. The authors concluded that the shift in the relative contribution of the 2 markers appears as a continuous spectrum from well to poorly controlled disease.<sup>18</sup> A similar relationship may also exist with postchallenge plasma glucose (PCPG) levels. Woerle et al<sup>19</sup> showed that while both FPG and PCPG are positively associated with A1C, the 2-hour PCPG level increased at a rate 4 times greater than FPG and accounted for a greater proportion of A1C. Furthermore, many individuals with normal A1C levels (ie, 6.0%–7.0%) had normal FPG but abnormal 2-hour PCPG. Given such evidence, the ADA<sup>10</sup> recommends FPG levels of 5.0 to 7.2 mmol/L (90–130 mg/dL) and a peak PPG level of  $<$ 10.0 mmol/L ( $<$ 180 mg/dL), while the AACE<sup>11</sup> recommends values of  $<$ 6.1 mmol/L ( $<$ 110 mg/dL) and  $<$ 7.8 mmol/L ( $<$ 140 mg/dL), respectively.

**P**atients with type 2 DM should also be treated to target both fasting blood glucose and postprandial blood glucose levels.

## OPTIONS FOR INTRODUCING INSULIN THERAPY

Insulin preparations can be divided into 3 broad classes: basal, prandial, and premixed.

### Basal Insulin

Basal insulin therapy involves the addition of insulin with a protracted action to ongoing oral therapy. The intermediate-acting neutral protamine Hagedorn (NPH) insulin has been the mainstay of basal insulin therapy for the last 60 years. However, a number of disadvantages are inherent with this preparation, including the risk of hypo- and hyperglycemia associated with a peak in the time-action profile, high inter- and inpatient variability, and the need to put it into suspension before injection.<sup>20</sup> Nevertheless, NPH insulin remains the benchmark against which all new

insulin preparations are measured, and a number of studies have compared the efficacy of new basal analogues with NPH insulin (discussed below).

Insulin glargine is a QD, long-acting, human insulin analogue with a 24-hour duration of action,<sup>21</sup> a time-action profile with no pronounced peak, and significantly lower interpatient variability than NPH insulin (0.64 vs 1.05 mg/kg per minute;  $P < 0.05$ ).<sup>22</sup> Studies have demonstrated that insulin glargine QD is at least as effective as NPH insulin QD or BID in achieving glycemic control in patients with type 2 DM.<sup>20,23–25</sup> Insulin glargine and NPH insulin in combination with oral therapy produced similar reductions in A1C and FBG levels in an investigation of 426 patients with type 2 DM.<sup>20</sup> However, patients receiving insulin glargine experienced less nocturnal hypoglycemia (9.9% vs 24.0% of all patients, insulin glargine vs NPH insulin;  $P < 0.001$ ) and lower postdinner glucose concentrations (9.9 vs 10.7 mmol/L [178 vs 193 mg/dL];  $P < 0.02$ ) than patients receiving NPH insulin. Greater reductions in A1C levels with insulin glargine compared with NPH insulin were observed in obese patients with type 2 DM ( $N = 570$ ).<sup>26</sup> A1C levels fell by 0.42% with an insulin glargine-based regimen and by 0.11% with an NPH insulin-based regimen ( $P < 0.024$ ).

A second long-acting insulin analogue, insulin detemir, also offers advantages over NPH insulin. Insulin detemir has an intermediate duration of action, a flatter peak of action, and lower inter- and inpatient variability than NPH insulin.<sup>27</sup> The analogue can be administered QD or BID, although the European Committee for Proprietary Medicinal Products reported that a study of QD insulin detemir plus metformin failed to establish noninferiority with QD NPH insulin plus metformin.<sup>28</sup> However, a second study in the same report did demonstrate noninferiority for insulin detemir with NPH insulin when both were administered QD or BID as part of a basal-bolus regimen. It was concluded that insulin detemir should only be used as part of a basal-bolus regimen in patients with type 2 DM.<sup>28</sup> Subsequently, Haak et al<sup>29</sup> compared insulin detemir with NPH insulin, both QD and BID, in combination with the mealtime administration of insulin aspart in patients with type 2 DM ( $N = 505$ ). During the 26-week study, A1C levels fell significantly with both regimens, although the decrease was greater with NPH insulin ( $-0.4%$ ;  $P < 0.001$ ) than with insulin detemir ( $-0.2%$ ;  $P = 0.004$ ). Reductions in FPG levels and the incidence of hypoglycemia were comparable between treatment groups. However, although body weight increased in both groups, patients receiving insulin detemir gained significantly less body weight than those who were administered NPH insulin (1.0 and 1.8 kg, respectively;  $P = 0.017$ ). A third study, in 395 patients, demonstrated similar reductions in both A1C ( $P = 0.515$ ) and FPG ( $P = 0.855$ ) with insulin detemir plus insulin aspart and NPH insulin plus regular human insulin (RHI).<sup>30</sup> Weight gain was reduced more with the insulin detemir regimen compared with the NPH insulin regimen (0.51 and 1.13 kg, respectively;  $P = 0.038$ ), and the risk of nocturnal hypoglycemia was 38% lower with insulin detemir.

These data demonstrate, therefore, that insulin glargine and insulin detemir each offers specific features that assist patients with type 2 DM to achieve at least equivalent glycemic control compared with NPH insulin but with lower rates of hypoglycemia and less weight gain.

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### Prandial Insulin

An alternative approach to basal insulin is to administer premeal doses of a short-acting insulin (a “bolus”) to control postprandial hyperglycemic peaks. Through the 1990s, RHI—a short-acting form of human insulin—became the prandial insulin of choice. However, the tendency of RHI to form hexamers results in a delayed onset of action and increased total duration of action compared with the physiologic prandial insulin response.<sup>31</sup> This led to the development of the rapid-acting insulin analogues: insulin aspart, insulin lispro, and insulin glulisine. All 3 analogues have a faster onset of action than RHI; the peaks in their activity occur earlier; and their duration of action is shorter.<sup>32–34</sup> All can be administered immediately before meals<sup>35–37</sup> and are therefore well suited to mealtime insulin replacement in prandial regimens. The rapid onset of action of insulin glulisine also allows for its administration shortly after meals.<sup>38</sup>

A study of 37 patients compared RHI injected 30 minutes before a meal versus insulin aspart injected immediately before a meal.<sup>36</sup> The time to maximum serum insulin concentration was 27 minutes shorter with insulin aspart than with RHI ( $P = 0.039$ ), despite the 30-minute delay in administration. In addition, postprandial glycemic excursions were 20% lower with insulin aspart than with RHI ( $P = 0.034$ ).

Insulin glulisine conferred small but significant improvements in glycemic control over RHI in a study of 876 patients with well-controlled type 2 DM using NPH insulin as the basal insulin.<sup>37</sup> A1C levels decreased by 0.46% with insulin glulisine compared with 0.30% with RHI ( $P < 0.003$ ). PPG levels were also lower with insulin glulisine versus RHI (postbreakfast: 8.66 vs 9.02 mmol/L [156 vs 162 mg/dL],  $P < 0.05$ ; postdinner: 8.54 vs 9.05 mmol/L [154 vs 163 mg/dL],  $P < 0.05$ ).<sup>37</sup>

In patients with type 2 DM whose disease was not adequately controlled with sulfonylurea therapy, insulin lispro administered before meals significantly reduced 2-hour PPG concentrations compared with sulfonylureas alone, from 18.6 to 14.2 mmol/L (335 to 256 mg/dL;  $P < 0.001$ ).<sup>39</sup> The FPG levels decreased from 10.9 to 8.5 mmol/L (196 to 153 mg/dL;  $P < 0.001$ ) and mean A1C values were reduced from 9.0% to 7.1% ( $P < 0.001$ ). However, patients gained significantly more weight with insulin lispro than with the sulfonylureas alone ( $P < 0.001$ ). Insulin lispro has also been shown to have

a greater impact on glycemic control than a single bedtime injection of NPH insulin in combination with glyburide.<sup>35</sup> At end point, mean (SD) A1C levels were significantly lower with insulin lispro (7.7% [0.9%]) compared with NPH insulin (8.5% [1.4%];  $P = 0.003$ ) as were 2-hour PPG levels (10.9 [2.9] mmol/L [196 (52) mg/dL] vs 12.2 [3.1] mmol/L [220 (56) mg/dL];  $P = 0.052$ ). However, FBG levels at end point were significantly lower with NPH insulin (8.5 [2.4] mmol/L [153 (43) mg/dL]) compared with insulin lispro (10.6 [2.0] mmol/L [191 (36) mg/dL];  $P = 0.001$ ).<sup>35</sup>

In patients with mild to moderate hyperglycemia (ie, A1C <8.5%), PPG excursions may play a clinically important role in metabolic disturbances.<sup>18</sup> However, the relative contribution of PPG diminishes with worsening of glycemic control (ie, A1C  $\geq 8.5\%$ ), and FBG becomes more dominant.<sup>18</sup> Therefore, in newly diagnosed type 2 DM patients with poor glycemic control (ie, A1C  $\geq 8.5\%$ ), the addition of basal insulin to manage FBG may be more beneficial compared with prandial insulin to control PPG, at least until the A1C level falls to <8.5%. Preliminary results have been reported from the APOLLO study—A 44-week, Parallel, open-label, randomized, multinational study comparing the efficacy and safety of an Oral regimen plus either Lantus QD or mealtime insulin Lispro in type 2 DM patients failing to improve with Oral treatment.<sup>40</sup> The study results suggest that while mealtime insulin lispro was associated with better control of PPG, and insulin glargine exerted better control of FBG, improvements in A1C were equivalent for both insulins. However, insulin glargine was associated with better nocturnal blood glucose control along with a lower incidence of hypoglycemia.<sup>40</sup>

### Premixed Insulin

The third option for the initiation of insulin in patients whose disease is not being controlled with oral therapy is premixed insulin. Nearly 40% of all patients with insulin-treated DM worldwide are treated using premixed insulin.<sup>41</sup> A recent study compared the efficacy of adding insulin glargine QD to OADs versus 70/30 premixed insulin BID in 371 patients with type 2 DM whose disease was insufficiently controlled by oral therapy.<sup>42</sup> The decrease in mean A1C levels from baseline was significantly more pronounced with insulin glargine plus OADs versus 70/30 premixed insulin (−1.64% vs −1.31%;  $P < 0.001$ ), as was the decrease in FBG (adjusted mean difference, −0.9 mmol/L [−17 mg/dL];  $P < 0.001$ ). Additionally, more patients reached glycemic targets (ie, A1C  $\leq 7.0\%$  and FBG  $\leq 5.5$  mmol/L [ $\leq 100$  mg/dL]) without confirmed episodes of nocturnal hypoglycemia using insulin glargine plus OADs than with 70/30 premixed insulin. Indeed, there were fewer confirmed hypoglycemic episodes with insulin glargine plus OADs than with 70/30 premixed insulin (mean, 4.07 vs 9.87 episodes/patient-year;  $P < 0.001$ ). Therefore, in patients poorly controlled with oral therapy, the addition of insulin glargine to OADs is safer and more effective than discontinuing oral therapy and initiating 70/30 premixed insulin BID.<sup>42</sup>

In a study comparing the addition of either BID biphasic insulin aspart (BIAsp 70/30) or insulin glargine versus metformin therapy (N = 233), more patients reached target A1C levels <7.0% with BIAsp 70/30 compared with insulin glargine (66% vs 40%;  $P < 0.001$ ), and the reduction in A1C was greater with BIAsp 70/30 (-2.79% vs -2.36%;  $P < 0.01$ ).<sup>43</sup> However, in this study, BIAsp 70/30 was also associated with a greater incidence of hypoglycemia (3.4 vs 0.7 episodes/year;  $P < 0.05$ ), greater weight gain (5.4 vs 3.5 kg;  $P < 0.01$ ), and higher insulin dosage (78.5 vs 51.3 U/d;  $P < 0.05$ ) at the end of the study, compared with insulin glargine.

## BARRIERS TO THE INTRODUCTION OF INSULIN THERAPY

Despite evidence supporting the early initiation of insulin therapy in patients with type 2 DM, many potential barriers to such treatment exist due to concerns from both patients and physicians. Concerns include the possibility of weight gain, a fear of injections, the belief that insulin regimens are complex, and skepticism that patients will follow the titration algorithms needed to achieve the stringent glycemic control targets.

Obesity is a major risk factor in the development of type 2 DM and, therefore, any treatment associated with weight gain is likely to be viewed with caution. Insulin therapy is generally associated with some weight gain due to the inhibition of glycosuria, the stimulation of lipogenesis, and by increased snacking to prevent hypoglycemia.<sup>44,45</sup> However, in studies of obese patients with type 2 DM, the weight gained was not sufficient to adversely influence cardiovascular risk factors such as blood pressure and lipid profiles; on the contrary, these parameters were improved.<sup>46,47</sup> The long-term clinical benefits of insulin treatment with respect to glycemic control appear to outweigh any risk from insulin-related weight gain. Weight gain can be minimized with the administration of the basal insulin analogues insulin glargine<sup>24</sup> or insulin detemir.<sup>29</sup> Insulin glargine QD and insulin detemir QD or BID are associated with significantly reduced weight gain compared with NPH insulin ( $P < 0.001$ <sup>24</sup> and  $P = 0.017$ ,<sup>29</sup> respectively) at equivalent levels of glycemic control. In contrast, multiple injections of the prandial insulin analogue insulin lispro are associated with increased weight gain compared with NPH insulin.<sup>35</sup> Thus, the initiation of long-acting basal insulin analogues rather than prandial insulin should help to dispel reservations by patients and physicians regarding potential weight gain.

Patients and physicians may also be reluctant to start insulin therapy because they perceive the regimens to be complex. Indeed, some regimens necessitating 2 basal and 2 to 4 prandial insulin injections are complex and may deter patients with needle phobias. It is essential, therefore, that insulin regimens are acceptable to patients, particularly at initiation, to promote treatment adherence. It is unlikely that patients in the early stages of type 2 DM will require multiple insulin injections. The addition of basal insulin to existing oral therapy is usually sufficient to achieve glycemic

control. Indeed, a regimen of bedtime insulin glargine or NPH insulin added to existing oral therapy was sufficient to bring ~60% of patients with inadequately controlled disease (ie, A1C >7.5%) to target levels (ie, A1C ≤7.0%).<sup>23</sup> However, rates of confirmed hypoglycemia (blood glucose ≤4.0 mmol/L [72 mg/dL]) were lower with insulin glargine compared with NPH insulin (9.2 vs 12.9 events/patient-year, respectively;  $P < 0.005$ ). Short-acting insulin analogues administered before meals to target PPG are also effective in attaining glycemic control in combination with oral therapy.<sup>35</sup> However, the multiple injections required before every meal are again likely to be less attractive than a QD injection of basal insulin.

## GUIDELINES FOR INTRODUCING INSULIN THERAPY

The evidence for initiating insulin therapy in patients with type 2 DM whose disease is not being controlled with oral therapy is clear, and the support for initiating insulin at an earlier stage of the disease is mounting. To ensure that insulin regimens are acceptable to patients and implemented by physicians, they should be as simple and efficient as possible. Recent studies have demonstrated the effectiveness of simple titration regimens for the initiation of basal insulin.

The evidence for initiating insulin therapy in patients with type 2 DM whose disease is not being controlled with oral therapy is clear, and the support for initiating insulin at an earlier stage of the disease is mounting. To ensure that insulin regimens are acceptable to patients and implemented by physicians, they should be as simple and efficient as possible.

The Treat-to-Target Trial<sup>23</sup> compared the abilities of insulin glargine and NPH insulin to reduce A1C levels to a target of <7.0% when added to ongoing oral therapy in type 2 DM patients whose disease is poorly controlled. The study used a simple algorithm for insulin dosage titration seeking a FPG target of ≤5.5 mmol/L (≤100 mg/dL). Daily insulin doses were increased by 2, 4, 6, or 8 units on a weekly basis, depending on the preceding 2 days' FPG values. At end point, both insulins reduced mean A1C levels from 8.6% at baseline to 7.0% at end point, with ~60% of patients achieving A1C levels ≤7.0%. Mean FPG levels were 6.5 mmol/L (117 mg/dL) with insulin glargine and 6.7 mmol/L (120 mg/dL) with NPH insulin. However, the risk of hypoglycemia was considerably less with insulin glargine than with NPH insulin (symptomatic hypoglycemia: 13.9 vs 17.7 events/patient-year;  $P < 0.02$ ). The authors concluded that one factor in the success of the study was the level of patient adherence to the treatment protocol. Reported levels of patient adherence were 90%, indicating that this regimen was easy to follow.<sup>23</sup> The treat-to-target approach has also been investigated with insulin detemir versus NPH insulin.<sup>48</sup> In this study (N = 476), improvements in A1C were similar with

both insulin formulations, but the risk of hypoglycemia was reduced with insulin detemir (by 47%;  $P < 0.001$ ) compared with NPH insulin and mean weight gain was lower with insulin detemir (1.2 vs 2.8 kg;  $P < 0.001$ ). The results from these 2 studies show that the treat-to-target approach offers a straightforward method by which basal insulin can be introduced to patients with type 2 DM.

The goal of the LANMET study<sup>49</sup> was to determine if good glycemic control could be achieved in insulin-naïve patients with type 2 DM by the use of insulin and infrequent physician visits (every 3 months), self-monitored FPG, and self-adjusted insulin doses. Patients ( $N = 110$ ) were randomized to receive metformin oral therapy with either bedtime insulin glargine or NPH insulin (titrated to a target FBG of 4.0–5.5 mmol/L [72–100 mg/dL]). Patients increased their insulin dose by 2 units every 3 days if all FPG values were above target. At end point, FPG averaged 5.7 mmol/L (103 mg/dL) with insulin glargine and 6.0 mmol/L (108 mg/dL) with NPH insulin. Mean plasma glucose was lower in the insulin glargine group versus the NPH insulin group before dinner (8.6 vs 10.1 mmol/L [155 vs 182 mg/dL];  $P = 0.002$ ). A1C levels decreased from baseline to end point in both treatment groups (insulin glargine, 9.13% to 7.14%; NPH insulin, 9.26% to 7.16%). Symptomatic hypoglycemia was 44% more frequent with NPH insulin versus insulin glargine (8.0 vs 5.4 episodes/patient-year;  $P = 0.12$ ).<sup>49</sup>

Another study demonstrated that simple titration regimens for the initiation of insulin glargine in patients with type 2 DM are effective in diverse clinical settings.<sup>50</sup> The AT.LANTUS study—A Trial comparing Lantus Algorithms to achieve Normal blood glucose Targets in subjects with Uncontrolled blood Sugar—was a large (611 patients), multicenter, multinational (59 countries) study employing 2 simple insulin glargine algorithms. Algorithm 1 was physician led and similar to that used in the Treat-to-Target Trial<sup>23</sup> with daily insulin glargine doses increasing by 2, 4, 6, or 8 units on a weekly basis depending on the preceding 3 days' FBG values. With algorithm 2, patients self-adjusted their basal insulin every 3 days depending on FBG values, as in the LANMET study.<sup>49</sup> At end point, there was a significant reduction in A1C levels with both algorithms but a greater decrease ( $P < 0.001$ ) with algorithm 2 (–1.22%) versus algorithm 1 (–1.08%).<sup>50</sup> Similarly, the reduction in FBG was slightly greater ( $P < 0.001$ ) with algorithm 2 (–3.4 mmol/L [–62 mg/dL]) versus algorithm 1 (–3.2 mmol/L [–57 mg/dL]).

Both the LANMET<sup>49</sup> and AT.LANTUS<sup>50</sup> studies confirm that good glycemic control can be achieved with a simple basal insulin regimen, and they highlight the ability of patients to successfully self-monitor and self-adjust their basal dose. Patients can therefore be encouraged to participate in the management of their disease, and this empowerment may encourage treatment adherence.

Initiation of insulin therapy using a basal analogue with adequate titration allows FBG levels to be normalized; all other glycemic states will decrease proportionally, thereby improving overall glycemic control. If insulin therapy is ini-

tiated early enough, and A1C levels are not too high, the risk of weight gain is particularly low with basal insulin analogues.<sup>23,48</sup> Initiating insulin treatment with basal insulin also facilitates the intensification of therapy to a more physiologic basal-bolus regimen. Indeed, owing to the progressive nature of type 2 DM, the basal insulin regimen will need to be intensified over time. Increasing the basal insulin dose may be attempted, but this strategy can increase the risk of hypoglycemia and will not address elevated PPG levels, which may no longer be controlled with OADs. Although exogenous basal insulin helps to control blood glucose levels throughout the day, patients may need to advance to basal-bolus therapy, whereby a prandial fast-acting insulin analogue is introduced to further control PPG. Treatment could begin with basal insulin and follow with the addition of 1 prandial injection before the largest meal of the day, followed by the stepwise introduction of further prandial injections as required. The Opposing Step-by-Step Insulin Reinforcement to Intensified Strategy Study is under way investigating the stepwise approach of introducing bolus insulin.<sup>51</sup>

## DISCUSSION AND CONCLUSIONS

Accumulating evidence recommends the early introduction of insulin therapy to prevent or delay DM-associated complications; however, the best method of initiating insulin remains a subject of debate. Given the progressive nature of type 2 DM, it is imperative that treatment regimens should be tailored to the glycemic needs of each individual patient and that they should adapt to changing needs as the disease advances. The treat-to-target approach of initiation with a basal insulin analogue followed by stepwise intensification to basal-bolus therapy permits this individualization. The simplicity and flexibility of dosing may result in greater patient compliance and, thus, improved glycemic control. Although adding prandial insulin therapy to oral therapy can be effective, the multiple daily bolus injections required may be a barrier to treatment adherence in insulin-naïve patients.

Although it is clear that both FBG and PPG levels contribute to glycemic control, several arguments lead to the conclusion that FBG levels should first be normalized in patients with newly diagnosed type 2 DM. In light of the evidence outlined in this review, it can be concluded that the addition of a long-acting basal insulin analogue to oral therapy is effective in achieving glycemic control targets in patients with type 2 DM while minimizing the risk of hypoglycemia and weight gain. This is also reflected in the recent joint consensus statement from the ADA and the European Association for the Study of Diabetes, which advocates the early use of insulin and that initial insulin therapy should target fasting glucose.<sup>52</sup> The early initiation of a basal insulin analogue also provides a foundation for treatment that allows patients to add or adjust other therapies as necessary. The insulin regimen should be intensified gradually with the introduction of prandial insulin to enable patients to achieve glycemic control targets.

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