Practical Guidance on Effective Basal Insulin Titration for Primary Care Providers

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IN BRIEF Basal insulin therapy is well established for glycemic control in patients with diabetes but often is not optimally implemented, leading to poor clinical outcomes and adherence. Primary care providers can and should work together with other members of the diabetes care team to allow for effective titration of basal insulin that involves patients and their caregivers. Adequate guidance and monitoring during the titration process can minimize some of the adverse effects caused by basal insulin administration, while improving glycemic control in a timely manner.

Control of blood glucose, blood pressure, and lipids plays a substantial role in reducing the micro- and macrovascular complications of type 2 diabetes. Adequate control of these three critical elements is encouraged in the American Diabetes Association (ADA) *Standards of Medical Care in Diabetes* (1), American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) consensus statements (2), and a joint position statement from the ADA and the European Association for the Study of Diabetes (EASD) (3). Despite overwhelming evidence supporting intervention, data from the National Health and Nutrition Examination Surveys for the years 1988–2010 indicated that ~33–49% of adults with type 2 diabetes in the United States did not meet the recommended targets for any of these individual parameters (4,5).

The ADA currently recommends an A1C target of <7.0% for most nonpregnant adults, <6.5% for selected patients if this can be achieved without significant hypoglycemia or adverse effects, and <8.0% in patients with a history of severe hypoglycemia, limited life expectancy, advanced micro- or macrovascular complications, other significant comorbid conditions, or long-standing diabetes (1). To help achieve this goal, fasting blood glucose (FBG; also known as prebreakfast glucose) levels of 80–130 mg/dL are recommended, although this may be individualized for patients depending on factors such as duration of diabetes, age/life expectancy, and comorbid conditions (1).

Basal insulin is an important and often essential tool to reduce blood glucose levels in patients with type 2 diabetes; however, patients and clinicians may be reluctant to initiate its use for multiple reasons. Suboptimal insulin utilization can include failure to employ insulin in a timely manner when indicated, inefficient insulin titration methods, and "overbasalization" (i.e., titrating to excess levels of basal insulin when prandial glycemic control is indicated). In this review, we discuss initiation and titration of basal insulin and how this process may be optimized to provide patients with timely glycemic control, while alleviating concerns regarding insulin therapy.

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TABLE 1. Recommendations for Basal Insulin Therapy Initiation

Treatment Guidelines	Starting Dose of Insulin	Insulin Dose Increments	Frequency	Maximum Insulin Dose	Target FPG, mg/dL
ADA/EASD (1,3)	10 units/day or 0.1–0.2 units/kg/day	5–15% or 1–4 units	1–2 times per week	0.5 units/kg/day	80–130
AACE/ACE (2)	0.1–0.2 units/kg/day for A1C <8.0%; 0.2–0.3 units/kg/day for A1C >8.0%	2 units for fixed regimen	Every 2–3 days	—	<110*
IDF (18)	—	2 units	Every 3 days	—	<115

**Target FBG. IDF, International Diabetes Federation.*

Timely Initiation of Insulin

Achievement of lower A1C levels during the initial stages of type 2 diabetes with early and aggressive glucose-lowering treatments may improve long-term glycemic control, usually with modest weight gain and incidence of hypoglycemia (6). Despite these potential benefits, in a retrospective cohort study conducted in the United Kingdom, the median time to intensification with insulin was >7.1, >6.1, or 6.0 years for patients receiving one, two, or three oral antidiabetes drugs, respectively (7).

Clinical inertia regarding insulin therapy is most commonly reflected by failure to initiate or titrate insulin in a timely manner. Awareness of the obstacles that patients commonly encounter when starting insulin can often obviate its suboptimal use. Such obstacles include *1*) a view that requiring insulin is in some way a personal failure, *2*) concerns that the requirement for insulin indicates particularly serious diabetes, *3*) fear of hypoglycemia, *4*) overestimation of pain associated with injections, *5*) anxiety about weight gain, and *6*) concerns generated by observation of others (family or friends) in whom the administration of insulin was associated with a noticeable decline in their condition. Moreover, primary care providers (PCPs) and patients often perceive initiation of insulin treatment to be complex and time consuming, resulting in another barrier to its timely initiation. In addition to concerns about hypoglycemia and weight gain, PCPs also contribute to clinical inertia by considering insulin titration to be a process that requires heavy investments in patient education and, hence, in time (8–10).

However, a series of technological advances have addressed some of these concerns. Long-acting basal insulins such as insulin glargine 100 units/mL and insulin detemir 100 units/mL result in less weight gain and reduced hypoglycemia risk compared to older basal formulations such as NPH insulin. The newest basal insulins, namely insulin glargine 300 units/mL and insulin degludec 100 and 200 units/mL, have pharmacokinetic profiles demonstrating prolonged half-lives, extended durations of action, and very flat glucose control profiles, which can reduce the risk for hypoglycemia.

Insulin pens allow for controlled and precise dosing, and needles in modern pen devices are very short and thin, thus minimizing and sometimes even eliminating complaints of injection-associated pain (9). A systematic review of patient-reported outcomes in clinical trials evaluating currently available insulin pens revealed that, in general, patients preferred insulin pens over vials and syringes for reasons of convenience, social acceptance, and reduced injection pain in 23 of 24 studies (11). Although the cost of pen devices is higher than that of syringes and vials, these costs may be offset by greater adherence with pen devices, thus resulting in reduced hospitalization rates (12), diabetes-related costs, and outpatient care costs (13).

Education, for both patients and physicians, is the most important tool in addressing patient-related inertia factors. Patients should be aware that, far from being a personal failure, the addition of basal insulin to their treatment regimen is another tool to address the progressive nature of type 2 diabetes. Unless other more effective treatment approaches emerge, basal insulin will be required for the majority of patients in the long run (14). Additionally, diabetes educators and PCPs should work closely with patients during insulin initiation to ensure that they understand and are comfortable with their chosen insulin product. This collaboration will empower them to take control of their treatment (15). Finally, the titration process should be closely monitored to ensure that guidance and training programs are being followed (9,16).

Approaches to Basal Insulin Titration

The titration algorithms for basal insulin initiation provided by various medical associations are, in general, quite similar. The target fasting plasma glucose (FPG) level is <130 mg/dL in the ADA/EASD position statement (17), but other clinical guidelines may have different reference values, so clinicians should become familiar with one or more of the current guidelines and follow whichever particular goals they personally endorse (Table 1) (1,12,18).

Starting doses of basal insulin are generally low, at either 10 units/day or 0.2 units/kg/day (19). Titration is rec-

ommended every 2–3 days for insulin glargine 100 units/mL and detemir 100 units/mL (19,20). However, the newer, long-acting insulin formulations—insulin glargine 300 units/mL and insulin degludec 100 and 200 units/mL—should be titrated less frequently, every 3–4 days, to minimize the risk of hypoglycemia resulting from their prolonged half-lives and a longer time to reach steady state (21,22).

Various titration strategies have been used in clinical trials, such as adjusting insulin doses based on a single blood glucose reading or on the average of daily readings. Once-weekly insulin degludec dose titration algorithms based on a single prebreakfast blood glucose value or on three consecutive values showed similar effectiveness in reducing A1C and FPG (23). No differences in the number of patients achieving fasting self-monitoring of blood glucose (SMBG) levels ≤100 mg/dL without nocturnal hypoglycemia were seen in a randomized pilot study of insulin glargine 300 units/mL that compared a simplified daily titration protocol with a weekly protocol based on the median value of three SMBG measures (24). Moreover, the degree of increase in treatment satisfaction scores and reduction in perceived hypoglycemia and hyperglycemia were similar between titration protocols, which also had a similar proportion of patients making proper dose adjustments (24). PCPs should therefore tailor the titration scheme to the particular needs of each patient because no one titration method has proven to be meaningfully more effective than another. Keep in mind, however, that slower titration protocols (i.e., every 4–7 days instead of every 3–4 days, as recommended in the prescribing information) have been tested and may be used for long-acting insulin glargine 300 units/mL and insulin degludec 100 and 200 units/mL owing to the longer time needed to reach steady state (23,24).

Several comparative studies have sought to determine the potential benefits of patient-driven titration algorithms versus conventional titration protocols in the clinical setting (Table 2) (24–29). In two randomized, prospective studies, a simplified patient-led insulin titration protocol carried out every 3 days resulted in significantly greater A1C and FPG reductions compared to physician-led titration, with no significant difference in the incidence of severe hypoglycemia between groups (27,29). A smaller study in Asian patients showed similar patient satisfaction and quality-of-life scores with both patient- and physician-led titration (28). Moreover, patients self-adjusting their insulin doses who

TABLE 2. Studies Comparing Basal Insulin Titration Protocols

Study	Protocol Description
INITIATE (25)	Type of titration: patient-driven; in groups of four to eight patients or individually
	Insulin: insulin glargine 100 units/mL
	Starting dose: 10 units/day at bedtime
	Frequency of dose adjustment: every 3 days based on FPG values for 3 consecutive days
	Algorithm: +2 to +4 units if FPG >100 mg/dL; −2 units if FPG <72 mg/dL and presence of symptomatic hypoglycemia with no apparent cause
	Target FPG: 72–100 mg/dL
	Main findings: similar A1C levels and incidence of hypoglycemia, but greater weight gain (+3.7 vs. +2.2 kg, P <0.02) for titration in groups versus individual titration; similar treatment satisfaction rates, but less total time spent with titration visits/phone calls (−48%) for titration in groups versus individual titration
GOAL A1C (27)	Type of titration: patient-driven, with no unsolicited physician contact between visits (standard titration) or weekly contact (active titration)
	Insulin: insulin glargine 100 units/mL
	Starting dose: 10 units/day at bedtime
	Frequency of dose adjustment: weekly and at every visit (every 6 weeks) based on the mean FBG of the previous 2–4 days
	Algorithm: +0 to +2 units if 120 mg/dL <FBG ≥100 mg/dL; +2 units if 140 mg/dL <FBG ≥120 mg/dL; +4 units if 160 mg/dL <FBG ≥140 mg/dL; +6 units if 180 mg/dL <FBG ≥160 mg/dL; +8 units if FBG ≥180 mg/dL; decrease to previous lower dose if FBG <70 mg/dL
	Target FPG: 70–100 mg/dL
	Main findings: greater A1C reduction (1.5 vs. 1.3%, P <0.0001) for active titration versus standard titration; greater incidence of hypoglycemia (6.0 vs. 3.7 episodes/patient-year, P = 0.001) for active titration versus standard titration

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TABLE 2. Studies Comparing Basal Insulin Titration Protocols, *continued from p. 370*

Study	Protocol Description
AT.LANTUS (28)	Type of titration: patient-driven and physician-led
	Insulin: insulin glargine 100 units/mL
	Starting dose: 10 units/day (or numerically equivalent to the highest FBG over the previous 7 days for self-titration) at bedtime
	Frequency of dose adjustment: weekly (physician-led titration) or every 3 days for self-titration (patient-driven titration) based on mean FBG value for the prior 3 consecutive days
	Algorithm: +0 to +2 units/day if 120 mg/dL > FBG ≥100 mg/dL; +2 units/day if 140 mg/dL > FBG ≥120 mg/dL; +4 units/day (+2 units/day for self-titration) if 180 mg/dL > FBG ≥140 mg/dL; +6 to +8 units/day (+2 units/day for self-titration) if FBG ≥180 mg/dL
	Target FPG: ≤100 mg/dL
	Main findings: higher hypoglycemia (33.3 vs. 29.8%, P <0.01), but greater A1C reduction (−1.22 vs. −1.08%, P <0.001) for self-titration vs. physician-led titration
ATLAS (29)	Type of titration: patient-driven and physician-led; Asian patients
	Insulin: insulin glargine 100 units/mL
	Starting dose: 10 units/day (8–10 units/day in India and 4 units/day in Japan) at bedtime
	Frequency of dose adjustment: at every visit (physician-led titration) or twice per week (self-titration) based on intermediate value of last three consecutive measurements
	Algorithm: dose decrease at physician's discretion if FBG ≤56 mg/dL; −2 units if FBG ≤70 mg/dL or symptomatic hypoglycemia; no adjustment if 70 mg/dL < FBG ≤110 mg/dL; +2 units if 110 mg/dL < FBG ≤ 160 mg/dL; +4 units if FBG >160 mg/dL
	Target FPG: 110 mg/dL
	Main findings: greater A1C reduction (−1.40 vs. −1.25%, P = 0.043) and higher incidence of nocturnal hypoglycemia (16.4 vs. 6.5%, P = 0.002) and symptomatic hypoglycemia (36.0 vs. 25.6%, P = 0.02) for self-titration versus physician-led titration; similar weight gain and treatment satisfaction
PREDICTIVE 303 (26)	Type of titration: patient-driven and physician-led
	Insulin: insulin detemir 100 units/mL
	Starting dose: not reported
	Frequency of dose adjustment: every 3 days based on the mean of three adjusted* FPG measurements (self-titration)
	Algorithm: −3 units if adjusted FPG <80 mg/dL; no adjustment if 80 mg/dL < adjusted FPG < 110 mg/dL; +3 units if adjusted FPG >110 mg/dL
	Target FPG: 80–100 mg/dL
	Main findings: similar weight gain, but greater A1C reduction (−0.6 vs. −0.5%, P = 0.0106) and incidence of hypoglycemia (6.44 vs. 4.95%, P <0.0001) for patients self-titrating vs. physician-led titration
BEGIN (23)	Type of titration: patient-driven
	Insulin: insulin degludec 100 units/mL
	Starting dose: 10 units/day, with an interval of 8–40 hours between injections
	Frequency of dose adjustment: weekly, based on one FBG value (simple titration) or on the lowest of three consecutive FBG values (stepwise titration)
	Algorithm: −4 units if FBG <56 mg/dL; −2 units if 56 mg/dL < FBG < 70 mg/dL (stepwise titration only); no adjustment if 71 mg/dL < FBG < 90 mg/dL; +4 units (simple titration) or +2 units (stepwise titration) if 91 mg/dL < FBG < 126 mg/dL; +4 units if 127 mg/dL < FBG < 144 mg/dL (stepwise titration only); +6 units if 145 mg/dL < FBG < 162 mg/dL (stepwise titration only); +8 units if FBG >162 mg/dL (stepwise titration only)
	Target FPG: 71–90 mg/dL
	Main findings: similar A1C reduction, incidence of hypoglycemia, and weight change

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TABLE 2. Studies Comparing Basal Insulin Titration Protocols, *continued from p. 371*

Study	Protocol Description
TITRATION (24)	Type of titration: physician-led (as in the EDITION studies [32]) and patient-driven (as in the INSIGHT study [30,31])
	Insulin: insulin glargine 300 units/mL
	Starting dose: 0.2 units/day for insulin-naive patients, or pre-study dose for patients receiving once-daily insulin glargine 100 units/mL, insulin detemir or NPH, or 80% of pre-study dose for patients receiving twice-daily insulin detemir or NPH, in the evening
	Frequency of dose adjustment: at least once weekly, but not more than every 3 days (EDITION) based on median FPG from the previous 3 days; daily (INSIGHT)
	Algorithm: EDITION: +6 units/day if FPG ≥140 mg/dL; +3 units/day if 100 mg/dL < FPG < 140 mg/dL; no adjustment if FPG 80–100 mg/dL; −3 units/day if 60 < FPG < 80 mg/dL; −3 units/day if FPG <60 mg/dL or occurrence of two or more symptomatic or one severe hypoglycemia event in the previous week; INSIGHT: +1 unit/day if FPG ≥100 mg/mL
	Target FPG: 80–100 mg/dL
	Main findings: similar A1C reduction (−0.8% for both algorithms), incidence of hypoglycemia, and weight change (+0.1 vs. +0.4 kg for EDITION and INSIGHT, respectively); similar treatment satisfaction rate, but 86% of health care providers preferred the INSIGHT algorithm because of its simplicity, effectiveness, and safety

**Adjusted FPG was capillary blood glucose level calibrated to equivalent plasma glucose values. AT.LANTUS, A Trial Comparing Lantus Algorithms to Achieve Normal Blood Glucose Targets in Subjects With Uncontrolled Blood Sugar; ATLAS, Asian Treat to Target Lantus Study; GOAL A1C, Glycemic Optimization with Algorithms and Labs at Point of Care; INITIATE, Initiate Insulin by Aggressive Titration and Education; INSIGHT, Implementing New Strategies with Insulin Glargine for Hyperglycaemia Treatment; PREDICTIVE, Predictable Results and Experience in Diabetes through Intensification and Control to Target: An International Variability Evaluation.*

participated in an educational program individually or in groups of four to eight patients showed similar levels of glycemic control and treatment satisfaction, but the total time spent with titration was greater for patients in the individual education arm (25).

When using a patient-led approach, it may be beneficial to place an emphasis on the simplicity of the titration protocol because this may make it more likely that insulin is administered correctly. A post hoc analysis of data from a randomized trial using a simple, easy-to-understand self-titration protocol for insulin glargine 100 units/mL, with once-daily injections at the same time each day, and dose increases of 1 unit daily until FPG targets were reached, demonstrated that PCPs could easily help patients initiate such a basal insulin regimen in most settings (30,31). Furthermore, a pooled analysis of data of randomized trials of insulin glargine 100 units/mL showed similar A1C reductions for an increase of 1 unit daily depending on FPG levels (or an increase of 2 units every 2–3 days), compared to weekly increases of 2–8 units based on 2-day mean FPG levels. In addition, the incidence of hypoglycemia was lower for the two simplified protocols (32).

The approach of increasing by 1 unit/day until the goal is reached for the older long-acting insulins versus the newer and more concentrated formulations is easy to remember, and therefore easier to adhere to, and is preferred by the authors because it eliminates the irregularity of 2- to 3-day cycles and the need to average daily FPG results. However, it is important to teach patients to stop titrating and notify the provider if they encounter hypoglycemia and also to put a cap on the total dose for patients using this algorithm to avoid unnecessarily large basal doses of insulin. In addition, patients should avoid large snacks at night or inconsistent dietary compliance while titrating.

Regardless of the titration strategy, clear communication between the PCP and patient is essential. Patients should be informed that they will start treatment with low doses of insulin and titrate upward to achieve their individual FPG goal. This allows them to understand that dose increases are expected and do not mean that the treatment is failing (33). However, an online survey revealed that only 16–28% of patients recalled discussing insulin titration at their initiation visit and that as many as 32–42% were unaware of the need to increase the dose over time. The majority of patients and health care providers surveyed agreed that more effective support tools were required to increase the confidence and willingness of patients to self-titrate insulin (34).

Moreover, it is important to clarify that hypoglycemia is a risk of insulin therapy and that the initial doses of insulin are aimed at avoiding hypoglycemia episodes and, for some patients, unlikely to substantially change glucose levels. PCPs may specifically address patients' concerns regarding maximal dosing by referring

to a mean dose of 0.4–0.6 units/kg used in clinical trials and how these doses translate to clinical practice for a particular patient. Because patients may not be comfortable calculating what 0.4–0.6 units/kg means, using a simple example of a 220-lb patient typically using 40–60 units/day should suffice to clarify what ultimate insulin dose is anticipated (23,27,29,30,35).

PCPs should also provide patients with clear guidance on how to avoid, recognize, and treat hypoglycemia episodes. An effective and simple method for treating hypoglycemia is the "rule of 15." When patients have a blood glucose reading <70 mg/dL, they are advised to ingest 15 g of carbohydrates, wait 15 minutes, then test their blood glucose again. If glucose levels are still <70 mg/dL, the process should be repeated. Minor episodes of hypoglycemia can be easily managed by patients through ingestion of glucose tablets, table sugar dissolved in water, or essentially any foods or beverages rich in sugar or simple carbohydrates (36).

Prevention of hypoglycemia must be emphasized, with recommendations to inject basal insulin at the same time of the day, although some insulins offer flexibility in the time of injection; insulin glargine 300 units/mL can be injected up to 3 hours before or after the regular dosing time (37), and insulin degludec may be dosed with intervals of 8–40 hours between injections without negatively affecting glycemic control or safety (38). Dosing time must also be taken into consideration because the effects of insulin may differ because of the circadian cycle. For example, insulin glargine 100 units/mL shows greater activity in the period of 0–12 hours after administration in the morning, but after the evening injection, its activity is greater in the period of 12–24 hours (39). In addition, if there is a hypoglycemia trend (i.e., more than once a week) despite adequate basal insulin titration to meet the FPG target, PCPs should explore various options to avoid this. For example, patients with hypoglycemia before dinner (not taking prandial insulin at lunch time) can either increase their lunch calories or have dinner slightly earlier. Changing the timing of the basal insulin injection from morning to afternoon (or evening) may also be of benefit. If patients take prandial insulin for lunch, its dose should be reduced.

Proper management of hypoglycemia involves the identification of patients at higher risk, such as those not administering insulin correctly or at the proper time, those showing increased tissue sensitivity to insulin, or those who have variable diet or exercise schedules (9). It is important that patients know how to down-titrate according to the algorithm prescribed in case of a hypoglycemic event. In case of a single premeal hypoglycemic event, patients can eat their meals and recheck their blood glucose levels, and if they are in a safe range, they can then take the mealtime insulin. If there is a pattern of hypoglycemia episodes, the therapy may be reviewed to determine whether it can be optimized with regard to meal content/spacing and insulin dosing/timing to prevent further occurrences of hypoglycemia.

Finally, patients should be closely followed up during self-titration, with daily SMBG levels and frequent contact with the diabetes care team by telephone, email, or visits to the clinic (e.g., 1 week after the first week of titration, then 2 weeks later, and then monthly until FPG control is attained) (17). If a patient is titrating for the first time, it is desirable to schedule a session with a diabetes educator and follow up in person 1–2 weeks after treatment initiation.

Despite the current treatment recommendations by different medical societies, PCPs must bear in mind that targets can differ from the reference values used in clinical trials and in so-called real-life settings and that guidelines can also show high variability in choice of insulin regimen. A systematic review of insulin initiation studies identified a disparity between the glycemic control obtained in highly controlled settings (i.e., clinical trials) and in actual clinical practice, where poor adherence, complex insulin regimens, and reduced monitoring may have more impact on outcomes (40). Another recent study has shown that errors in insulin self-administration (e.g., overdosing, underdosing, and incorrect timing) are relatively common and may lead to suboptimal glycemic control and adverse events (41). This again highlights the importance of patient education and training, as well as the simplicity of the administration and titration procedure. The ADA advises that all patients with type 2 diabetes should receive standardized general diabetes education, initially focusing on lifestyle modifications (1), but with initiation of insulin, this educational effort should be expanded to include glucose monitoring, injection technique, adequate insulin storage, and recognition of hypoglycemia symptoms.

Digital Aids for Basal Insulin Titration

Certified diabetes educators are a valuable resource to properly teach patients all the aspects of glycemic control, especially if PCPs are time constrained. Online educational tools and mobile technology may also facilitate some of these functions. Virtual interventions replacing traditional face-to-face meetings with health care providers have been shown to improve both communication with patients and glycemic control (42,43). In addition, mobile platforms can potentially contribute to sustained lifestyle changes (44,45), and modest effects on glycemic control were revealed in a systematic review and meta-analysis of randomized controlled trials in patients with type 2 diabetes (46).

A pilot study evaluating the use of a smartphone application to calculate insulin doses based on the mean FPG value over 3 days showed no statis-

tically significant differences in A1C reductions from baseline compared to the use of conventional paper-and-pencil calculations for patients initiating insulin therapy. However, the daily basal insulin dose increased more rapidly for those patients using the mobile application, with mean doses of 0.43 and 0.36 units/kg at the end of the study for patients using their smartphones and those using a conventional titration approach, respectively ($P = 0.03$) (47). Similarly, a randomized study comparing a web-based tool for insulin titration with a diabetes education program showed no significant difference in A1C reduction or hypoglycemia incidence, but satisfaction scores were higher for patients using the digital tool, and the number of additional needed visits to the clinic was lower (48).

Despite the scarcity of studies focusing on basal insulin titration, mobile-based applications and algorithms currently under development may, in the near future, enhance patient-physician communication regarding titration guidance and monitoring, ultimately promoting a more effective titration process (9).

Ending Basal Insulin Titration

Basal insulin is used to improve glycemic control with a focus on the overnight and fasting component of blood glucose management, but overall glycemic control and A1C levels are the result of a combination of both FPG and postprandial glucose (PPG) levels. If FPG levels are brought into control but A1C levels are still not at target, additional treatment options will then need to be explored. However, it can sometimes be difficult to know when to cease basal insulin titration and intensify treatment by the addition of other antihyperglycemic agents.

Current guidelines lack clarity regarding the point at which a basal insulin regimen is optimized. Once FPG is optimized, elevated A1C levels strongly suggest inadequate control of PPG excursions (49), and treatments specifically chosen to address this aspect of glucose control (e.g., rapid-acting prandial insulins, glucagon-like peptide 1 [GLP-1] receptor agonists, and α-glucosidase inhibitors) will be necessary. Unfortunately, overbasalization may occur when a clinician tries to continue increasing basal insulin when addressing PPG excursions is indicated. With FPG under control, any further escalation of basal insulin increases the risk of hypoglycemia (50). Therefore, one important caveat for patients self-titrating is that they should be given well-established ranges of insulin doses, particularly with regard to upper dose limits and optimal FPG targets, to avoid overbasalization. Patients failing to achieve the glycemic goal after reaching the upper dose limit and safe FPG targets should then be encouraged to discuss alternative management strategies with their PCPs.

In an exploratory dose-response study using data from three titration studies of insulin glargine 100 units/mL, FPG reductions were progressively smaller with increasing doses of basal insulin, with a plateau observed at a dose of 0.5 units/kg. This finding may be a useful indication of the need to introduce a prandial therapy into patients' regimen (51). Moreover, an analysis of patient-level data from 15 randomized trials of patients receiving insulin glargine with or without oral antidiabetes drugs showed that doses >0.5 units/kg did not always provide incremental benefits in A1C target achievement or mean FPG levels (52).

Both the ADA (1) and the AACE/ACE (2) provide guidance regarding insulin intensification if optimized basal insulin therapy remains insufficient to achieve glycemic control, but they do not specify exactly when this should be done. The ADA recommends that, if acceptable FBG levels have been achieved (or the basal insulin dose is >0.5 units/kg/day) but A1C levels remain above goal, combination injectable therapy should be considered (1). The AACE/ACE recommends the addition of prandial insulin or a GLP-1 receptor agonist when patients require prandial control; however, sodium–glucose cotransporter 2 inhibitors or dipeptidyl peptidase-4 inhibitors may also be added (2).

A pooled analysis of six clinical trials showed that, in patients with optimized basal insulin therapy, elevated A1C (≥7.0%) with fasting glucose levels <130 mg/dL indicates a need to intensify therapy for PPG excursions to improve glycemic control rather than continue basal insulin titration (49). Whereas rapid-acting insulin offers improved flexibility versus premixed insulin formulations with regard to coordinating meals with insulin administration, the recently approved fixed-ratio combinations of a basal insulin and a GLP-1 receptor agonist (insulin glargine/lixisenatide and insulin degludec/liraglutide) provide complementary control of fasting and postprandial glycemia (through the action of basal insulin and the incretin agent, respectively), with less hypoglycemia and weight gain than with the individual components, and the convenience of once-daily dosing (1).

Conclusion

Basal insulin remains a vital treatment for patients with type 2 diabetes, but many patients and PCPs remain resistant to adding it to their regimens. Often, it is only initiated when other antihyperglycemic agents fail, despite the fact that timely intensification with basal insulin is beneficial in the short term and potentially in the long term. Pharmacists, nurses, and diabetes educators provide support to both PCPs and patients, and a team-based approach to insulin initiation can greatly enhance the transition for patients and lessen the burden on the health care team.

Patient-led basal insulin titration seems to result in greater glycemic control without increased hypoglycemia. Adequate education and guidance should be provided by the

diabetes care team to enable patients to successfully self-titrate.

The availability of new basal insulin formulations with improved pharmacokinetic and pharmacodynamic properties, as well as fixed-ratio basal insulin/GLP-1 receptor agonist combination therapies, can potentially facilitate the titration process, improve adherence, and better match a healthy physiologic function. Once patients experience the benefits of insulin therapy, they are more likely to persist with their new regimen. PCPs and other health care professionals involved in the management of type 2 diabetes play a crucial role in transitioning patients to insulin.

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Author Contributions

All authors interpreted the data and critically reviewed the manuscript drafts, provided final approval of the version of the manuscript submitted, and are accountable for the accuracy and integrity of the manuscript. L.K. is the guarantor of this work and, as such, had full access to all the data reviewed and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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