Insulin initiation and titration is a challenge for many primary care providers (PCPs) involved in the treatment of patients with type 2 diabetes (1). Clinical inertia, the failure to initiate or intensify insulin therapy when indicated, is a multifactorial problem resulting from barriers to insulin initiation and intensification, including treatment regimen inconvenience, needle phobia, and fear of hypoglycemia (2–5) and has important consequences for patients, significantly increasing the risk of microvascular complications such as retinopathy, nephropathy, and neuropathy (6).

A desirable basal insulin therapy regimen includes an insulin analog possessing a pharmacokinetic profile that mimics the naturally occurring basal endogenous insulin secretion profile, which can provide adequate and reproducible glucose control. Basal insulin analogs from recombinant DNA technology represent a significant advancement from human NPH insulin, an intermediate-acting insulin that, despite the need for twice-daily dosing and a relatively high incidence of hypoglycemia, remains in use today (7). The first-generation basal insulin analogs, insulin glargine 100 units/mL (Gla-100) and insulin detemir 100 units/mL provided a near-24-hour glucose-lowering effect with low variability in insulin action and a lower incidence of hypoglycemia than NPH insulin (8). The more recently approved second-generation basal insulin analogs, insulin glargine 300 units/mL (Gla-300) and insulin degludec 100 units/mL (IDeg U100) or 200 units/mL (IDeg U200), with their prolonged duration of action and more evenly distributed activity profiles, are associated with reduced incidences of hypoglycemia and similar A1C control compared to earlier basal analogs (9,10). They also provide the advantage of once-daily dosing with reduced intra-individual variability (11).

Despite the introduction of insulin analogs, refinement of insulin regimens, and improvements in injection devices such as pens with fine-gauge needles, advocacy for early insulin
initiation, and continuous titration algorithms, many patients with type 2 diabetes continue to experience poor glycemic control (12). This review discusses the initiation and titration of insulin and ways this approach may be optimized by PCPs to help overcome clinical inertia and provide patients with timely glycemic control.

TREATMENT DELAYS AND BARRIERS

Patient and clinician factors contribute to delays in adding insulin to treatment regimens or in transitioning from oral antidiabetic agents (OADs) to insulin. Patient barriers are numerous and include the inconvenience of insulin regimens, a need for more frequent self-monitoring of blood glucose (SMBG) (13,14), fear of hypoglycemia, weight gain, and injection pain. Many patients lack confidence in their ability to self-manage their diabetes (15–17), with emotional factors such as an unwarranted sense of failure, guilt, and shame representing some of the most significant barriers to insulin use (13,15,18). In the Diabetes Attitudes, Wishes, and Needs study, 48% of patients initiating insulin believed they had failed to manage their diabetes correctly, 52% were worried about initiating insulin, and only 23% believed insulin would help manage their diabetes (2). Additionally, nonscientific beliefs such as the notion that insulin causes limb loss or kidney failure (18), lack of awareness of improved insulin delivery devices (19), and concerns about treatment costs are important factors that influence insulin adherence (20).

Among PCPs, there is often resonance with patients with regard to fear of hypoglycemia, as well as a lack of confidence in patients’ ability to manage insulin therapy. Factors such as a patient’s presumed unwillingness or inability to inject contribute to the reluctance of PCPs to initiate insulin (16). Importantly, a lack of awareness of patient fears, beliefs, and expectations may affect the quality of PCP-patient relationships and create further barriers to achieving glycemic control (18). Provider or clinician factors, including a lack of integrated care (20), uncertainty regarding insulin type, complexity of titration algorithms, and concerns that the complexity of insulin therapy is too great to be managed in primary care often lead PCPs to delay insulin initiation (19).

ADVANCED BASAL INSULIN ANALOGS AND FIXED-RATIO COMBINATIONS

Advanced insulin analogs and prefilled pen delivery devices are helping to overcome some of the barriers to insulin initiation and titration experienced by some patients and PCPs. Gla-300, a new formulation of insulin glargine, is available in prefilled pens containing 450 and 900 units and requires only one-third of the injection volume to deliver the same number of units as the Gla-100 pen (21,22). The decreased surface area of the smaller injection depot leads to a slower release rate of insulin, resulting in protracted and stable delivery into the circulation (7,21,23). Gla-300 also provides the advantage of once-daily dosing and reduced intra-individual variability (22), while offering similar glycemic control and a lower risk of hypoglycemia than Gla-100 (10).

It is recommended that unit-to-unit conversions are used when patients are switched from Gla-100 to Gla-300. However, it should be noted that Gla-100 and Gla-300 are not bioequivalent; therefore, when switching from Gla-100 to Gla-300, a higher Gla-300 dose (by ~10–18%) may be needed to maintain the same level of glycemic control. Conversely, when switching from Gla-300 to Gla-100, the initial dose may need to be similarly reduced to limit the risk of hypoglycemia (24). Overall, it is advised that careful glycemic monitoring and individualized dose adjustments be made when switching from one type of basal insulin to another.

Insulin degludec is a novel, long-acting, once-daily insulin that exists as a stable dihexameric complex that forms long soluble multihexameric chains after injection. Its mechanism of protraction is due to binding to albumin to form bound complexes, from which it dissociates very slowly, thus providing a prolonged and stable delivery of insulin (7,25). Insulin degludec is available in two different concentrations, with IDeg U200 demonstrating similar glycemic control with significantly lower risk of overall and nocturnal hypoglycemia compared to Gla-100 (26). Pre-filled IDeg U100 pens contain 300 units, with a maximum dose per injection of 80 units, whereas pre-filled IDeg U200 pens contain 600 units, with a maximum dose per injection of 160 units. IDeg U200 provides the same dose as 100 units/mL basal insulin, but in half the volume. As with Gla-300, a 1:1 total daily conversion ratio is recommended when transitioning from long- or intermediate-acting basal insulins, followed by individual dosing adjustments (27).

A follow-on Gla-100 insulin available in the United States is a long-acting human insulin analog with similar pharmacological/therapeutic effects and safety profile to Gla-100 (28), which can be administered subcutaneously at any time of the day, providing 24-hour glycemic control (29,30).

Two fixed-ratio combinations of a glucagon-like peptide 1 (GLP-1) receptor agonist and a basal insulin analog delivered in a single injection received approval from the U.S. Food and Drug Administration in 2016 (30,31). GLP-1 receptor agonists provide complementary mechanisms of action to basal insulin by stimulating insulin secretion from pancreatic β-cells, suppressing glucagon secretion from α-cells, and delaying gastric emptying (32,33). Both combinations (IDegLira [IDeg U100 and liraglutide] [30,31]) demonstrate improved glycemic control compared to their individual components alone,
with no increased risk of hypoglycemia or weight gain (34–36).

The fixed ratio of Gla-100 and lixisenatide in iGlarLixi provides basal insulin doses of 15–60 units as a single daily injection corresponding to lixisenatide doses of 5–20 µg. Starting doses depend on previous therapy; for patients previously treated with lixisenatide or with a basal insulin dose of <30 units daily, the recommended starting dose of iGlarLixi is 15 units (which includes 5 µg lixisenatide), whereas the recommended starting dose for patients previously taking 30–60 units of basal insulin is 30 units (which includes 10 µg lixisenatide). Up or down titration should occur in 2- to 4-unit increments every week, based on individual patient requirements (30).

IDegLira is provided in doses of insulin ranging from 16 to 50 units, corresponding to liraglutide doses of 0.58–1.8 mg. The recommended starting dose is 16 units, which can be titrated up or down in 2-unit increments every 3–4 days. The pens can administer doses as low as 10 units (with 0.36 mg liraglutide), but doses <16 units are only recommended as temporary for down titration; patients persistently requiring <16 units/day should be transitioned to a different treatment (31).

Current Guidelines for Insulin Initiation and Titration

American Diabetes Association Guidelines

The American Diabetes Association (ADA) recommends initiation of basal insulin at 10 units/day or 0.1–0.2 units/kg/day, adjusted by 10–15% or 2–4 units once or twice weekly to reach a target fasting plasma glucose (FPG) in patients whose A1C remains uncontrolled after >3 months of triple combination therapy, whose A1C is >10%, whose blood glucose is >300 mg/dL, or who are symptomatic of hyperglycemia (37). Figure 1 details treatment intensification recommendations for patients whose A1C remains uncontrolled after basal insulin initiation and titration. Three regimen options should be considered:

• Regimen 1: Administer one rapid-acting insulin injection before the meal with the greatest carbohydrate content; if the glycemic target is not met, progress to two or more rapid-acting insulin injections before meals (basal-bolus regimen).

• Regimen 2: Add a GLP-1 receptor agonist. If target A1C remains unmet or the regimen is not tolerated, patients may discontinue the GLP-1 receptor agonist and switch to regimen 1 or 3.

• Regimen 3: Replace basal insulin with premixed insulin at a 75/25, 70/30, or 50/50 mix twice (usually before breakfast or dinner) or thrice daily (before breakfast, lunch, and dinner). Basal insulin and GLP-1 receptor agonists should be discontinued before initiating premixed insulin.

For regimens 1 and 3, insulin doses should be increased by 1–2 units or 10–15% until target A1C and blood glucose values are met. If appropriate, oral agents other than metformin can be discontinued to avoid regimens that are too complex and expensive. If the targets remain unmet, patients may switch to the alternative regimen. If hypoglycemia occurs, the cause should be investigated, and, if no clear cause is found, the insulin dose should be reduced as recommended in Figure 1.

American Association of Clinical Endocrinologists Guidelines

The American Association of Clinical Endocrinologists (AACE) recommends initiating long-acting basal insulin at a total daily dose (TDD) of 0.1–0.2 units/kg for patients with an A1C <8% or 0.2–0.3 units/kg for patients with an A1C >8%, with insulin titration every 2–3 days to reach the glycemic target (38). For those on fixed regimens, the TDD may be increased by 2 units, whereas for those on adjustable regimens, the dose should be adjusted by 1 unit or 10–20% of the TDD according to FPG values, as indicated in Figure 2. For patients taking a sulfonylurea, the dose may have to be reduced or discontinued during titration due to increased risk of hypoglycemia (38). If the A1C target is unmet, a GLP-1 receptor agonist, sodium–glucose cotransporter 2 inhibitor, dipeptidyl peptidase-4 inhibitor, or prandial insulin may be added to the treatment regimen. Two approaches to initiating prandial insulin may be used as follows.

• Regimen 1: Begin prandial insulin at 10% of basal dose or 5 units before the largest meal (basal + 1). If A1C target is unmet, progress to injections before meals 2 or 3 (basal + 2 or basal + 3).

• Regimen 2: Begin prandial insulin before each meal with a 50% basal/50% prandial ratio to achieve a TDD of 0.3–0.5 units/kg, starting at 50% of the TDD in three divided doses before meals.

For both regimens, insulin should be titrated every 2–3 days until glycemic targets are met, as recommended in Figure 2.

Insulin Titration Algorithms

A number of titration algorithms have been evaluated that aim to simplify insulin titration and enable patient empowerment through self-titration to effectively participate in the management of their disease (4,39–42), the details of which are summarized in Table 1. Several studies have demonstrated that simple algorithms for titrating basal insulin in small increments at short intervals (e.g., every 3 days based on the mean of three self-monitored FPG values or increasing by 1 unit/day) allow patients to achieve comparable glycemic control as with physician-directed titration (43–45).

Simplified self-titration algorithms have also been successfully evaluated for basal-bolus regimens (46,47) and prandial regimens (48). Several studies have also revealed that, in some cases, certain patients can achieve
adequate A1C control using more complex titration algorithms combined with regular support from PCPs (49).

**When Too Much Insulin Has Little Effect on Glycemic Target**

Current use of basal insulin has been shaped by treat-to-target trials that have emphasized systematically titrating the insulin dose without limit until an FPG of 100–130 mg/dL is reached (50). “Overbasalization” is said to occur when FPG is uncontrolled despite uptitration of basal insulin and the A1C target remains unmet (51). Since basal insulin is not designed for postprandial coverage, patients may experience hypoglycemia in the fasting state without seeing any additional reduction in their A1C. Furthermore, patients are prone to experience postprandial hyperglycemia due to a lack of mealtime insulin as a result of β-cell failure. Overbasalization may cause hypoglycemia during the day and evening hours (in the nonfasting state) if insulin dose adjustments are based on fasting blood glucose values. Increased activity levels during the day

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**FIGURE 1.** ADA-recommended approach to initiating and titrating insulin in type 2 diabetes. Reprinted with permission from ref. 37; adapted with permission from ref. 61. ©2015 American Diabetes Association. FBG, fasting blood glucose; GLP-1RA, GLP-1 receptor agonist; hypo, hypoglycemia.
can lead to hypoglycemia if too much basal insulin is given daily. Therefore, it is important to ensure that patients monitor their blood glucose values at different times of the day. This practice was derived from the concept of “fix fasting first,” which developed as a consequence of fasting hyperglycemia being shown to be the primary contributor to hyperglycemia at higher A1C levels in patients taking only OADs (52). Riddle et al. (53) expanded this concept by showing how treatment intensification affects the relative contributions of fasting hyperglycemia and postprandial hyperglycemia in patients with an A1C >7% taking only OADs (53). The observed changes depend on the main effect of the treatment used. Treatment intensification with basal insulin results in a marked reduction in fasting hyperglycemia, and this accounts for approximately one-third of total hyperglycemia in patients who are close to their A1C target. These findings highlight the importance of addressing both fasting and postprandial hyperglycemia to normalize glycemic exposure.

A basal insulin dose >0.5 units/kg (37,54), a >50 mg/dL difference between bedtime (Be) and the next morning’s (AM) SMBG value (known as the “BeAM value”), or an absolute morning glucose level <70 mg/dL (54) should be recognized as potential overbasalization. Increasing basal insulin to >0.5 units/kg has been shown to not improve A1C or mean FPG and is associated with weight gain (55). Patients whose FPG is near or within the target range but whose A1C remains elevated after treatment intensification with basal insulin should be considered for therapy that effectively reduces postprandial glycemia (37).

Managing Insulin Regimens in the Primary Care Setting

It is important to gain an understanding of a patient’s background and lifestyle before initiating insulin to ensure that the treatment regimen takes into account the patient’s needs and preferences as well as clinical characteristics (37,56,57). The key to successful initiation and titration of insulin is to communicate effectively the benefits of insulin and develop a shared decision-making process that enables patients to feel confident in and in control of their treatment regimens,
facilitating their decision to start and engage with insulin therapy. Factors to consider when initiating insulin regimens include patients’ age, daily schedule, activity level, eating pattern, social situation, cultural factors, diabetes-related complications, comorbidities, preferences for self-management, and life expectancy (14).

Although it has been demonstrated that some patients can successfully manage their insulin regimen (43,44), the titration regimen must be simple and easy to manage and support both patients and PCPs in optimizing insulin therapy. Careful support and education about available treatments are instrumental to intensifying insulin therapy and should be provided to help overcome barriers such as fear of injections, hypoglycemia, and lack of knowledge and to manage patients’ expectations (58).

Patients should be closely monitored during titration, and their therapy should be adjusted accordingly until their A1C target is achieved (56). Some patients may require more frequent contact with their PCPs (59) and diabetes management team during titration to reduce the risk of overbasalization (60). As the target FPG is approached, smaller and less frequent insulin dose adjustments should be used to reduce the risk of hypoglycemia. If hypoglycemia occurs, its cause should be investigated because it may be due to non–insulin-related factors such as a missed meal or increased physical activity. If no cause can be found, the insulin dose should be reduced accordingly (59). It also may be necessary to adjust other noninsulin therapies when insulin is added, especially agents that increase hypoglycemia risk—namely, insulin secretagogues (i.e., sulfonylureas and glinides).

Once a stable insulin dose and adequate A1C control have been achieved, the frequency of patient evaluation and monitoring should be reviewed (59). PCPs should continue to communicate with patients in a timely manner to ensure that they are persistent with treatment, successfully managing their disease, and kept up to date on new guidelines, treatment options, and insulin delivery devices.

**Conclusion**

Multiple insulin algorithms have been developed to help PCPs with insulin initiation and titration and to enable

### TABLE 1. Titration Algorithms Evaluated in Clinical Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study Group</th>
<th>Comparison Group</th>
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<tbody>
<tr>
<td>Treat-to-target (50)</td>
<td>Algorithm 1: Gla-100 titration</td>
<td>Algorithm 2: NPH titration</td>
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<tr>
<td></td>
<td>Increase Gla-100 dose by:</td>
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<tr>
<td></td>
<td>• 8 units with FPG ≥180 mg/dL</td>
<td></td>
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<tr>
<td></td>
<td>• 6 units with FPG 140–180 mg/dL</td>
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<td></td>
<td>• 4 units with FPG 120–140 mg/dL</td>
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<td></td>
<td>• 2 units with FPG ≥100–120 mg/dL</td>
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<tr>
<td>ATLANTUS study (43)</td>
<td>Algorithm 1: Patient self-titration</td>
<td>Algorithm 2: Physician titration</td>
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<tr>
<td></td>
<td>Increase Gla-100 dose by:</td>
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<tr>
<td></td>
<td>• 6–8 units with FPG ≥180 mg/dL</td>
<td></td>
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<tr>
<td></td>
<td>• 4 units with FPG 140–180 mg/dL</td>
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<tr>
<td></td>
<td>• 2 units with FPG 120–140 mg/dL</td>
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<tr>
<td></td>
<td>• 0–2 units with FPG ≥100–120 mg/dL</td>
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<tr>
<td>PREDICTIVE study (44)</td>
<td>Patient self-titration</td>
<td>Standard care</td>
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<tr>
<td></td>
<td>Decrease insulin detemir by 3 units with mean FPG &lt;80 mg/dL</td>
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<tr>
<td></td>
<td>Keep insulin detemir dose the same with mean FPG 80–100 mg/dL</td>
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<tr>
<td></td>
<td>Increase insulin detemir dose by 3 units with FPG &gt;110 mg/dL</td>
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<tr>
<td>INSIGHT trial (45)</td>
<td>Patient self-titration</td>
<td>EDITION algorithm</td>
</tr>
<tr>
<td></td>
<td>Increase Gla-300 dose by 1 unit/day if FPG &gt;100 mg/dL</td>
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<tr>
<td></td>
<td>• Increase Gla-300 dose by:</td>
<td></td>
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<tr>
<td></td>
<td>• 3 units if SMPG value &gt;100 and &lt;140 mg/dL</td>
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<tr>
<td></td>
<td>• 6 units if SMPG value ≥140 mg/dL</td>
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<tr>
<td></td>
<td>• Decrease by 3 units if SMPG value &lt;79 mg/dL</td>
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</table>

*SMPG, self-monitoring of plasma glucose.*
patient self-management. New insulin formulations such as Gla-300 and IDeg U100/U200 have helped to address barriers such as fear of hypo-glycemia, the need for multiple daily injections, and pain associated with large injection volumes, while the introduction of pen devices has helped simplify insulin delivery. Although these advances have helped to simplify treatment regimens, effective communication that takes patients’ beliefs and preferences into account is essential to educating patients about the benefits of insulin therapy. Enhanced support from PCPs, including assistance with insulin titration and timely follow-up, may help to improve adherence to insulin regimens by patients with type 2 diabetes.

Acknowledgments
The authors received writing/editorial support in the preparation of this manuscript, provided by Georgina Bowden, PhD, of Excerpta Medica and funded by Sanofi US.

Duality of Interest
J.C. is an advisory board member for Sanofi and is on a Speakers bureau for AstraZeneca. J.S. is on speakers bureaus for AstraZeneca, Boehringer Ingelheim/Lilly, Janssen, Novo Nordisk, and Sanofi; is an advisory board member for Ascencia Diabetes, Novo Nordisk, and Sanofi; is a consultant for the American Diabetes Association and Novo Nordisk; and has received authorship support from Sanofi. S.U. is on speakers bureaus for AstraZeneca and Novo Nordisk; is an advisory board member for Sanofi; and is a consultant for Novo Nordisk. No other potential conflicts of interest were reported.

Author Contributions
The contents of this article and the opinions expressed within are those of the authors, and it was the decision of the authors to submit the manuscript for publication. All authors researched data, reviewed and edited the manuscript, and contributed to the discussion. J.C. is the guarantor of this work and, as such, takes responsibility for the integrity of the information and the accuracy of the data interpretation.

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