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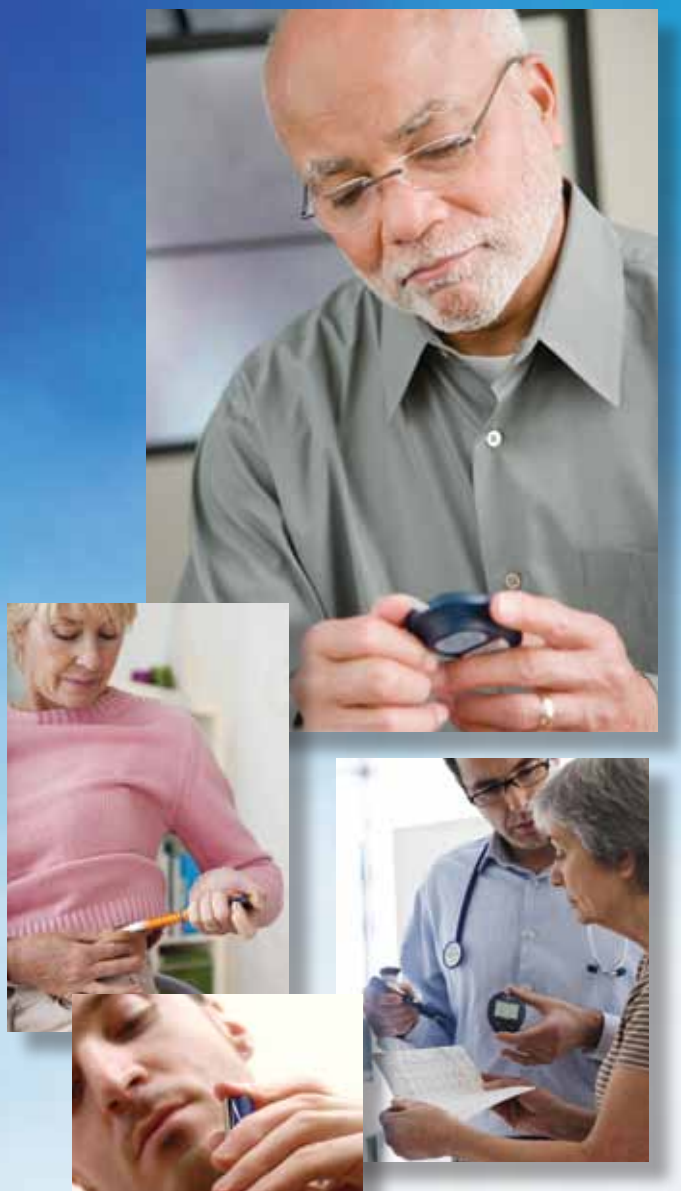

# Update On Insulin Management in Type 2 Diabetes

## FACULTY AND AFFILIATIONS

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## LEARNING OBJECTIVES

After reading this supplement, the family physician will be able to:

- Compare the pharmacokinetics and pharmacodynamics of rapid-acting and long-acting insulin analogs with recombinant human insulins
- List the features of pens and other devices used to deliver insulin
- Describe the role of insulin in the management of patients with type 2 diabetes mellitus
- Identify strategies to address patient barriers to insulin therapy
- Identify different approaches to initiate insulin therapy
- Describe the results of phase 3 trials of ultra–long-acting insulin degludec

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## FACULTY DISCLOSURES

Dr. Brunton disclosed that he is on the advisory boards and speakers' bureaus for Eli Lilly, KOWA, and Novo Nordisk.

Dr. Heile disclosed that he is on the advisory board and is a speaker for Novo Nordisk, and is a speaker for Amylin Pharmaceuticals.

Dr. Schneider disclosed that he is on the advisory board for Novo Nordisk.

Dr. Meneghini disclosed that he is on the advisory board and is a consultant for Novo Nordisk, is on the advisory board for Sanofi Diabetes, is a consultant for Valeritas, and has received grants or research support from Boehringer Ingelheim, Mannkind, and Pfizer. Dr. Meneghini is also a self-managed stock/shareholder in Dexcom.

Dr. Reid disclosed that he is on the advisory boards and speakers' bureaus for Novo Nordisk and Sanofi.

Dr. King disclosed that he is a speaker and consultant for, and has received research support from, Eli Lilly, Novo Nordisk, and Sanofi.

# Update on Insulin Management in Type 2 Diabetes




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# Introduction

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The clinical milieu of type 2 diabetes mellitus (T2DM) is undoubtedly one of the most challenging faced by family physicians. The association of T2DM with other chronic diseases, such as hypertension, dyslipidemia, cardiovascular disease, and obesity, speaks to the complex issues that must be addressed. Considering the complexity of these issues, it is important to recognize that, as a chronic disease, T2DM is largely self-managed and patients mostly control their own DM-related health outcomes. To assist patients with T2DM to successfully take on this responsibility, family physicians should raise and discuss the treatment options available to achieve agreed upon goals, and, in consultation with the patient, recommend treatment options that best address the patient's clinical issues and meet the patient's needs. These steps are important to help motivate the patient and promote long-term treatment adherence. Among the treatment options available for T2DM, the challenges of self-management are perhaps greatest with insulin.

Insulin is the most physiologic and effective glucose-lowering agent available, and is recommended as glucose-lowering therapy over the spectrum of T2DM.[1,2] Yet studies show that the initiation of insulin treatment is often delayed, sometimes for years, following loss of glycemic control with oral glucose-lowering agents.[3,4] Once initiated, adherence to insulin tends to be moderate at best.[5,6] It is crucial that family physicians address the issues that contribute to low levels of acceptance and adherence to insulin treatment. In addition, physicians need a firm understanding of how to initiate, modify, and intensify insulin therapy. The primary goal of this supplement is to provide the family physician with a detailed understanding of the current recommendations for, and advances in, insulin treatment.

This supplement includes three articles; the first of which is a historical review of the discovery of insulin. Also included in that article, by Michael Heile, MD, and Doron Schneider, MD, FACP, is a review of the evolution of insulin, including a comparison of the clinical pharmacology of human and analog insulins. The second article begins with a discussion of the conceptual strategies to address patient barriers that have a dramatic impact on the acceptance of, and self-management with, insulin. Building on that foundation, Luigi Meneghini, MD, MBA, and Timothy Reid, MD, present 4 case studies that detail how to assist patients in the implementation of these strategies when initiating or intensifying insulin therapy. The case studies also provide practical considerations with respect to dosing basal, basal-bolus, and premixed insulin. The third article examines advances in insulin, with a focus on the investigational agent, ultra–long-acting insulin degludec. Allen King, MD, provides a solid foundation of the clinical pharmacology of insulin degludec and the clinical experience to date regarding the use of insulin degludec in patients with type 1 DM or T2DM.

It is hoped that the information in this supplement will prove helpful for the practicing family physician in managing patients with this increasingly common disease and its associated clinical dilemmas. ■

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# The Evolution of Insulin Therapy in Diabetes Mellitus

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## Discovery of Insulin

The discovery of insulin in 1921 by Banting and Best ushered in a new age of treatment—and hope—for patients with diabetes mellitus (DM). First administered to 14-year-old Leonard Thompson on January 11, 1922, insulin transformed the lives of patients with type 1 DM (T1DM). No longer were starvation diets the primary mode of treatment.[1,2] Life saving in patients with T1DM, insulin has since become an important treatment option in patients with type 2 DM (T2DM) as well.

But as is often the case with medical breakthroughs, the discovery of the hormone that first reversed diabetic coma in dogs was only the beginning. Recognizing the crudeness of the pancreatic extract that he called *isletin* (after the islets of Langerhans, the insulin-producing tissue of the pancreas), Banting turned to chemist James Collip, also at the University of Toronto, who developed a process to remove the toxins and impurities from the pancreatic extract. Banting also recognized the limitation of using dogs as the source of isletin (the name of which was changed to *insulin* by the university) so he quickly turned to cattle as a more plentiful source. Not surprisingly, the demand for insulin skyrocketed within months of its first testing in humans by Banting and Best, so, in July 1922, licenses for the manufacture of insulin were given to several pharmaceutical companies.[1,2]

## Evolution of Insulin

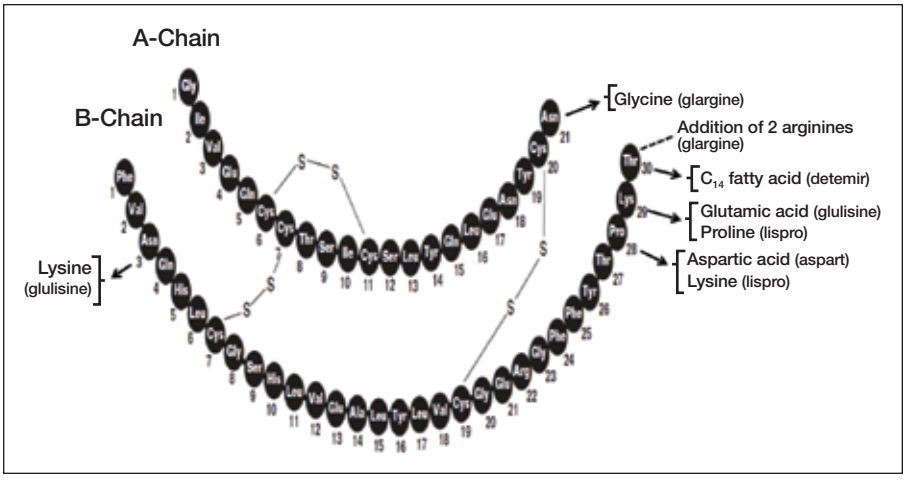
While the clinical effects of insulin in patients with T1DM were dramatic, such as waking people from diabetic coma, enabling them to consume a normal diet, and improving long-term prognosis, problems were encountered.[2] One was the challenge of balancing normoglycemia without causing hypoglycemia. The early insulin preparations acted relatively quickly and had a peak effect, but they did not provide a continuous, low level of basal insulin in the same manner as did pancreatic β cells. The time-action profile was, therefore, far from physiologically similar to endogenous insulin. The second problem was allergic reactions since the source of the insulin was nonhuman.[2] Resolving these issues was the focus of intensive research over many decades.

To better balance normoglycemia without causing hypoglycemia, intermediate- and long-acting insulins were subsequently developed as basal insulins to prolong the duration of effect. Discovered in 1936, neutral protamine Hagedorn (NPH) insulin was released in 1950 as an intermediate-acting basal insulin.[3] Although NPH insulin remains widely used today, recent guidelines have recommended against its use since the availability of insulin analogs (detemir and glargine), which provide a relatively flat profile for 24 hours and "yield better reproducibility and consistency, both between patients and within patients, with a corresponding reduction in the risk of hypoglycemia."[4] Other basal insulins such as Lente and Ultralente were introduced in the 1950s and used extensively for many years,[3] but they had important limitations, such as wide variability in absorption and duration of effect, which led to inconsistent blood glucose control.

Along with efforts to prolong the duration of action of insulin, much scientific work was undertaken to reduce the risk for the allergic reactions first encountered with canine insulin, and then with bovine and porcine insulins.[3] While the purity

**FIGURE 1** Modifications of human insulin to make insulin analogs

**Arrows denote substitution; dashed line denotes addition**




of these formulations improved over time with advances in chromatography, allergic reactions remained a limitation for some patients. The use of animal-derived insulins eventually gave way to synthetic human insulins, first approved by the US Food and Drug Administration in 1982.[5] Consisting of the same amino acid sequence as insulin secreted by the human pancreas, synthetic human insulins are less likely to cause allergic reactions and have a faster onset and shorter duration of action compared with animal-derived insulins. The short-acting regular human insulin has now been largely replaced by rapid-acting insulin analogs (aspart, glulisine, and lispro) because the analogs are more physiologically similar to endogenous insulin and provide improved safety and tolerability.[4] While allergic reactions do occur with insulin analogs, the prevalence is low.[6-17]

## Insulin Analogs

Some of the early insulin formulations included zinc for the binding of insulin to protamine to alter the pharmacokinetic properties of the drug. With the availability of recombinant DNA technology, it became possible to modify the insulin structure so as to yield analogs of human regular insulin with pharmacokinetic and pharmacodynamic properties that more closely mimic the effects of endogenous insulin secreted by the pancreas (**FIGURE 1**). Two groups of insulin analogs were developed: (1) those with an onset of action more rapid than that of regular human insulin (ie, the rapid-acting insulin analogs); and (2) those with a duration of action longer than that of NPH human insulin (ie, the long-acting basal insulin analogs) (**TABLE 1**).[18-23] Premix insulin formulations are also available that combine a rapid-acting insulin analog with its intermediate-acting protamine suspension.

### Rapid-Acting Insulin Analogs

The pharmacokinetic and pharmacodynamic profiles of the rapid-acting insulin analogs have been compared with those of short-acting regular human insulin. Many of those investigations have used the euglycemic clamp technique, which allows for the assessment of insulin absorption and insulin activity through simultaneous intravenous infusion of insulin and glucose to maintain a consistent glucose level, with close monitoring of blood glucose levels. Investigations have generally not measured the onset of biologic activity directly but have measured surrogate markers, such as the time to maximum plasma concentration ($t_{max}$). One comparison reported a $t_{max}$ of 70 minutes for insulin aspart compared with 129 minutes for regular human insulin, and 42 minutes for insulin lispro compared with 101 minutes for regular human insulin.[24,25]

Onset of activity, duration of activity, and glucose-lowering effect are dependent on absorption of the insulin molecules from the injection site. Variability in absorption has been a limitation of some insulins, but variability is lower with the rapid-acting insulin analogs. The variability of $t_{max}$ between injections in the same patient with insulin aspart and regular human insulin has been reported to be 15% and 24% ($P < .05$), respectively. The respective variability of $t_{max}$ between individuals was 20% and 37% ($P < .001$).[24] Greater variability in $t_{max}$ may contribute to greater variability in blood glucose levels as well as risk of hypoglycemia.

The shorter onset of action of the rapid-acting insulin analogs more closely mimics the postprandial physiologic profile of endogenous insulin secretion and activity relative to regular human insulin. Thus it would be expected that the rapid-acting insulin analogs may be administered within 15 minutes of a meal compared with the necessary 30 minutes with regular human insulin. The shorter preprandial administration time with the rapid-acting insulin analogs may improve patient-perceived convenience. Treatment outcomes may also be improved due to less potential for insulin administration to be followed by a missed or incompletely eaten meal.

Because the rapid-acting insulin analogs are more physiologically similar to endogenous insulin and provide a more rapid onset and time to peak activity relative to regular human insulin, the frequency of severe hypoglycemia observed with the rapid-acting insulin analogs after meals

**TABLE 1** Insulins commonly used in the United States[18-23]

| Generic | Brand | Form | Time of action (h) | | |
|---|---|---|---|---|---|
| | | | Onset | Peak | Duration |
| **Bolus or prandial insulin** | | | | | |
| Rapid-acting | | | | | |
| Aspart | Novolog | Analog | <0.25 | 1-3 | 3-5 |
| Glulisine | Apidra | Analog | <0.25 | 1-2 | 3-4 |
| Lispro | Humalog | Analog | <0.25 | 1-2 | 3-4 |
| Short-acting | | | | | |
| Regular | Humulin R; Novolin R | Human | 0.5-1 | 2-3 | 3-6 |
| **Basal insulin** | | | | | |
| Intermediate-acting | | | | | |
| NPH | Humulin N; Novolin N | Human | 2-4 | 4-10 | 10-16 |
| Long-acting | | | | | |
| Detemir | Levemir | Analog | 1-2 | Relatively flat | ≤24 |
| Glargine | Lantus | Analog | 1-2 | Relatively flat | ≤24 |

NPH, neutral protamine Hagedorn.

may be reduced.[26] A Cochrane review of 49 randomized controlled studies reported that the incidence of severe hypoglycemia with rapid-acting insulin analogs was approximately half that of regular human insulin in patients with T1DM (median, 21.8 vs 46.1 episodes/100 patient-years, respectively) and one fifth that in patients with T2DM (median, 0.3 vs 1.4 episodes/100 patient-years, respectively). However, the review also reported that the incidence of all hypoglycemic episodes with the rapid-acting insulin analogs was similar to that with regular human insulin, with similar glycemic control.[27] This finding contradicts our clinical experience which suggests that the incidence of hypoglycemia is lower with the rapid-acting insulin analogs compared with regular human insulin.

## Basal Insulin Analogs

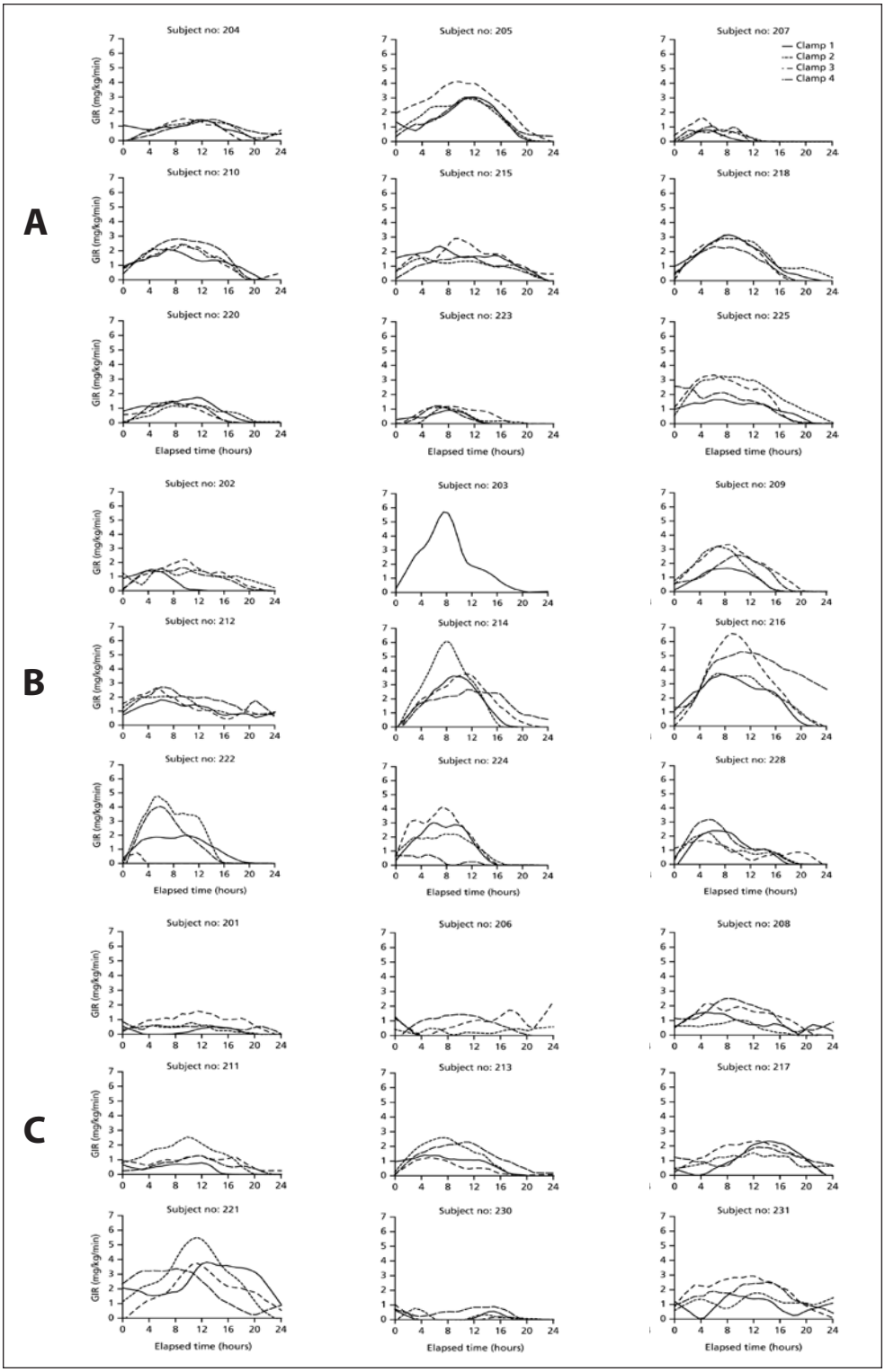
Approved in 2000, insulin glargine was the first basal insulin analog to become available in the United States. Insulin detemir was subsequently approved in 2005. Insulin glargine is formulated in an acidic solvent with pH 4.0 that forms stable hexamers following subcutaneous injection. For insulin detemir, modification of the insulin structure to include a long-chain fatty acid facilitates self-association and binding to serum albumin.[28] Through these different mechanisms, both insulin detemir and insulin glargine are slowly absorbed following subcutaneous administration, such that they have a longer duration of action than does NPH insulin and a relatively flat time-concentration profile.

Also using the euglycemic clamp technique, the pharmacokinetic and pharmacodynamic properties of insulin detemir and insulin glargine were compared with those of NPH insulin in patients with T1DM or T2DM.[29-32] One study was a head-to-head comparison of insulin detemir, insulin glargine, and NPH insulin in 54 patients with T1DM.[32] Over the 24-hour period following the administration of 4 single subcutaneous doses of 0.4 U/kg, the time-action profiles (ie, the glucose infusion rates over time) of insulin detemir and insulin glargine were reported to be relatively flat, whereas that of NPH insulin had a more pronounced peak (**FIGURE 2**).[32]

Insulin detemir was reported to have significantly less intraindividual pharmacodynamic variability compared with insulin glargine and NPH insulin. The variability (as assessed by the coefficient of variation) of the glucose infusion rate area under the curve for the first 12 hours was 27% for detemir, 46% for glargine, and 59% for NPH insulin ($P < .001$ vs insulin glargine and NPH insulin). Over the first 24 hours, the coefficients of variation were 27% for detemir, 48% for glargine, and 68% for NPH insulin ($P < .001$ vs insulin glargine and NPH insulin). With respect to pharmacokinetics, the coefficients of variation of the maximum plasma insulin concentration were 18% for detemir, 34% for glargine, and 24% for NPH insulin.

Despite these pharmacodynamic and pharmacokinetic differences favoring the basal insulin analogs compared with

**FIGURE 2** **Individual time-action profiles (glucose infusion rates over time) of patients randomized to (A) insulin detemir, (B) NPH insulin, or (C) insulin glargine. The 4 euglycemic clamps in one subject are summarized in one plot[32]**






NPH insulin, evidence-based systematic reviews have concluded that overall glucose control is similar among the 3 basal insulins.[28,33] These findings should be interpreted cautiously since the basal insulins were generally administered once daily in the studies included in the systematic reviews, although a few studies used a twice-daily regimen for insulin detemir or NPH insulin.[28] Furthermore, some of the studies included in the systematic reviews used a treat-to-target design, in which equal glucose-lowering efficacy was maintained among treatments, thereby allowing comparisons of other insulin properties. An important difference between the basal insulin analogs and NPH insulin identified in the systematic reviews concerns hypoglycemia, particularly nocturnal hypoglycemia. Detemir and glargine were associated with significant reductions in nocturnal hypoglycemia compared with NPH insulin (both, relative risk [RR] = .54; $P < .001$). The risk for overall hypoglycemia was also reported to be lower with insulin detemir and insulin glargine compared with NPH insulin (RR = .68 and RR = .89, respectively; $P < .001$ and $P = .002$). The risk for severe hypoglycemia was similar for insulin glargine or insulin detemir compared with that of NPH insulin.

A recent meta-analysis comparing insulin glargine (once daily) to insulin detemir (once or twice daily) examined data from 4 trials

lasting 24 to 52 weeks and involving 2250 people.[34] The meta-analysis found no differences between the 2 basal insulin analogs with respect to glycemic control, as measured by the percentage of patients who achieved A1C ≤7.0% with or without hypoglycemia. In addition, no significant differences in overall, severe, and nocturnal hypoglycemia were identified. Insulin detemir was associated with less weight gain and insulin glargine with a lower number of injection-site reactions.

## Evolution of Insulin Delivery

In addition to progressive improvements in purity and the time-action profile of insulin, there have been major advances in the devices used to deliver insulin that provide clinicians greater flexibility to meet patients' needs and to resolve patients' concerns. Advances in delivery systems include pens with shorter, smaller gauge, highly polished needles; pens with a "dial-a-dose" gauge that is easier to read; easy portability; and insulin-prefilled pens. These advances improve ease of use and dosage accuracy, likely reduce injection pain, facilitate discrete use in public places, and increase patient acceptance and adherence.[35-42] Of note, however, insulin pens must never be used in more than one individual, even if a needle has been changed, as is sometimes done in institutions. A clinical reminder from the US Centers for Disease Control and Prevention in January 2012 cautioned against pen reuse and sharing, citing an incident in which more than 2000 individuals were potentially exposed to the transmission of bloodborne pathogens because of inappropriate reuse and sharing of insulin pens.[43] Another advance in insulin delivery is insulin-pump therapy, which has become even more promising with the advent of continuous glucose-monitoring devices and the availability of rapid-acting insulin analogs.

## Role of Insulin in Diabetes

Recently, insulin has been recognized as a key treatment option for patients with T2DM, and is no longer considered last-line therapy.[4,44] When used appropriately, insulin is the most effective glucose-lowering therapy available, with essentially no limit to the magnitude of glucose lowering. Insulin, particularly the insulin analogs, provides many treatment benefits, although some limitations remain.

## Benefits of Insulin

Basal-bolus therapy using the combination of a rapid-acting insulin analog and a basal insulin analog may closely mimic the release of insulin from the pancreatic β cells. The use of an insulin pump, which uses only a rapid- or short-acting insulin (rapid-acting analog preferred) may also provide insulin in a pattern that most closely mimics endogenous insulin secretion. The administration of insulin via an insulin pump may be a good treatment option in patients with T1DM or those with T2DM who require intensive basal-bolus therapy.

The reduction of microvascular complications, such as nephropathy, neuropathy, and retinopathy, by achieving intensive glycemic control with the use of insulin, has been well established in patients with T1DM or T2DM.[45-48] Nonetheless, the landscape of glycemic control changed with the completion of the Action to Control Cardiovascular Risks in Diabetes (ACCORD) trial, the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, and Veterans Affairs Diabetes Trial (VADT).[49,50,51] Based on the findings from those trials, caution is advised against the indiscriminate setting of very low glycemic targets. Findings from subanalyses of data from those trials suggest that while most patients are likely to achieve a microvascular benefit from intensive control, others may potentially be harmed by cardiovascular events. Those likely to benefit are those with short-duration DM, a long life expectancy, and no significant cardiovascular disease. Those who may be harmed and in whom an A1C goal <7.0% may not be appropriate are those with a history of severe hypoglycemia, a limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbidities, or long-standing DM in whom the more stringent A1C goal may be difficult to attain.[52]

## Misconceptions and Limitations Regarding Insulin

Insulin therapy is considered by some clinicians and patients to be the most complicated and time-consuming of the glucose-lowering therapies. Concerns about self-injection, the need for dosage adjustment, and cost, as well as the stigma of insulin as last-line therapy, are common. Additionally, in some studies with follow-up to 24 months, patients' adherence to insulin therapy has been reported to be 54% to 81% in patients with T2DM.[53-55] When used properly, insulin is the most efficacious glucose-lowering therapy and, therefore, may help motivate patients to adhere to insulin therapy. Hypoglycemia and weight gain are also common concerns of patients and clinicians, although insulin analogs are an improvement compared with older insulins. The risk for hypoglycemia requires that patients be educated regarding the signs and symptoms and actions to be taken should a hypoglycemic episode occur. Self-monitoring of blood glucose is required and is of crucial importance in patients using multiple insulin injections or insulin-pump therapy.[56] Devices for continuous glucose monitoring may also be used to reduce the incidence of hypoglycemia. Because weight gain associated with insulin therapy may be a demotivating factor in patients, lifestyle management and patient educa-

tion are essential. Education should include consequences of poor glycemic control and disease progression, and the expected benefits with regard to quality of life. Using a collaborative approach to individualize therapy and to match the type of insulin and insulin dosing with a patient's lifestyle habits, such as food intake and daily activities, fosters patient self-management and may help to minimize the risks and maximize the benefits of insulin therapy.

## Conclusions

Since its discovery nearly a century ago, insulin has evolved to greater purity, with pharmacokinetic and pharmacodynamic profiles that more closely resemble insulin secretion by the pancreas. The insulin analogs are now recommended for treatment of patients with T1DM or T2DM because they are better tolerated and more physiologically similar to endogenous insulin compared with older formulations, including human insulins. Insulin analogs delivered and monitored with current pens and devices provide clinicians with improved ability to better manage patients with DM. ■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# Individualizing Insulin Therapy

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Dr. Meneghini disclosed that he is on the advisory board and is a consultant for Novo Nordisk, is on the advisory board for Sanofi Diabetes, is a consultant for Valeritas, and has received grants or research support from Boehringer Ingelheim, Mannkind, and Pfizer. Dr. Meneghini is also a self-managed stock/shareholder in Dexcom. Dr. Reid disclosed that he is on the advisory board and speakers' bureau for Novo Nordisk and Sanofi.

The modern management of diabetes mellitus (DM) began with the discovery of insulin by Banting and Best in 1921 (see *The Evolution of Insulin Therapy in Diabetes Mellitus* in this supplement). Since that time, numerous additional classes of glucose-lowering agents have been introduced for the treatment of type 2 DM (T2DM). These medications primarily act by addressing 2 of the key defects of T2DM, insulin resistance and pancreatic β-cell dysfunction. T2DM is a progressive disease process that requires continued adjustment of therapy to maintain treatment goals. Most patients with T2DM will require insulin therapy at some point in their lives.

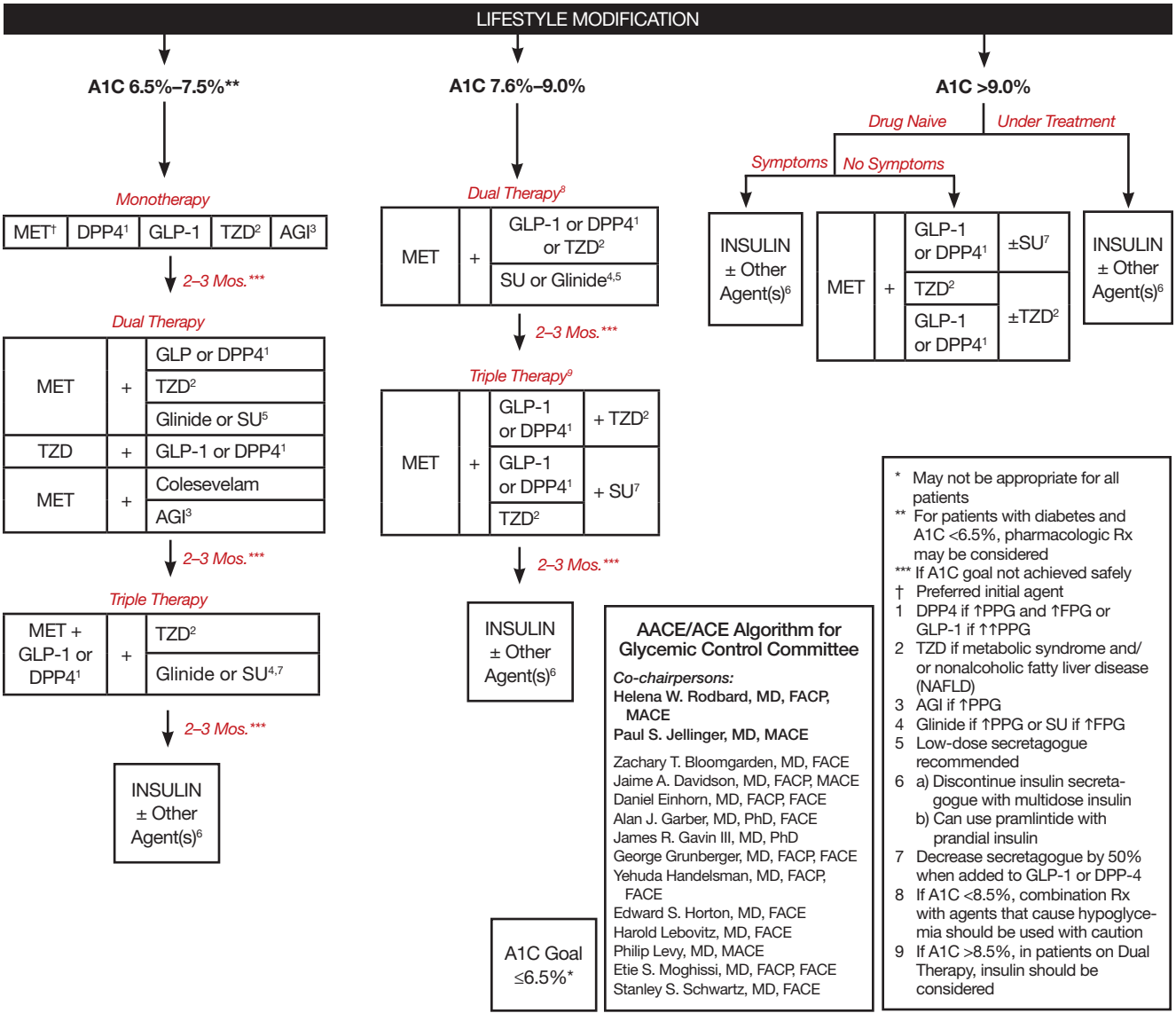
## Role of Insulin in Type 2 Diabetes Mellitus Management

Consensus guidelines developed by the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) recommend initiating insulin when oral therapy fails to achieve glycemic control, A1C > 9.0% in treatment-naïve patients, or if the patient is symptomatic with glucose toxicity (polyuria, polydipsia, and weight loss) (**FIGURE 1**).[1]

Similar consensus guidelines developed by the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) advise the initiation of glucose-lowering therapy for most patients with T2DM with the combination of lifestyle modifications, diet, and metformin (**FIGURE 2**).[2] For patients who do not achieve or maintain glycemic control over 3 months, or thereabouts, with metformin, a second oral agent should be added. Alternatives include a glucagon-like peptide-1 receptor (GLP-1R) agonist or basal insulin. Insulin should be strongly considered as initial therapy for a patient with significant symptoms of hyperglycemia and/or plasma glucose >300-350 mg/dL or A1C ≥10.0%.

The major role of insulin in the management of patients with T2DM stems from several important attributes. First, insulin is the only treatment that works in patients with advanced β-cell deficiency. It acts directly on tissues to regulate glucose homeostasis, unlike other glucose-lowering agents that require the presence of sufficient endogenous insulin to exert their effects as insulin sensitizers, secretagogues, incretin mimetics, amylin analogs, and other factors. This also means that the mechanism of action of insulin is complementary to those of other glucose-lowering agents. Second, there is less of a ceiling effect with insulin. That is, increasing the dose of insulin results in a progressive lowering of blood glucose in the majority of patients, with the major limitation being the risk for hypoglycemia. Third, the glucose-lowering efficacy of insulin is durable, unlike that of other glucose-lowering agents that depend on endogenous insulin secretion for continued effectiveness. Fourth, insulin improves the lipid profile, particularly triglyceride levels.[2-5] Fifth, regarding the long-term safety and tolerability of insulin, it is well established that weight gain, likely mediated via reduction of glycosuria, and hypoglycemia are typically the most concerning adverse events encountered. Allergic reactions, which were a more common complication of animal-sourced insulins, are infrequent with the insulin analogs.[6-17] Finally, the availability of insulin in different formulations allows for targeting fasting plasma glucose or postprandial glucose, and individualization of therapy (see *The Evolution of*

**FIGURE 1** **Role of insulin in the management of patients with type 2 diabetes mellitus according to the AACE/ACE[1]**




AACE, American Association of Clinical Endocrinologists; ACE, American College of Endocrinology; AGI, α-glucosidase inhibitor; DPP4, dipeptidyl-peptidase-4 inhibitor; FPG, fasting plasma glucose; GLP-1, glucagon–like peptide-1 agonist; MET, metformin; PPG, postprandial glucose; SU, sulfonylurea; TZD, thiazolidinedione.

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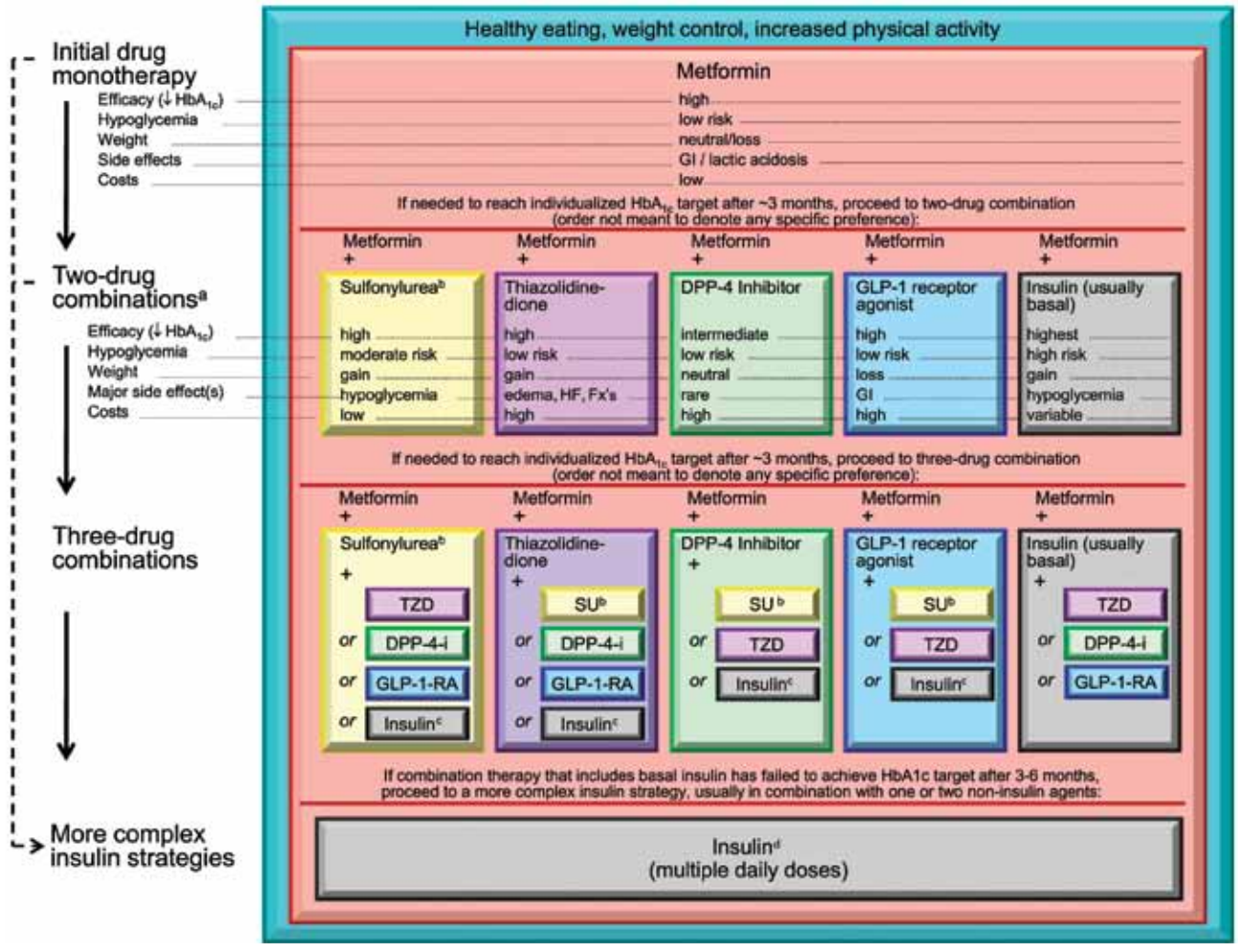
*Insulin Therapy in Diabetes Mellitus* in this supplement.)

While both the AACE/ACE and ADA/EASD consensus guidelines provide treatment "algorithms," both make it clear that these are suggested approaches suitable for the population with T2DM (**FIGURE 1, FIGURE 2**). The specific treatment approach must be individualized based on patient-specific factors such as age, comorbid conditions, and tolerance of hypoglycemia.

## Individualizing Therapy

The importance of individualizing therapy in a way that allows patients with T2DM to effectively self-manage their disease cannot be overstated. A study involving 1381 patients with T2DM cared for by 42 primary care physicians was conducted to estimate the magnitude of effect that physicians have on glycemic control.[18] Hierarchical linear modeling showed that physician-related factors were associated with a

**FIGURE 2** **Role of insulin in the management of patients with type 2 diabetes mellitus according to the ADA/EASD[2]**




Moving from the top to the bottom of the figure, potential sequences of antihyperglycemic therapy. In most patients, begin with lifestyle changes; metformin monotherapy is added at, or soon after, diagnosis (unless there are explicit contraindications). If the $HbA_{1c}$ target is not achieved after ~3 months, consider 1 of the 5 treatment options combined with metformin: an SU, TZD, DPP-4-i, GLP-1-RA, or basal insulin. (The order in the chart is determined by historical introduction and route of administration and is not meant to denote any specific preference.) Choice is based on patient and drug characteristics, with the over-riding goal of improving glycemic control while minimizing side effects. Shared decision making with the patient may help in the selection of therapeutic options. The figure displays drugs commonly used both in the United States and/or Europe. Rapid-acting secretagogues (meglitinides) may be used in place of SUs. Other drugs not shown (α-glucosidase inhibitors, colesevelam, dopamine agonists, pramlintide) may be used where available in selected patients but have modest efficacy and/or limiting side effects. In patients intolerant of, or with contraindications for, metformin, select initial drug from other classes depicted and proceed accordingly. In this circumstance, while published trials are generally lacking, it is reasonable to consider 3-drug combinations other than metformin. Insulin is likely to be more effective than most other agents as a third-line therapy, especially when $HbA_{1c}$ is very high (eg, ≥9.0%). The therapeutic regimen should include some basal insulin before moving to more complex insulin strategies. Dashed arrow line on the left-hand side of the figure denotes the option of a more rapid progression from a 2-drug combination directly to multiple daily insulin doses, in those patients with severe hyperglycemia (eg, $HbA_{1c}$, ≥10.0–12.0%).

DPP-4, dipeptidyl peptidase-4; DPP-4-i, DPP-4 inhibitor; Fx's, bone fractures; GI, gastrointestinal; GLP-1, glucagon-like peptide 1; GLP-1-RA, GLP-1 receptor agonist; $HbA_{1c}$, hemoglobin A1c; HF, heart failure; NPH, neutral protamine Hagedorn; SU, sulfonylurea; TZD, thiazolidinedione.

[a]Consider beginning at this stage in patients with very high $HbA_{1c}$ (eg, ≥9%); [b]Consider rapid-acting, non-SU secretagogues (meglitinides) in patients with irregular meal schedules or who develop late postprandial hypoglycemia on SUs; [c]Usually a basal insulin (NPH, glargine, detemir) in combination with noninsulin agents; [d]Certain noninsulin agents may be continued with insulin. Consider beginning at this stage if patient presents with severe hyperglycemia (≥16.7–19.4 mmol/L [≥300–350 mg/dL]; $HbA_{1c}$ ≥10.0–12.0%) with or without catabolic features (weight loss, ketosis, etc).



statistically significant but modest variability in A1C change (2%) for the entire patient group. On the face of it, this finding might be discouraging. Further analysis showed, however, that for patients whose A1C did improve, physician-related factors accounted for 5% of the overall change in A1C ($P$ = .005). On the other hand, physician-related factors had no

impact on patients whose A1C did not improve or worsened. These results support the role that physicians play in affecting patient outcomes. The results also make it clear that without a physician's influence, a patient's glycemic outcomes may be difficult to change. The question is: How best can a physician influence patient outcomes?

A 2011 survey of patients with DM, general practitioners, and DM specialists reported that clinicians tended to underestimate patients' perceived seriousness of the disease, while overestimating patients' level of distress. In addition, physicians had difficulty identifying which DM-related complications concerned patients most and the information and support patients needed to feel more at ease with DM. Patients placed greater importance on having easy access to their physicians rather than more time with them. But most importantly, the survey investigators concluded that patients generally wished for greater involvement in decision making and being provided more information.[19] These findings suggest that patients understand that T2DM is a largely self-managed, chronic disease, and want a collaborative relationship with their physician.

## Patient Barriers to Insulin Therapy

Numerous factors have been identified as impeding patients' willingness to initiate insulin therapy (**TABLE 1**).[20-24] Barriers often vary from patient to patient and, in fact, may change over time in an individual patient. It is crucial, therefore, to identify the root reasons for a patient's apprehension with insulin when talking about options for intensifying treatment. Once insulin has been initiated, the patient should be asked about continuing or new concerns regarding insulin therapy (and DM management in general), including adherence.

A recent, international survey of 1400 patients with insulin-naïve T2DM reported that 3 negative beliefs about insulin were prominent: (1) feeling that the disease was worsening; (2) fear of injection; and (3) a feeling of personal failure.[20] Certain patient comorbidities, such as poor eyesight, arthritis, and forgetfulness, might also serve as barriers to self-management of DM with insulin. Additional comorbidities may contribute as indirect barriers, such as the need for polypharmacy, which may make the initiation of additional treatments such as insulin logistically or financially difficult.

It is possible that the discussion about initiating insulin may uncover patient concerns about T2DM in general. The Diabetes Attitudes, Wishes, and Needs (DAWN) study reported that psychosocial issues were the major source of difficulty in patient self-management (**TABLE 2**).[25] In fact, 85% of people who reported a high level of distress at the time of diagnosis of T2DM continued to experience psychological distress at a mean follow-up of 15 years.

**TABLE 1 Barriers to insulin therapy identified by patients[20-24]**

| |
|---|
| Lack of understanding of serious nature of type 2 diabetes mellitus |
| Fear of addiction to insulin |
| Fear of hypoglycemia |
| Concern about weight gain |
| Repeated experiences of failing to achieve satisfactory glycemic control |
| Perception that quality of previous treatment was low |
| Needle phobia |
| Treatment complexity |
| Concern of social stigmatization |
| Perceived failure and low self-efficacy |
| Belief of becoming more ill |
| Out-of-pocket cost |
| Perceived negative impact on quality of life |
| Comorbidities such as poor eyesight, arthritis, forgetfulness |

**TABLE 2 Patients experiencing various aspects of diabetes-related distress[25]**

| Diabetes-related distress | Respondents who agree (%) |
|---|---|
| I feel stressed because of my diabetes. | 32.7 |
| I feel burned out because of my diabetes. | 18.1 |
| I feel that diabetes is preventing me from doing what I want to do. | 35.9 |
| I am constantly afraid of my diabetes getting worse. | 43.8 |
| I worry about not being able to carry out my family responsibilities in the future. | 30.1 |
| My diabetes causes me worries about my financial future. | 25.8 |
| My family and friends put too much pressure on me about my diabetes. | 14.7 |
| The community I live in is intolerant of diabetes. | 13.6 |



Addressing psychosocial issues and other barriers is crucial in the discussion of self-management because those with more negative feelings about starting insulin are most unwilling to start insulin.[20] One factor that may contribute to these negative feelings is repeated experiences of failing to achieve satisfactory glycemic control with oral glucose-lowering agents.[23] Conversely, those who have experienced improved glycemic control with intensification of prior glucose-

lowering therapy may be more accepting of initiating insulin therapy.[23,26] These findings are a reminder of the importance of a treat-to-target approach to management, in which the target glycemic goal, generally A1C < 7.0%, is achieved within 2 to 3 months of diagnosis and maintained at that level through intensification of therapy as needed.

Addressing psychosocial issues can be a challenge in today's busy primary care practice due to limited time and lack of training in the management of such issues. However, implementation of various strategies has been reported to facilitate and, in some cases, shorten a patient's visit. For example, one small study reported that visits were shorter if the physician acknowledged and responded positively to a patient's stated or implied concerns (17.6 minutes vs 20.1 minutes).[27] Missing or ignoring the patient's concerns often led the patient to bring up the same concern one or more additional times resulting in a longer office visit. These results underscore the importance of asking patients to identify their concerns or questions at the beginning of the office visit. The patient can fill out a questionnaire in the waiting room or be encouraged to write down and prioritize their questions and concerns specific to the visit. If the patient identifies more concerns or questions than can be reasonably addressed in one visit, there should be agreement to address the most pressing ones during the current visit and the remaining concerns and questions during the next visit. This "agenda-setting" approach has been reported to offer several advantages.[28] From the patient's perspective, the quality of the physician-patient interaction was much improved, in part because physicians took time to explain points in a way that was easy to understand. Advantages to the physician with an agenda-setting approach included "feeling more in control," "less stressed by simply knowing what was on the patient's mind," "feeling less rushed," and "enjoying patient encounters more." Contrary to the study cited above, physicians found that patients' visits often were longer, especially those of older patients. One physician, however, noted that the visit "takes more time now, but saves time later." As noted in this study, additional time spent with the patient can lead to improved job satisfaction for the physician.[29]

The agenda-setting approach requires that the physician ask the patient to list his or her concerns and questions, and then actively listen to the patient. Once the agenda for the visit is established, employing the "ask, listen, empathize" communication style can lead to effective physician-patient communication and problem-solving. Using this approach, the physician asks questions to gain a clear understanding of the patient's concerns and then uses active listening with little, if any, interruption.[30,31] Since the goal is to solve problems *with* rather than *for* the patient, active listening without offering opinions, judgements, or advice while offering empathy is essential. Through reflection and discussion, the physician can help the patient to identify his or her issues and acceptable solutions.

**TABLE 3** General strategies for initiating insulin therapy

| |
|---|
| Invite the patient to take an active role in treatment decisions. |
| Remind the patient that type 2 diabetes is primarily self-managed. |
| Discuss the progressive nature of β-cell dysfunction in type 2 diabetes. |
| Emphasize the physiologic role of insulin to maintain glucose homeostasis. |
| Discuss that insulin will help to achieve glycemic control and minimize the risk for long-term complications. |
| Discuss that treatment will be modified as needed to maintain glycemic control and to best meet their needs, capabilities, and interest. |
| Utilize insulin pen devices whenever possible. |
| Emphasize the importance of lifestyle management. |
| Ask if hearing other patients talk of their experiences with insulin therapy would be helpful; consider a group office visit. |
| Discuss and provide the patient with an individualized, written action plan that includes insulin dosing, self-monitoring of blood glucose, and signs/symptoms of hypoglycemia and other adverse events with appropriate action(s) to take. |
| Simplify diabetes (and comorbidities) treatment whenever possible. |

The importance of good communication between physician and patient cannot be overstated. Additional communication skills to keep in mind are: (1) speak slowly using nonmedical language; (2) limit the amount of information and repeat it; (3) draw pictures and/or use visual aids; and (4) ask the patient to repeat instructions and key concepts. In addition to enhancing patients' understanding, visual images may be particularly beneficial in keeping patients motivated to improve self-management, including adherence to therapy. For example, it may be helpful to graphically track the patient's glycemic progress. This can be done by establishing an actionable A1C goal (generally < 7.0%) and a time frame to achieve the goal (eg, 2 to 3 months).[32] A graph can be constructed beginning with the patient's current, preinsulin A1C level, with updates at each visit. In addition to motivating the patient and reinforcing adherence, the graph can also be used to demonstrate when further treatment intensification is needed. Additional general strategies that can be employed when considering the initiation of insulin are shown in **TABLE 3**. Implementation of strategies such as these by family physicians provides patient outcomes comparable to those implemented by endocrinologists or diabetes specialists.[33]

The remainder of this article uses case studies to further explore various patient barriers to insulin therapy and strategies for addressing them with the patient. While other thera-

**TABLE 4** Case study 1: Chart notes

| Physical examination | Laboratory tests | Lifestyle habits | Current therapy | |
|---|---|---|---|---|
| | | | Glucose-lowering | Other |
| BP: 126/80 mm Hg<br>Weight: 176 lb (79.2 kg)<br>BMI: 27 kg/m$^2$<br>Eyes: no retinopathy<br>Neurology: intact<br>Skin: intact | SCr: 1.4 mg/dL<br>Albuminuria: negative<br>A1C: 8.2%<br>Cholesterol:<br>Total: 204 mg/dL<br>LDL: 134 mg/dL<br>HDL: 36 mg/dL | Exercise: Walks 2 miles 3-4 d/wk<br>Nutrition: eats 3-4 meals/d | Metformin 1000 mg BID<br>Glimepiride 8 mg QD<br>Pioglitazone 45 mg QD | Lisinopril 30 mg QD<br>Simvastatin 40 mg QD<br>ASA 80 mg QD |

ASA, acetylsalicylic acid; BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SCr, serum creatinine.

pies may be appropriate in the case studies below as recommended by current guidelines, these case studies will focus on insulin. In addition, dosing strategies for initiating and intensifying insulin therapy are discussed. Changes to the treatment plan to adjust for comorbidities, such as hypertension and dyslipidemia, or for smoking cessation or aspirin therapy, are not addressed in these cases, but are crucial components of comprehensive management.

## CASE STUDY 1 ▶

RF is a 49-year-old female insurance analyst diagnosed with T2DM 6 years ago. Initial therapy with lifestyle modifications and metformin has since been intensified. Glimepiride was added, then pioglitazone was added 1.5 years ago when the A1C had risen to 7.5%. There is no evidence of cardiovascular disease. She reports bothersome lower extremity edema and an 8-pound weight increase since starting pioglitazone treatment. RF states that she takes her medications every day, although she acknowledges that she sometimes forgets on Sundays.

### Clinical Impression

After taking her history, performing a physical examination, and reviewing her laboratory and self-monitored blood glucose (SMBG) data, her physician concludes that her treatment plan needs to be changed (**TABLE 4, TABLE 5**).

### Treatment Plan

- Initiate basal insulin once daily in the evening.
- Continue glimepiride, but reduce pioglitazone to 15 mg once daily (or discontinue if cost is a concern).
- Ask RF to monitor fasting blood glucose and self-adjust insulin doses as appropriate.

### Barriers

While discussing the need to change the treatment plan and the physician's suggestion that RF begin basal insulin, RF asks her physician for another few months on her current regimen stating that she will try harder to take her medications on Sundays. She also voices concern that insulin treatment requires injections and that she is concerned about what her coworkers and friends might think. The physician confirms that these concerns are understandable; he also confirms that RF is fearful of needles. The following are possible responses that RF's physician could use to address these concerns.

**TABLE 5** Case study 1: Self-monitored blood glucose (mg/dL) over the previous 2 weeks

| Day | Fasting | 2 h Post-breakfast | 2 h Post-lunch | 2 h Post-dinner |
|---|---|---|---|---|
| Wednesday | | | | 205 |
| Thursday | 158 | | | |
| Friday | | 179 | | |
| Saturday | | 201 | 162 | |
| Sunday | | | | |
| Monday | 166 | | | |
| Tuesday | | | | 189 |
| Wednesday | | | | |
| Thursday | 153 | | | 221 |
| Friday | | | 150 | |
| Saturday | | 199 | 186 | 213 |
| Sunday | | | | |
| Monday | 181 | | | |
| Tuesday | 167 | | | |

**Patient's concern:** Perceived failure/low self-efficacy

**Physician responses:**

- We all forget to do things from time to time, but overall I think you have done a great job taking your medications.

- As we have talked about before, with T2DM there is a progressive loss of insulin production over time regardless of what you do. That is why we added glimepiride and then pioglitazone and that is why we need to make a change now and put you back in control of your diabetes. It is likely that further changes will be needed and we can discuss and agree on them together.

**Patient's concern:** Social stigmatization

**Physician responses:**

- We can begin by having you administer insulin once daily in the evening in the privacy of your home.
- The insulin can be administered with a device that looks like a pen. It is small and can be carried in your purse; it does not need to be refrigerated once opened. If the time comes that you will need to administer a dose of insulin during the day, you can easily administer the insulin discretely in a public restroom or your work area.
- The use of insulin is more common than it was even a few years ago. In fact, about 5 million people in the United States use insulin to replace what is missing, control blood sugars, and decrease the risk for diabetes complications.[34]

**Patient's concern:** Fear of needles

**Physician's responses:**

- Insulin can be injected using a pen device with short, ultrathin needles that makes most of the injections painless. I would like you to see how simple and painless the injection can be by using this sample pen here in the office.
- Many patients are concerned about giving themselves an injection at first, but they quickly become comfortable doing so.

## Dosing

Treatment with basal insulin can be initiated using one of several approaches. Using the treat-to-target approach, basal insulin 10 U once daily is initiated.[35] The starting dose should be reduced to 6 U if the initial pre-breakfast or pre-dinner blood glucose is < 126 mg/dL or the patient's body mass index (BMI) is < 26 kg/m$^2$.[36] Alternatively, the ADA/EASD recommends starting with 0.2 U/kg, which may be more practical in very overweight or obese patients.[2] Titration of the basal insulin dose can be accomplished using one of the following physician-directed or patient-driven treat-to-target titration algorithms (**TABLE 6**).[35,37,38] The insulin dose should be titrated based on the pre-breakfast fasting blood glucose level.

## Follow-Up Visit

RF begins basal insulin 10 U in the evening and is given simple instructions for insulin dose titration based on fasting plasma glucose results. At her follow-up visit, RF reports that she has

**TABLE 6** Physician-directed or patient-driven treat-to-target titration algorithms

| Riddle et al[35] | | Davies et al[37] | | | Meneghini et al[38] | |
|---|---|---|---|---|---|---|
| Start with 10 U/d bedtime basal insulin and adjust weekly | | Start with 10* U/d bedtime basal insulin and adjust weekly (physician-directed)<br>Or<br>Start with a dose numerically equivalent to the highest FPG (in millimoles/L)† over the previous 7 days and adjust every 3 days (patient-managed) | | | Start with basal insulin once daily and adjust every 3 days | |
| Mean of self-monitored FPG values from preceding 2 days | Change in insulin dose (U/d)# | Mean of self-monitored FPG values from preceding 3 days | Change in insulin dose (U/d) (physician-directed) | Change in insulin dose (U/d) (patient-managed) | Mean of self-monitored FPG values from preceding 3 days | Change in insulin dose (U/d) |
| ≥180 mg/dL | +8 | ≥180 mg/dL (≥10 mmol/L) | +6 to +8 | +2 | >110 mg/dL | +3 |
| 140-180 mg/dL | +6 | | | | 80-110 mg/dL | 0 |
| 120-140 mg/dL | +4 | 140-179 mg/dL (7.8-9.9 mmol/L) | +4 | +2 | <80 mg/dL | -3 |
| 100-120 mg/dL | +2 | 120-139 mg/dL (6.7 – 7.7 mmol/L) | +2 | +2 | | |
| | | 100-119 mg/dL (5.5-6.6 mmol/L) | 0 to +2 | 0 to +2 | | |

FPG, fasting plasma glucose.

*In insulin-naive patients. †For example, if the highest FPG over the previous 7 days was 7 mmol/L, start with 7 U. #Small insulin dose decreases (2-4 U/d per adjustment) were allowed if severe hypoglycemia (requiring assistance) or plasma-referenced glucose < 56 mg/dL was documented in the preceding week.

increased her basal insulin to 18 U administered once daily. Review of her SMBG results show that her blood glucose levels throughout the day have improved, but are still not at goal. RF's physician commends her on the progress she has made. RF and her physician agree that she should continue to increase her basal insulin dose. Eight months after beginning basal insulin, RF is administering 28 U (0.35 U/kg) of basal insulin in the evening. Review of her SMBG results over the previous 2 weeks show that her blood glucose rises during the day and is highest after dinner; her current A1C is 7.2%.

## Treatment Plan

- Discuss dietary and lifestyle complements to insulin therapy such as:
  - Reduce dinner calories, especially carbohydrates.
  - Eat dinner earlier.
  - Exercise in the afternoon or after dinner.
- Use SMBG to identify foods that raise her blood glucose.

## CASE STUDY 2 ▶

LW is a 64-year-old male with longstanding hypertension diagnosed with T2DM 8 years ago for which he was treated initially with lifestyle management and metformin. He has since been treated with other oral agents as add-on therapy; glipizide was discontinued due to hypoglycemia when he skips meals (usually lunch); pioglitazone was discontinued after the patient expressed concerns about the risk for bladder cancer he heard on television. He has mild retinopathy and mild loss of vibration sensation in the feet; there is no evidence of cardiovascular disease. He was diagnosed with osteoarthritis 3 years ago.

## Clinical Impression

After taking his history, performing a physical examination, and reviewing his laboratory and SMBG data, his physician concludes that his treatment plan needs to be changed (**FIGURE 3, TABLE 7, TABLE 8**).

## Treatment Plan

- Discontinue metformin since LW's serum creatinine is >1.5 mg/dL.
  - Alternatively, the dose of metformin could be reduced.
- Initiate either basal insulin once daily in the evening or premix insulin at dinner.
  - Alternatively, the acarbose and sitagliptin could be discontinued and a GLP-1R agonist initiated. If necessary, a basal insulin could then be added to improve the fasting blood glucose. [**Note:** the following combinations are not currently approved by the US Food and Drug Administration (FDA): exenatide twice daily and prandial insulin; exenatide once weekly and insulin; liraglutide and prandial insulin.]

**FIGURE 3** Case study 2: A1C levels for April 2004 to March 2012

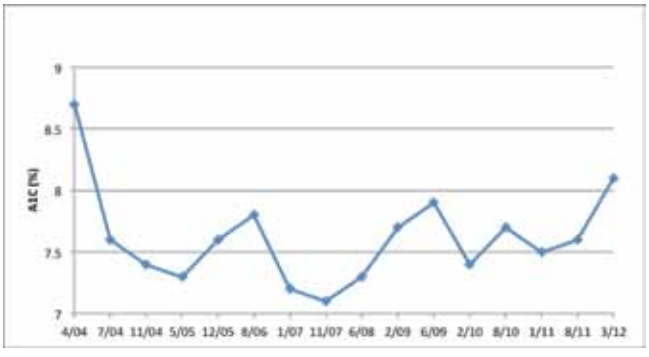



**TABLE 7** Case study 2: Chart notes

| Physical examination | Laboratory tests | Lifestyle habits | Current therapy | |
|---|---|---|---|---|
| | | | Glucose-lowering | Other |
| BP: 124/76 mm Hg<br>Weight: 204 lb (92.7 kg)<br>BMI: 31 kg/m$^2$<br>Eyes: mild retinopathy<br>Neurology: occasional tingling on bottom of right foot<br>Skin: intact | SCr: 1.9 mg/dL<br>eGFR: 51 mL/min<br>Albuminuria: negative<br>A1C: 8.1%<br>Cholesterol:<br>Total: 218 mg/dL<br>LDL: 118 mg/dL<br>HDL: 55 mg/dL<br>Triglyceride: 204 mg/dL | Exercise: takes dog on occasional walk but otherwise sedentary<br>Nutrition: eats 4 meals/d | Metformin 1000 mg BID<br>Acarbose 50 mg TID<br>Sitagliptin 100 mg QD | Lisinopril/HCTZ 20/25 mg QD<br>Amlodipine 10 mg QD<br>Acetaminophen extended-release 650 mg TID<br>ASA 80 mg QD |

ASA, acetylsalicylic acid; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HCTZ, hydrochlorothiazide; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SCr, serum creatinine.

**TABLE 8** Case study 2: Self-monitored blood glucose (mg/dL) over the previous 2 weeks

| Day | Fasting | 2 h Post-breakfast | 2 h Post-lunch | 2 h Post-dinner |
|---|---|---|---|---|
| Tuesday | 135 | | | |
| Wednesday | | | | |
| Thursday | | | | 196 |
| Friday | | 152 | 174 | |
| Saturday | | | | |
| Sunday | | | | 208 |
| Monday | 142 | | | 193 |
| Tuesday | | | | |
| Wednesday | 130 | 156 | | |
| Thursday | | | | |
| Friday | | | | |
| Saturday | | | | |
| Sunday | 151 | | | |
| Monday | | | | |

**TABLE 9** 1-2-3 Study algorithm[39]

| Pre-breakfast SMBG (mg/dL) | Adjustment of pre-dinner dose (U) |
|---|---|
| <80 | -3 |
| 80-110 | No change |
| 111-140 | +3 |
| 141-180 | +6 |
| > 180 | +9 |

SMBG, self-monitored blood glucose.

- Ask LW to monitor his blood glucose and self-adjust insulin doses as appropriate.
- Stress the importance of exercise and proper nutrition; gain agreement on short-term goals for exercise and nutrition.

## Barriers

LW's physician recommends that his treatment plan be changed and insulin therapy initiated. LW quickly responds that previous changes to his treatment regimen have not resulted in his achieving an A1C < 7.0%. He also doubts that he can use a syringe to draw up the correct dose and then self-administer due to his arthritis. The following are possible responses his physician could use to address these concerns.

**Patient concern:** Repeated experience of failing to achieve glycemic control, ie, A1C < 7.0%

**Physician responses:**

- While achieving an A1C < 7.0% is a realistic goal that reduces the risks for vascular complications of diabetes, any reduction of A1C will be of benefit.
- I would like to work with you to implement a new plan that we both believe will enable you to improve your diabetes control and ideally achieve an A1C < 7.0%.

**Patient concern:** Self-administering due to arthritis

**Physician responses:**

- Instead of using a syringe and vial to draw up and administer insulin, I would like you to use an insulin pen device. As you can see, it is easy to handle and you can easily select the correct dose.
- If you choose to start on premix insulin, the pen device contains both types of insulin together in one dose.

## Dosing

Treatment with basal insulin once daily in the evening can be initiated and titrated based on pre-breakfast blood glucose as in Case Study 1. Alternatively, treatment with premix insulin can be initiated at a dose of 12 U administered within 15 minutes of dinner initiation. The premix dose can be titrated using the algorithm employed in the 1-2-3 Study based on pre-breakfast blood glucose (**TABLE 9**).[39] After 16 weeks, 41% of patients in the 1-2-3 Study achieved an A1C < 7.0% from a baseline A1C of 8.6%.

## Follow-Up Visit

LW began basal insulin 10 U in the evening. Over the next 5.5 months, he titrated his dose such that his current dose is 46 U (0.50 U/kg) in the evening. His current A1C is 7.3%. Review of his SMBG shows consistently high 2-hour post-lunch blood glucose levels. Although further increasing his basal insulin dose is an option, in most of the treat-to-target studies, the daily dose of basal insulin given once daily averaged between 0.4 and 0.6 U/kg.[35,37,40,41] LW and his physician agree that adding rapid-acting insulin at lunch is the best option. The starting dose of rapid-acting bolus insulin is 4 to 6 U administered prior to the largest meal of the day or, as in this case, prior to the meal with the largest postprandial blood glucose excursion.[42,43] Alternatively, the dose of rapid-acting insulin could be calculated as 10% of the total daily dose of basal insulin, which in this case is 5 U (10% x 46 U). The dose of basal insulin would be reduced by 5 U if the rapid-acting insulin is given at dinner in order to reduce the risk for nocturnal hypoglycemia. The dose of the bolus insulin can be titrated using the

**TABLE 10** Algorithms for adjusting insulin aspart[42]

| ExtraSTEP algorithm | | SimpleSTEP algorithm | | |
|---|---|---|---|---|
| 2-h Post-meal PG level (mg/dL) | Insulin aspart adjustment (U) | Pre-meal BG (mg/dL) | Bedtime BG (mg/dL) | Insulin aspart adjustment (U) |
| <72* | -2 | <72* | <72* | -2 |
| 72-144 | 0 | 72-108 | 72-144 | 0 |
| 145-180 | +2 | 109-162 | 145-180 | +2 |
| >180 | +4 | >162 | >180 | +4 |

BG, blood glucose; PG, plasma glucose.
*One or more PG values <72 mg/dL without obvious explanation.

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**TABLE 11** Case study 3: Chart notes

| Physical examination | Laboratory tests | Lifestyle habits | Current therapy | |
|---|---|---|---|---|
| | | | Glucose-lowering | Other |
| BP: 142/88 mm Hg<br>Weight: 176 lb (79.2 kg)<br>BMI: 27 kg/m$^2$<br>Eyes: no retinopathy<br>Neurology: intact<br>Skin: intact | SCr: 1.4 mg/dL<br>Microalbumin:creatinine ratio: 140 mg/g creatinine<br>Ketonuria: 1+<br>A1C: 10.8%<br>Cholesterol:<br>Total: 210 mg/dL<br>LDL: 146 mg/dL<br>HDL: 30 mg/dL | Exercise: light yard work, no regular exercise<br>Nutrition: 3 meals/d, eats most meals in a restaurant (lunch M-F; dinner 3-4 nights/wk) | None | None |

BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SCr, serum creatinine.

ExtraSTEP algorithm (**TABLE 10**).[42] Alternatively, the SimpleSTEP algorithm can be used which does not require a 2-hour postprandial glucose measurement.[42]

## Plan

- Begin rapid-acting insulin 5 U at lunch.
- Continue basal insulin at 46 U in the evening.
- Ask LW to continue to titrate basal insulin based on the pre-breakfast blood glucose level and the lunch time bolus insulin dose based on the 2-hour post-lunch SMBG (ExtraSTEP); alternatively, adjust based on the pre-dinner blood glucose level (SimpleSTEP).

## CASE STUDY 3 ▶

MB is a 46-year-old male who had not consulted a physician since having a physical examination 6 years ago. He presented 2 weeks ago with frequent urination (7-8 times/day) and feeling tired; he also noted losing 5 pounds (2.25 kg) over the preceding 3.5 months despite no changes in his diet. MB is a regional salesperson with an erratic schedule. During the week, he eats lunch and most dinners in a restaurant. On the weekend, he goes to a local bar with his friends. He does light yard work, but does not exercise regularly. He is a current smoker with a 36 pack-year history. Urinalysis shows ketonuria and microalbuminuria. His A1C reported back today is 10.8%, confirming a diagnosis of uncontrolled and symptomatic DM.

## Clinical Impression

After taking his history, performing a physical examination, and reviewing his laboratory data, MB's physician confirms a diagnosis of DM (**TABLE 11**). While it is likely that MB has T2DM, his physician wants to rule out type 1 DM and latent autoimmune diabetes of the adult (LADA), so he orders tests for antibodies (GAD, IA-2, ICA). The antibody testing is negative, making T2DM the most likely diagnosis.

## Treatment Plan

- Initiate basal-bolus therapy with fixed bolus doses of rapid-acting insulin at each meal (prandial insulin).
- Ask MB to monitor blood glucose before meals and at bedtime.

- Provide MB with a supplemental scale to correct hyperglycemia before meals.
- Stress the importance of exercise and proper nutrition; gain agreement for short-term goals for exercise and nutrition; refer for diabetes and nutrition education if available.
- Discuss the importance of smoking cessation; develop a plan.
- Consider metformin and other non-insulin therapies when A1C is under control.

## Barriers

MB is surprised that he has T2DM and is clearly anxious at receiving the diagnosis. He expresses concern about starting insulin because his uncle died within a year of starting insulin. MB also recalls that his uncle was always giving himself shots and monitoring his blood glucose level. He wants to know whether there is a simpler treatment option if he agrees to start insulin treatment. He also wants to know whether he will have to remain on insulin for the rest of his life. The following are possible responses his physician could use to address these concerns.

**Patient concern:** Fear of death

**Physician responses:**

- Uncontrolled high blood sugars over a long period of time can cause serious complications, such as kidney and heart disease that can result in death. That is why it is important that we work together to gain control of your blood sugar levels over the next few months and then modify your treatment as needed to maintain control.
- Unfortunately for many patients in the past, treatment with insulin was not used until it was too late and people already had serious complications from DM. This is likely the case for your uncle.

**Patient concern:** Treatment complexity

**Physician responses:**

- Right now we have to control your blood glucose rapidly so your pancreas can regain some function and your body can better respond to insulin.
- I will also provide you with step-by-step written instructions you can follow that describe how to start insulin and how to monitor your blood glucose.
- We will communicate as often as you need to adjust your insulin doses over the next few weeks; when you feel comfortable, I can even show you how to adjust your insulin dose before a meal to correct a high blood sugar.
- We can try this treatment for 3 months and then reevaluate your response, how you feel, and whether you want to continue to modify your treatment plan to keep your blood sugars controlled.

**Patient concern:** Lack of understanding that T2DM is a serious disease

**Physician responses:**

- Please understand that T2DM is a serious disease that increases your risk for heart disease, stroke, blindness, and other diseases. Unfortunately, since diabetes does not cause bad symptoms until it is actually too late, many patients do not make the effort to properly control their diabetes. By working together, we can reduce the risk for these complications and do some screening tests to detect any complications before they become irreversible.

## Dosing

There are several approaches to determining the initial doses of basal and prandial (bolus) insulin. One approach is to estimate the total daily dose (TDD) of insulin by multiplying the patient's weight in kilograms by 0.5 U/kg/d.[44] Half of the TDD is given as basal insulin replacement; the other half is divided into 3 fixed preprandial doses of rapid-acting insulin. When the patient is ready to take on more complex management, the supplemental dose for bolus insulin can be calculated using a correction factor. If the bolus insulin is a rapid-acting insulin analog, 1800 is divided by the TDD of insulin; 1500 is used for a short-acting human insulin. This correction factor is an estimate of the fall in blood glucose per unit of bolus insulin. In our patient, the TDD would be: 80 kg x 0.5 U/kg/d or 40 U/d of insulin. Thus, 1 U of insulin should lower the blood glucose by about 45 mg/dL (1800/40 U = 45 mg/dL). For every 45 mg/dL above the pre-meal target, the patient would add 1 U of rapid-acting insulin to correct the hyperglycemia over the next 4 to 5 hours. The basal and prandial insulin doses would be titrated on a periodic basis (perhaps every 1 to 2 weeks) until the daytime levels of blood glucose are on target. The fasting (pre-breakfast) blood glucose would be used to adjust the basal insulin dose, while the pre-lunch, pre-dinner, and bedtime blood glucose results would be used to adjust the pre-breakfast, pre-lunch, and pre-dinner prandial (rapid-acting) insulin doses, respectively.

An alternative approach to initiating basal-bolus therapy is the PREFER algorithm.[45] Here, the basal insulin dose is 10 U initially. The bolus doses are administered in a 3:1:2 ratio, so if the total of the 3 bolus doses is 12 U/d, the initial bolus doses would be 6 (breakfast), 2 (lunch), and 4 (dinner) U. The mean basal (once-daily) and bolus insulin doses observed in PREFER are shown in **TABLE 12** and **TABLE 13**.

## Follow-up Visit

MB begins with basal insulin 20 U in the evening and bolus insulin at doses of 7 U before each meal. Over the next several months, MB has titrated his insulin doses; his current doses are: 32 U (basal), 11 U (bolus-breakfast), 7 U (bolus-lunch), and 10 U (bolus-dinner). He experienced 1 episode of mild hypoglycemia (SMBG, 50 mg/dL) one afternoon following a particularly active morning (**TABLE 14**). His current A1C is 7.4%. MB's physician con-

**TABLE 12** Case study 3: Calculating initial basal-bolus insulin doses

| Algorithm | Calculations | Patient MB |
|---|---|---|
| Meneghini[44] | TDD = (total body weight [kg]) (0.5 U/kg/d) | TDD = (0.5 U/kg/d)(80kg) = 40 U/d |
| | Basal insulin dose* = (50%) (TDD) | Basal = (50%) (40 U/d) = 20 U/d |
| | Bolus insulin dose† = (10%-20%) (TDD) | Bolus = (10%-20%) (40 U/d) = 4 to 8 U/meal |
| | | CF = 1800/40 U/d = 45 mg/dL per 1 unit |
| PREFER[45] | Basal insulin dose* = 10 U (14 U if BMI > 32 kg/m$^2$) | |
| | Bolus insulin dose† = ratio of 3:1:2 (breakfast:lunch:dinner) | |
| | **Note:** At week 26, the bolus insulin doses were divided into the 3 daily meals in approximately a 1:1:1 ratio | |

BMI, body mass index; CF, correction factor; TDD, total daily dose of insulin.

*Once daily; †Three meals per day.

**TABLE 13** Titrating the basal insulin dose using the PREFER algorithm[45]

| Pre-breakfast blood glucose (mg/dL) | Basal insulin dose adjustment (U) |
|---|---|
| < 56 | -4 |
| 56-72 | -2 |
| 73-125 | No change |
| 126-140 | +2 |
| 141-160 | +4 |
| 161-180 | +6 |
| 181-200 | +8 |
| > 200 | +10 |

**TABLE 14** Case study 3: Self-monitored blood glucose (mg/dL) over the previous 2 weeks

| Day | Fasting | 2 h Post-breakfast | 2 h Post-lunch | 2 h Post-dinner |
|---|---|---|---|---|
| Wednesday | | | | |
| Thursday | | | | 168 |
| Friday | 106 | 166 | 174 | |
| Saturday | 88 | | | |
| Sunday | | | | 195 |
| Monday | 134 | | | |
| Tuesday | | | | 172 |
| Wednesday | 130 | 156 | | |
| Thursday | 112 | | 168 | |
| Friday | 92 | | | 164 |
| Saturday | 50 | 149 | 159 | 176 |
| Sunday | 94 | | 174 | 210 |
| Monday | | 176 | | 184 |
| Tuesday | 117 | | | 169 |

gratulates him on the progress he has made in dramatically lowering his blood glucose level—and his risk for diabetes-related complications. While MB appreciates his physician's support and admits that he does not feel tired and generally feels better, which is likely due to resolution of glucotoxicity, he is not happy that he has gained 5.5 pounds (2.5 kg).[46] He also finds the timing and administration of bolus insulin difficult.

### Plan

- Continue basal insulin once-daily in the evening.
- Add metformin 500 mg BID and increase to 1000 mg BID as tolerated.
- Consider weaning down the bolus insulin doses and substituting them with a GLP-1R agonist, dipeptidyl peptidase-4 inhibitor, or short-acting secretagogue. If so, continue rapid-acting insulin during transition. [**Note:** the following combinations are not currently approved by the US FDA: exenatide twice-daily and prandial insulin; exenatide once-weekly and insulin; liraglutide and prandial insulin; linagliptin and insulin.]

## CASE STUDY 4 ▶

KW is a 62-year-old female diagnosed with T2DM 12 years ago. Treatment with lifestyle management and metformin initially provided glycemic control. Glimepiride was subsequently added and eventually the patient was started on basal insulin. The current dose of basal insulin is 60 U in the evening. Five months ago her A1C was found to be 7.9% and more recently 8.3%. She drinks alcohol occasionally and smokes. KW works as an executive secretary and has a consistent meal and activity schedule.

### Clinical Impression

Following completion of the history, physical examination, and review of her laboratory data, KW's phy-

**TABLE 15** Case study 4: Chart notes

| Physical examination | Laboratory tests | Lifestyle habits | Current therapy | |
|---|---|---|---|---|
| | | | Glucose-lowering | Other |
| BP: 126/78 mm Hg<br>Weight: 176 lb (79.2 kg)<br>BMI: 32 kg/m$^2$<br>Eyes: no retinopathy<br>Neurology: intact<br>Skin: intact | SCr: 1.0 mg/dL<br>Albuminuria: negative<br>A1C: 8.3%<br>Cholesterol<br>Total: 172 mg/dL<br>LDL: 96 mg/dL<br>HDL: 46 mg/dL<br>Triglycerides: 138 mg/dL | Exercise: sedentary<br>Nutrition: 3 meals/d with large dinner | Metformin 1000 mg BID<br>Basal insulin 60 U in the evening | ASA 80 mg QD<br>Pravastatin 40 mg qHS |

BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SCr, serum creatinine.

**TABLE 16** Case study 4: Self-monitored blood glucose (mg/dL) over the previous 2 weeks

| Day | Fasting | 2 h Post-breakfast | 2 h Post-lunch | 2 h Post-dinner |
|---|---|---|---|---|
| Friday | | | | |
| Saturday | 156 | | | 244 |
| Sunday | | 253 | | |
| Monday | | | | |
| Tuesday | | | | |
| Wednesday | 148 | | | 227 |
| Thursday | | | | |
| Friday | | | | |
| Saturday | | | 179 | |
| Sunday | 160 | | | |
| Monday | | | | |
| Tuesday | | | | |
| Wednesday | | | | |
| Thursday | | | | |

sician concludes that her insulin regimen should be intensified (**TABLE 15, TABLE 16**).

## Plan

- Discontinue basal insulin.
- Begin premix insulin twice daily before breakfast and dinner.
- Ask KW to monitor blood glucose two times daily and, if appropriate, teach her how to self-adjust insulin doses.
- Stress the importance of exercise and proper nutrition; gain agreement on short-term goals for exercise and nutrition.
- Discuss the importance of smoking cessation; develop a plan.

## Barriers

The physician discusses with KW that her consistent meal and activity schedule would make switching to premix insulin twice daily a good choice. KW is generally in agreement with the change, but wonders whether hypoglycemia might be more likely. She also asks if she might gain more weight in addition to the 3 pounds (1.35 kg) she has gained since starting basal insulin.

**Patient concern:** Hypoglycemia
**Physician responses:**

- Hypoglycemia remains a concern, and is more frequently seen with premix than with basal insulin; however, as long as you remain consistent with your meal and activity schedule, the risk for bad hypoglycemia is low.
- We should review your written action plan so that you are sure what signs or symptoms of a low blood sugar might occur and what you should do to treat them.

**Patient concern:** Weight gain
**Physician responses:**

- It is possible that you might gain a few additional pounds. You can avoid this by increasing your physical activity, and importantly, continue healthy eating. We should schedule a time for you to meet again with a dietician who can discuss options that might work for you.

## Dosing

There are different approaches for converting from basal insulin to twice-daily premix insulin. One approach is to determine the TDD of basal insulin, and give half at breakfast and the other half

at dinner as premix insulin.[39] Since KW is taking 60 U of basal in the evening, she should take 30 U at breakfast and 30 U at dinner. Dose titration is according to the 1-2-3 Study algorithm shown in case study 2.

Another approach is to administer biphasic insulin aspart 70/30 0.2 U/kg before breakfast and 0.1 U/kg before dinner as was done in the PREFER study (**TABLE 13**).[45] Subsequent dosing can be determined based on the PREFER algorithm below. Of note is that at study end, premix insulin doses were equally divided between breakfast and dinner. Breakfast and dinner doses are titrated based on blood glucose levels before dinner and breakfast, respectively. In the PREFER study, the use of premix insulin provided comparable A1C reduction as basal-bolus therapy (basal once daily + bolus TID) in insulin-naïve patients. However, patients previously treated with basal insulin such as KW experienced greater A1C reductions with basal-bolus insulin than with premix insulin. ■

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# Advances in Insulin Therapy: A Review of Insulin Degludec

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## Introduction

Basal insulin has been an important treatment option for patients with diabetes mellitus (DM) and, along with prandial insulin, has undergone major improvements in terms of purity and similarity to the action of physiologic human insulin. (see *The Evolution of Insulin Therapy in Diabetes Mellitus* in this supplement.) Lente and Ultralente formulations were used for decades but are no longer available. The use of neutral protamine Hagedorn (NPH) insulin is also being replaced with the basal insulin analogs detemir and glargine.[1] Basal insulin analogs generally cause less severe and nocturnal hypoglycemia compared with NPH insulin owing to their improved pharmacologic profiles.[2-4] In comparison to NPH insulin, insulin glargine causes similar weight gain, whereas insulin detemir causes less weight gain.[2-4] In addition, insulin detemir has been associated with a glucose-lowering effect that is more predictable than that of NPH insulin.[5] Despite the improvements observed with basal insulin analogs, their time-action profiles are not completely flat and are shorter than 24 hours in many patients.[5,6] In addition, severe hypoglycemia remains a concern, particularly in patients with type 1 DM (T1DM).[7,8] Consequently, the search for a better basal insulin continues.

The ideal basal insulin should possess numerous attributes. While each of the attributes listed in the **TABLE** is important, an overarching difficulty with basal insulin therapy is the need for administration at the same time each day.[9] This dosing limitation may be most difficult for those with busy or erratic schedules or who may forget to administer their insulin dose. This article will review the clinical experience with insulin degludec, an ultra–long-acting insulin under review by the US Food and Drug Administration (FDA).

## Clinical Pharmacology of Insulin Degludec

Removal of threonine at position 30 of the B chain of human insulin and the addition of a 16-carbon fatty diacid attached to lysine at position 29 of the B chain of human insulin via a glutamic acid spacer result in the insulin degludec molecule, which has several differences from available basal insulin analogs. Experimental investigations indicated that conditions mimicking subcutaneous injection of insulin degludec resulted in a reorganization of the insulin degludec molecule from dihexamers to multihexamer assemblies that remain in solution at physiologic pH.[10] Slow release of zinc ions from the multihexamers leads

**TABLE Attributes of the ideal basal insulin[9]**

| |
|---|
| Delivers a steady, stable, peakless, continuous insulin concentration for at least 24 hours, in a predictable manner, with low intraindividual and interindividual variability |
| Does not cause side effects such as weight gain or hypoglycemia |
| Does not induce mitogenicity |
| Can be used as monotherapy, as part of basal-bolus therapy, or in combination with oral glucose-lowering therapy |
| Equally efficacious, safe, and well-tolerated in patients with type 1 or type 2 diabetes mellitus |

to the slow release of insulin degludec monomers, which are easily absorbed into the systemic circulation.[11] The result is a half-life of insulin degludec that is longer than 24 hours, with a level that is detectable in circulation for at least 96 hours after administration of the dose.[10,12] The pharmacodynamic result is a relatively flat and consistent blood glucose–lowering effect with insulin degludec (**FIGURE 1**) reported to be longer than 24 hours in patients with T1DM or type 2 DM (T2DM).[11,12]

A randomized, double-blind, two-period, crossover comparison of insulin degludec and insulin glargine in patients with T1DM (N = 66) reported a half-life of 25.4 hours with insulin degludec compared with 12.5 hours with insulin glargine.[13] The serum exposure of insulin degludec was similar between the first and second 12-hour period postdose. On the other hand, approximately 60% of the serum exposure to insulin glargine occurred over the first 12 hours following administration. These results highlight that insulin degludec is an ultra–long-acting insulin preparation with improved pharmacodynamic stability.

Analysis of data in 54 patients with T1DM reported that the within-subject pharmacodynamic variability was lower with insulin degludec compared with insulin glargine during a 24-hour euglycemic glucose clamp.[14] Over 24 hours, the coefficient of variation (CV) with insulin degludec was lower for the area under the glucose infusion rate curve ($AUC_{GIR}$) for total $AUC_{GIR,0\text{-}24h}$ (CV, 23% vs. 72%; $P < .001$), for $GIR_{max}$ (CV, 21% vs. 53%; $P < .0001$), and for the fluctuation around the mean GIR value over 24 hours (CV, 31% vs. 62%; $P < .001$).

The findings from these investigations demonstrate that insulin degludec has a long half-life, resulting in a prolonged duration of blood glucose lowering with low within-subject pharmacodynamic variability.

## Efficacy, Safety, and Tolerability of Insulin Degludec

### Type 2 Diabetes Mellitus

Insulin degludec has been compared with insulin glargine in combination with oral glucose-lowering agents or in combination with a prandial insulin analog; one study investigated insulin degludec and insulin aspart in basal-bolus therapy in T2DM. In the basal-bolus treat-to-target trial, 992 patients with T2DM (mean A1C 8.3%) were randomized to receive insulin degludec or insulin glargine, each in combination with prandial insulin aspart ± metformin ± pioglitazone.[15] Basal insulin was titrated to achieve a fasting plasma glucose (FPG) <90 mg/dL. At 1 year, mean A1C values were reduced by 1.1% and 1.2% with insulin degludec and insulin glargine, respectively (estimated treatment difference [ETD], 0.08%; 95% confidence interval (CI), –0.05 to 0.21). FPG was reduced by 41 and 36 mg/dL, respectively (ETD, –5.2 mg/dL; 95% CI, –11.7 to 1.1; $P$ = non significant [NS]). Overall, the rates of confirmed hypoglycemia (plasma glucose <56 mg/dL or severe episodes requiring assistance) were lower in the group treated with insulin degludec than in the group treated with insulin glargine (11.1 vs 13.6 episodes/patient-year; estimated rate ratio [ERR], 0.82; 95% CI, 0.69 to 0.99; $P$ = .0359). Nocturnal confirmed hypoglycemia, defined as episodes occurring between midnight and 6 AM, occurred significantly less frequently in the insulin degludec group compared with the insulin glargine group (1.4 vs 1.8 episodes/patient-year, respectively; ERR, 0.75; 95% CI, 0.58 to 0.99; $P$ = .0399) (**FIGURE 2**). Rates of other adverse events were similar between the 2 groups. At 1 year, the total mean

**FIGURE 1** **Mean 24-hour glucose infusion rates (GIR) of insulin degludec at steady state[12]**

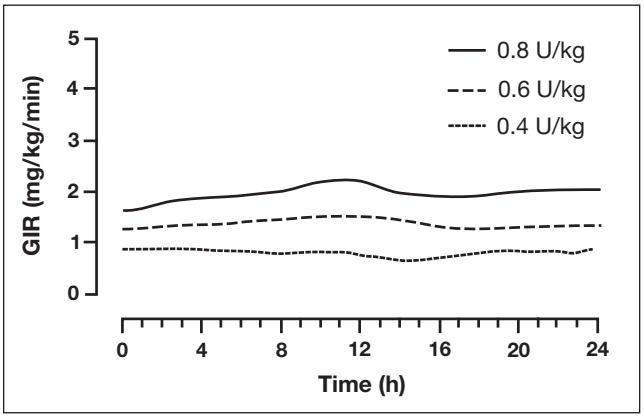
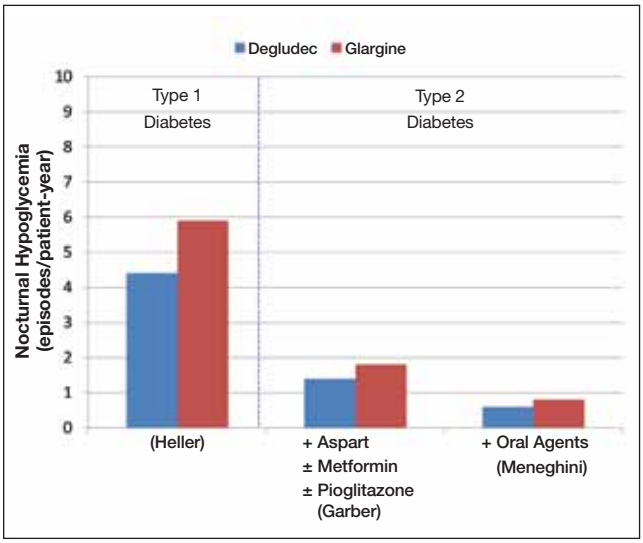





**FIGURE 2** **Incidences of nocturnal hypoglycemia with insulin degludec and insulin glargine[15,16,18]**



daily insulin doses were 1.46 and 1.42 U/kg in the insulin degludec and insulin glargine groups, respectively, with a ~50:50 basal:bolus ratio for both groups.

Based on these findings, insulin degludec was associated with glycemic control similar to insulin glargine when given as basal-bolus therapy. Overall, confirmed and nocturnal hypoglycemia occurred less frequently with insulin degludec than with insulin glargine.

### Type 1 Diabetes Mellitus

Insulin degludec has been investigated in the treatment of patients with T1DM. Two randomized trials involved basal-bolus therapy in combination with insulin aspart. A 1-year treat-to-target trial in 629 adults with T1DM (mean A1C 7.7%) compared insulin degludec with insulin glargine, each given once daily in a basal-bolus regimen with mealtime insulin aspart.[16] Both groups were reported to have improved glycemic control, with overall A1C decreased by 0.4%. Similar proportions of patients achieved A1C <7.0% with insulin degludec and insulin glargine (40% vs 43%; *P* = NS). Mean FPG values were reduced similarly (ETD, 5.9 mg/dL; *P* = .35). Compared with insulin glargine, rates of confirmed nocturnal hypoglycemia were 25% lower with insulin degludec (4.4 vs 5.9 episodes/patient-year; ERR, 0.75; 95% CI, 0.59 to 0.96; *P* = .021), whereas rates of overall confirmed hypoglycemia were similar between treatment groups (42.5 vs 40.2 episodes/patient-year; ERR, 1.07; 95% CI, 0.89 to 1.28; *P* = .48). Overall rates of other adverse events were similar between groups.

Insulin degludec in a fixed-ratio combined formulation with insulin aspart (IDegAsp) was compared with insulin detemir and insulin aspart in basal-bolus therapy in a 26-week, open-label, treat-to-target trial involving 548 patients with T1DM (mean A1C, 8.3%; mean FPG, 189 mg/dL at baseline).[17] IDegAsp was given once daily at any meal, with insulin aspart at the remaining meals, whereas insulin detemir was administered according to approved labeling with mealtime insulin aspart at all meals. The mean decrease in A1C was similar for IDegAsp and insulin detemir/insulin aspart (0.73% vs 0.68%, respectively). The decrease in mean FPG was also similar between groups (*P* = .52). The mean total daily insulin doses were 69 U (0.86 U/kg) for IDegAsp and 79 U (1.00 U/kg) for insulin detemir and insulin aspart. Rates of severe hypoglycemia were 0.33 and 0.42 episodes/patient-year with IDegAsp and insulin detemir, respectively. Rates of overall confirmed hypoglycemia were similar (39 vs 44 episodes/patient-year; *P* = .27), whereas confirmed nocturnal hypoglycemia was reported significantly less frequently with IDegAsp (3.7 vs 5.7 episodes/patient-year, respectively; *P* = .0003). Weight increase was significantly greater (by 1.04 kg) with IDegAsp compared with insulin detemir (*P* = .0021). Overall rates of other adverse events were similar between treatment groups.

Results from trials in patients with T1DM and T2DM are consistent and suggest comparable glycemic lowering between insulin degludec and the basal insulin analogs detemir and glargine, with less frequent nocturnal hypoglycemia in those treated with insulin degludec compared with insulins glargine and detemir (**FIGURE 2**).

### Flexibility of Dosing Time

Optimal glycemic benefits are achieved with the injection of basal insulin at a consistent time each day. However, consistent timing may be difficult owing to patients' busy or erratic schedules and/or in patients who may at times forget to administer their medications. These patient factors can lead to wide variability in the dosing interval and suboptimal results in fasting glucose control. These challenges may be improved upon with the investigational agent insulin degludec due to the stable and prolonged time-action profile of insulin degludec coupled with low within-subject pharmacodynamic variability, allowing for a more flexible once-daily dosing time. A 26-week, randomized, open-label trial in patients with T2DM (N = 459) aimed to compare insulin degludec in the setting of variable dosing intervals by administering insulin degludec once daily using a flexible regimen compared with insulin glargine given once daily at the same time each day.[18] Both insulins were added to an existing regimen of oral glucose-lowering therapy (if any) and titrated to achieve FPG <90 mg/dL. To ensure variability in the dosing interval, the once-daily regimen of insulin degludec involved a compulsory, rotating morning and evening schedule, creating 8- to 40-hour dosing intervals. From a baseline mean of 8.4%, A1C values were reduced by 1.28% and 1.26% with insulin degludec and insulin glargine, respectively, at 26 weeks, confirming noninferiority of the flexible regimen of once-daily insulin degludec compared with insulin glargine given at the same time each day. The mean FPG at week 26 was significantly lower for insulin degludec than insulin glargine (104 vs 112 mg/dL, respectively; *P* = .04). The rates of confirmed hypoglycemia (3.6 vs 3.5 episodes/patient-year) and nocturnal hypoglycemia (0.6 vs 0.8 episodes/patient-year) for insulin degludec compared with insulin glargine, respectively, and the numbers of severe hypoglycemia events (2 episodes/group), were similar between treatment groups. This trial demonstrates that when needed to accommodate changes in the patient's daily schedule, insulin degludec may be administered at differing times from day to day without compromising glycemic control or safety compared with insulin glargine administered at the same time each day.

## CONCLUSIONS

Insulin degludec, an ultra–long-acting basal insulin analog, possesses several desirable attributes. Findings from clinical trials have demonstrated that the new-generation once-daily basal insulin degludec provides similar A1C control compared to insulin glargine both administered as basal-oral therapy or in combination with insulin aspart, with the added benefit of lower rates of hypoglycemia, particularly nocturnal hypoglycemia. Insulin degludec has also been shown to offer dosing flexibility, with administration at any time of the day without compromising glycemic control or safety. Insulin degludec, pending FDA approval, will be an additional treatment to help patients with T1DM or T2DM achieve glycemic control. ■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