

Role of Emerging Insulin Technologies in the Initiation and Intensification of Insulin Therapy for Diabetes in Primary Care

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■ IN BRIEF This article explores some of the reasons for the delay in insulin initiation in primary care and evaluates new approaches to insulin therapy that may address these barriers and, therefore, improve insulin use by primary care providers.

Preventing the micro- and macrovascular consequences of prolonged hyperglycemia (1,2) and delaying the progressive loss of β -cell function during the natural progression of the disease are among the key goals of antidiabetes therapies (3). The benefits of early insulin initiation and intensification include improvements in glycemic control, as well as potential improvements in quality of life and treatment satisfaction (4). However, insulin is often initiated late in the natural history of type 2 diabetes despite recommendations that treatment should be intensified within 3–6 months of failure to meet glycemic targets (5,6).

International guidelines recommend an A1C target of <7.0% (5,6). Despite these recommendations, however, the average A1C level at which insulin is initiated has been shown in several studies to be >9.0% (7–9). Furthermore, not only is there a reluctance to initiate insulin treatment (10), but also the intensification of treatment may be delayed for several years (11).

With an estimated 90% of Americans with type 2 diabetes being treated by their primary care provider (PCP) (12), it is vital that PCPs have the knowledge and confidence to initiate and intensify insulin

therapy when necessary. The growing prevalence of type 2 diabetes and the limited availability of diabetes specialist resources necessitate the initiation and titration of insulin in the primary care setting. This article describes some of the reasons for the delay in insulin initiation in the primary care setting and evaluates new insulin formulations that may help improve insulin use by PCPs.

Guidelines for Initiation and Intensification of Insulin Therapy

Current management approaches initially aim to decrease basal hepatic glucose production and increase muscle glucose uptake. Treatment choice is based on patient history, present level of glucose control, patient preferences, and the mechanisms of action and side effect profiles of available agents. Measures to improve nutrition and lifestyle, together with oral metformin medication, are typically used in the first instance (5).

As the disease progresses, β -cell function declines, and the response to insulin in skeletal muscle and liver cells decreases (13,14). Patients eventually reach a point at which target blood glucose levels cannot be maintained on oral agents alone, and they require insulin to achieve glycemic goals (5).

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Initially, treatment with a basal insulin once or twice daily is used to suppress glucose production between meals and overnight. Recommended basal insulins include the long-acting insulin glargine and insulin detemir and intermediate-acting NPH insulin (5,6). Oral agents are often continued, although insulin secretagogues (e.g., sulfonylureas) increase the risk of hypoglycemia and are usually stopped as insulin regimens become more complex with the addition of a rapid-acting insulin. Basal insulin doses are started at 0.1–0.2 units/kg, depending on the degree of hyperglycemia (6). With proper education and guidance, patients can titrate doses to agreed-upon glycemic targets (5,6). Many patients, particularly those with limited health literacy and numeracy, benefit from tailored education and reinforcement to obtain the skills and confidence needed for insulin self-adjustment (15).

With continued disease progression or if glycemic targets are not met with basal insulin alone, patients may need to move on to a basal-bolus regimen in which the basal insulin is supplemented by mealtime bolus insulin (5,6). Here, the bolus is often a prandial dose of a rapid-acting insulin analog (insulin lispro, insulin aspart, or insulin glulisine) usually taken just before the meal (5,6). Initially, the prandial insulin may be added before the meal responsible for the largest glucose excursion, followed by additional mealtime doses as required (5). According to the guidelines, noninsulin agents may be continued, but sulfonylureas, dipeptidyl peptidase-4 inhibitors, and glucagon-like peptide-1 (GLP-1) receptor agonists are usually stopped once prandial regimens are introduced (5,6); however, this may not be consistently implemented in the primary care setting.

Alternatives to the basal-bolus approach include introducing a GLP-1 receptor agonist (16), which may help achieve target A1C without weight gain or increased hypogly-

cemia, or switching to a premixed insulin (5). Premixed insulin may be administered two or three times daily to improve convenience and may cause greater decreases in A1C compared to basal insulin alone, according to some research (17). However, as with any insulin, premixed insulins can cause hypoglycemia and weight gain (6).

Cardiovascular disease is the major cause of morbidity and mortality for patients with either type 1 or type 2 diabetes. Elevated fasting blood glucose levels have been shown to be an independent risk factor for adverse cardiovascular outcomes (18). Concerns exist regarding the long-term safety of basal insulin and adverse cardiovascular outcomes in type 2 diabetes (19–21). However, the long-term use and safety of insulin glargine 100 units/mL (Gla-100) is established (22) and has been shown to have a neutral effect on cardiovascular outcomes and cancer in a long-term clinical trial (23).

Gla-100 and the new insulin glargine 300 units/mL (Gla-300) are based on the same insulin glargine molecule. A substudy of the Gla-300 pharmacokinetic (PK)/pharmacodynamic (PD) study by Becker et al. (24) found that metabolism of insulin glargine is the same irrespective of formulation (25).

Factors Limiting the Use of Basal Insulin in the Primary Care Setting

Resistance to insulin initiation is a serious problem in the treatment of type 2 diabetes and results from several patient and clinician factors (10,26–28).

Patient Factors

Barriers to insulin initiation experienced by patients with diabetes are mainly psychological and include concerns over the safety and efficacy of insulin. For example, some patients hold strong beliefs that insulin is ineffective. This was demonstrated by the Diabetes Attitudes, Wishes, and Needs (DAWN) study (10), in which

only 27% of patients with type 2 diabetes who were not taking insulin believed that insulin would help manage their disease better. Other concerns are that it causes hypoglycemia or weight gain and misperceptions that include the belief that insulin itself is associated with complications or even death (27) and that it results in a loss of independence (26). The need for insulin therapy is also perceived by some patients as a personal failure to effectively manage their weight, nutrition, and physical activity (26,27). Others lack the knowledge, support, and confidence to live with the demands of insulin therapy (10,29).

Clinician Factors

Clinical inertia, defined as “the failure of health care providers (HCPs) to initiate or intensify therapy when indicated” (30), arises from several complex, interrelated factors, including a need for education about the benefits of appropriate initiation of insulin, interpretations of patient beliefs by HCPs, and limited resources for initial and ongoing patient education and follow-up in the primary care setting.

The need for education about the benefits of insulin therapy is illustrated by the responses of HCPs to various surveys (10,28,31). In the DAWN study, for example, roughly half of the nurses and physicians surveyed stated that they would delay insulin therapy until absolutely necessary. Only half of these HCPs felt that insulin could have a positive impact on diabetes care, and those who questioned the efficacy of insulin were more likely to delay its initiation (10).

Interpretation of patients' beliefs by PCPs can be a barrier to starting insulin; many PCPs believe that patients would not accept injection therapy. In the Translating Research Into Action for Diabetes study (28), the perception of patients' fear of and resistance to new types of oral and insulin therapies was reported by almost two-thirds of PCPs to be one of the main reasons for not initiating

TABLE 1. Overview of Published Clinical Trials of Novel Insulin Formulations

Study	Design	Treatment	Enrolled Population	Outcomes
Gla-300				
EDITION 1 (34) (n = 807)	Phase 3, MC, OL, 24-week, randomized	Gla-300 QD evening + mealtime insulin vs. Gla-100 QD evening + mealtime insulin	Type 2 diabetes patients insufficiently controlled with basal + mealtime insulin, aged 60 years, duration of diabetes 15.8 years, A1C 8.15%, BMI 36.6 kg/m ²	Change in A1C: LS mean change –0.83% (SE 0.06) in both groups Nocturnal hypoglycemia*: 44.6 and 57.5% for Gla-300 and Gla-100, respectively; RR 0.78 (95% CI 0.68–0.89) Change in body weight: +0.9 kg for both treatment groups
EDITION 1 extension (35) (n = 714)	24-week extension to 1 year	Gla-300 QD evening + mealtime insulin vs. Gla-100 QD evening + mealtime insulin	Type 2 diabetes patients insufficiently controlled with basal + mealtime insulin, aged 60 years, duration of diabetes 15.8 years, A1C 8.15%, BMI 36.6 kg/m ²	Endpoint A1C: LS mean difference –0.17% (95% CI –0.30 to –0.05) for Gla-300 vs. Gla-100 Nocturnal hypoglycemia*: 54.5 and 64.7% for Gla-300 and Gla-100, respectively; RR 0.84 (95% CI 0.75–0.94) Change in body weight: +1.17 and +1.40 kg for Gla-300 and Gla-100, respectively; LS mean difference –0.23 kg (95% CI –0.74 to 0.27)
EDITION 2 (36) (n = 811)	Phase 3, MC, OL, 24-week, randomized	Gla-300 QD evening vs. Gla-100 QD evening	Adult type 2 diabetes patients insufficiently controlled with basal insulin + OADs, aged 58.2 years, duration of diabetes 12.6 years, A1C 8.24%, BMI 34.8 kg/m ²	Change in A1C: LS mean change –0.57% (SE 0.09) and –0.56% (SE 0.09) for Gla-300 and Gla-100, respectively LS mean difference –0.01% (95% CI –0.14 to 0.12) Nocturnal hypoglycemia*: 28.3 and 39.9% for Gla-300 and Gla-100, respectively; RR 0.71 (95% CI 0.58–0.86) Change in body weight: 0.08 and 0.66 kg for Gla-300 and Gla-100, respectively (P = 0.015)
EDITION 2 extension (37) (n = 811)	24-week extension to 1 year	Gla-300 QD evening vs. Gla-100 QD evening	Adult type 2 diabetes patients insufficiently controlled with basal insulin plus OADs, aged 58.2 years, duration of diabetes 12.6 years, A1C 8.24%, BMI 34.8 kg/m ²	Change in A1C: improvements maintained at 12 months Nocturnal hypoglycemia*: incidence RR 0.84 (95% CI 0.71–0.99) for Gla-300 vs. Gla-100 Change in body weight: +0.42 and +1.14 kg for Gla-300 and Gla-100, respectively (P = 0.0091)
EDITION 3 (38) (n = 878)	Phase 3, MC, OL, 24-week, randomized	Gla-300 QD evening vs. Gla-100 QD evening	Adult insulin-naïve type 2 diabetes patients, aged 57.7 years, duration of diabetes 9.8 years, A1C 8.5%, BMI 33.0 kg/m ²	Reduction in A1C: LS mean change –1.42% (SE 0.05) and –1.46% (SE 0.05) for Gla-300 and Gla-100, respectively Nocturnal hypoglycemia*: RR 0.76 (95% CI 0.59–0.99) Change in body weight: +0.4 and +0.7 kg for Gla-300 and Gla-100, respectively
EDITION 4 (39) (n = 549)	Phase 3, MC, OL, 24-week, randomized	Gla-300 QD morning or evening + mealtime insulin vs. Gla-100 QD morning or evening + mealtime insulin	Adult type 1 diabetes patients, duration of diabetes 21.0 years, A1C 8.12%, BMI 27.6 kg/m ²	Change in A1C: LS mean change –0.40% (SE 0.05) and –0.44% (SE 0.05) for Gla-300 and Gla-100, respectively Nocturnal hypoglycemia*: 8.0 and 8.9 events per patient-year for Gla-300 and Gla-100, respectively; rate ratio 0.90 (95% CI 0.71–1.14) Change in body weight: difference –0.56 kg (95% CI –1.09 to –0.03; P = 0.037)

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TABLE 1. Overview of Published Clinical Trials of Novel Insulin Formulations
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Study	Design	Treatment	Enrolled Population	Outcomes
EDITION meta-analysis (40) (n = 2,496)	Meta-analysis of three phase 3, MC, OL, 24-week, randomized trials	Gla-300 QD evening vs. Gla-100 QD evening	Heterogeneous adult type 2 diabetes population, aged 58.6 years, duration of diabetes 12.6 years, A1C 8.3%, BMI 43.8 kg/m ²	Change in A1C: LS mean change -1.02% (SE 0.06) in both groups Nocturnal hypoglycemia*: 30.0 and 39.8% for Gla-300 and Gla-100, respectively; RR 0.75 (95% CI 0.68–0.83) Change in body weight: difference -0.26 kg (95% CI -0.55 to -0.01; P = 0.039)
Basal insulin peglispro				
Rosenstock et al. (41) (n = 137)	Phase 2, OL, CO, 8-week, randomized	BIL QD pre-breakfast + mealtime insulin vs. Gla-100 QD pre-breakfast + mealtime insulin	Type 1 diabetes patients, aged 38.2 years, duration of diabetes 18 years, A1C 7.75%, BMI 27.3 kg/m ²	Endpoint A1C: 7.07% (SE 0.07) and 7.22% (SE 0.08) for BIL and Gla-100, respectively LS mean difference -0.18% (95% CI -0.25 to -0.10; P < 0.001) Endpoint daily mean BG: 144.2 and 151.7 mg/dL for BIL and Gla-100, respectively LS mean difference -9.9 mg/dL (90% CI -14.6 to -5.2; P < 0.001) Nocturnal hypoglycemia*: 0.88 (SE 1.22) and 1.13 (SE 1.42) events/month for BIL and Gla-100, respectively (P = 0.012) Change in body weight: -1.2 and +0.7 kg for BIL and Gla-100, respectively (P < 0.001)
Bergental et al. (42) (n = 288)	Phase 2, OL, 12-week, randomized	BIL QD pre-breakfast vs. Gla-100 QD pre-breakfast	Type 2 diabetes patients previously treated with insulin glargine or NPH insulin, aged 60 years, duration of diabetes 12 years, A1C 7.75%, BMI 32.1 kg/m ²	Endpoint A1C: 7.0% (SE 0.1) and 7.2% (SE 0.1) for BIL and Gla-100, respectively (P = 0.279) Change in daily mean BG: -27.4 mg/dL (SE 2.5) and -19.6 mg/dL (SE 3.1) for BIL and Gla-100, respectively LS mean difference -8.8 mg/dL (95% CI -15.0 to -2.7; P = 0.017) Change in body weight: -0.6 (SE 0.2) and +0.3 kg (SE 0.2) for BIL and Gla-100, respectively LS mean difference -0.8 kg (95% CI -1.3 to -0.4; P = 0.001) Nocturnal hypoglycemia*: BIL had a 48% reduction in nocturnal hypoglycemia after adjusting for baseline hypoglycemia (P = 0.021)

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TABLE 1. Overview of Published Clinical Trials of Novel Insulin Formulations
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Study	Design	Treatment	Enrolled Population	Outcomes
Insulin degludec				
BEGIN Basal-Bolus Type 2 (43) (n = 992)	Phase 3, OL, MC, 52-week, treat-to-target, randomized	IDeg QD vs. Gla-100 QD	Type 2 diabetes patients previously treated with any insulin \pm OADs, aged 58.9 years, duration of diabetes 13.5 years, A1C 8.3%, FPG 165.8 mg/dL	Change in A1C: -1.1 and -1.2% for IDeg and Gla-100, respectively Mean difference -0.08% (95% CI -0.05 to 0.21) Nocturnal hypoglycemia*: 1.4 and 1.8 events/PYE for IDeg and Gla-100, respectively Mean difference 0.75 (95% CI 0.58–0.99; $P = 0.0399$) Overall confirmed hypoglycemia: 11.1 and 13.6 events/PYE for IDeg and Gla-100, respectively; estimated rate ratio 0.82 (95% CI 0.69–0.99; $P = 0.0359$)
BEGIN FLEX (44) (n = 687)	Phase 3, OL, MC, 26-week, treat-to-target, randomized	IDeg QD flexible timing vs. IDeg QD evening meal vs. Gla-100 QD	Type 2 diabetes patient who were insulin-naïve patients or previously treated with basal insulin \pm OADs, aged 56.4 years, duration of diabetes 10.6 years, A1C 8.4%, BMI 29.6 kg/m ²	Change in A1C: -1.28 , -1.07 , and -1.26% for IDeg flexible, IDeg evening, and Gla-100, respectively Treatment difference for IDeg flexible vs. Gla-100: 0.04% (95% CI -0.12 to 0.20) Nocturnal hypoglycemia*: rate ratio 0.77 (95% CI 0.44–1.35; $P = \text{NS}$) for IDeg flexible vs. Gla-100 Change in body weight: $+1.5$ and $+1.3$ kg for IDeg flexible and Gla-100, respectively Treatment difference $+0.27$ kg (95% CI -0.25 to 0.79 ; $P = \text{NS}$)
BEGIN: FLEX T1 (45) (n = 490)	Phase 3, OL, MC, 26-week, treat-to-target, randomized	IDeg QD flexible timing vs. IDeg QD evening meal vs. Gla-100 QD + insulin aspart at mealtimes	Type 1 diabetes patients previously treated with basal-bolus therapy, aged 43.7 years, duration of diabetes 18.5 years, A1C 7.7%, weight 80.5 kg	Change in A1C: -0.40 , -0.41 , and -0.58% for IDeg flexible, IDeg, and Gla-100, respectively Nocturnal hypoglycemia*: 40% lower rate with IDeg flexible vs. Gla-100 ($P = 0.001$) Change in body weight: $+1.3$ and $+1.9$ kg for IDeg flexible and Gla-100, respectively ($P = \text{NS}$)
BEGIN Once Long (46) (n = 1,030)	Phase 3, OL, 52-week, randomized	IDeg QD + metformin vs. Gla-100 QD + metformin	Insulin-naïve type 2 diabetes patients, aged 59 years, duration of diabetes 9 years, A1C 8.2%, BMI 31.3 kg/m ²	Change in A1C: -1.06 and -1.19% for IDeg and Gla-100, respectively Treatment difference 0.09% (95% CI -0.04 to 0.22) Nocturnal hypoglycemia*: 0.25 and 0.39 events/PYE for IDeg and Gla-100, respectively ($P = 0.038$) Change in body weight: $+2.4$ and $+2.1$ kg for IDeg and Gla-100, respectively ($P = 0.28$)

*Nocturnal hypoglycemia reported as confirmed or severe nocturnal hypoglycemia (≤ 3.9 mmol/L [≤ 70 mg/dL]).

BG, blood glucose; BIL, basal insulin peglispro LY2605541; CO, crossover; FPG, fasting plasma glucose; IDeg, insulin degludec; LS, least square; MC, multicenter; NS, not significant; OAD, oral antidiabetes drug; OL, open-label; PYE, patient-year of exposure; QD, once daily; RR, relative risk; SE, standard error.

ing insulin therapy. Almost 90% of PCPs agreed that the “injection route of administration is the greatest barrier to patients’ acceptance of insulin therapy” (31). Although many PCPs appear to believe that reluctance to begin injection therapy is a barrier to insulin for their patients, the number of patients with true needle phobia is very small (32).

Although PCPs did not report believing that training in the administration and use of insulin is too complicated for most patients, 40% reported that providing this training was too time-consuming for staff (31). This demonstrates the lack of time and resources in busy primary care practices and highlights another potential barrier to insulin initiation. Very remote practices have limited or no access to certified diabetes educators, nurse practitioners, or physician’s assistants. In such practices, PCPs become the sole decision-maker and educator for insulin initiation and intensification. PCPs also become solely responsible for the follow-up of insulin-using patients, which is often perceived as another barrier to insulin therapy. Furthermore, PCPs can become overwhelmed by the number of insulin formulations available (and emerging) and their seemingly complex titration schedules (12). Even among practices with access to specialist HCPs, there may be disagreement regarding whose role it is to initiate insulin and help patients manage their insulin use (33).

Strategies to Improve Basal Insulin Initiation in the Primary Care Setting

Several approaches have emerged to address the underlying causes of patient resistance and clinical inertia that may facilitate insulin therapy in the primary care setting. These approaches include novel insulin formulations, insulin delivery systems, and insulin initiation strategies.

New Basal Insulins

New insulin formulations that provide more straightforward initiation

and treatment schedules or improved tolerability profiles may help to overcome some of the barriers for PCPs. The new insulins currently in development are described below and their studies are summarized in Table 1 (34–46).

Gla-300

Gla-300 is a new insulin formulation that delivers the same number of insulin units as Gla-100, but in one-third of the injection volume. At steady-state in type 1 diabetes, Gla-300 was associated with a more constant PK profile compared to Gla-100, with longer and tighter blood glucose control and a duration of action of >24 hours (24,47). The prolonged PK/PD profile of Gla-300 may allow for variations in time of administration, as suggested by a 3-month substudy of patients with type 2 diabetes from two phase 3 EDITION trials (EDITION 1 and EDITION 2) comparing the efficacy and safety of Gla-300 injected once-daily using a fixed (24-hour) versus a flexible (24 ± 3 -hour) dosing scheme (48). This substudy demonstrated comparable results in terms of A1C change and the proportion of patients experiencing ≥ 1 overall or nocturnal hypoglycemic events (defined as blood glucose <70 mg/dL).

The EDITION 1 (34) and EDITION 2 (36) safety and efficacy studies demonstrated comparable effective glycemic control with Gla-300 and Gla-100 in type 2 diabetes patients at 6 months. However, the 6-month extension studies of these two trials showed that A1C reduction was maintained (EDITION 2) or improved (EDITION 1) with Gla-300 compared to Gla-100 over 12 months (35,37). In both studies, the percentage of patients experiencing ≥ 1 confirmed or severe nocturnal hypoglycemic event (blood glucose <70 mg/dL) after 12 months was lower with Gla-300 than with Gla-100 (35,37).

Results from the EDITION 3 trial, conducted in insulin-naïve patients with type 2 diabetes, and the

EDITION 4 trial, conducted in type 1 diabetes patients, demonstrated comparable effective glycemic control with Gla-300 and Gla-100 and no significant differences in the event rates of confirmed or severe nocturnal hypoglycemia (blood glucose <70 mg/dL) over the 6-month study period (38,39).

A meta-analysis of the EDITION 1, 2, and 3 trials confirmed no difference in mean change in A1C between Gla-300 and Gla-100, as seen in the individual studies (40). The proportion of patients experiencing ≥ 1 confirmed or severe hypoglycemic event at any time of the day (over 24 hours) and during the night over the 6-month period was significantly lower with Gla-300 compared to Gla-100 (40). The availability of Gla-300 may help reassure PCPs who are reluctant to prescribe basal insulin by providing peace of mind about hypoglycemia for patients, as well as being a treatment regimen that may allow for flexible dosing, low hypoglycemia rates during the titration period (34,36), and a potentially enhanced safety profile. Furthermore, Gla-300 may be a valuable treatment option for a challenging and growing population of patients with a longer duration of type 2 diabetes and with a high-dose insulin requirement.

Insulin Degludec

Insulin degludec is a new basal insulin analog with an ultra-long-acting (>42-hour) and relatively peakless PK profile (49). The greatly enhanced duration of action is the result of the formation at the injection site of soluble multihexamers that are gradually released into the circulation.

Insulin degludec demonstrates similar glycemic efficacy and lower PD variability than insulin glargine (43,44,46). A meta-analysis concluded that insulin degludec appears to be associated with a lower incidence of nocturnal hypoglycemia than insulin glargine, with similar A1C reduction (50). The enhanced time-action profile of insulin deglu-

TABLE 2. Basal and Prandial Insulin Initiation and Titration Algorithms From World Medical Societies (63)

Measure	ADA/EASD	AACE/ACE	IDF	CDA
Basal algorithm				
Initial dose	10 units/day	10 units/day	Not specified	10 units/day
Titration	2 units every 3 days	1–3 units every 2–3 days	2 units every 3 days	1 unit daily
Target A1C (%)	<7.0	≤6.5	≤6.5	≤7.0
Target FPG (mg/dL)	70–130	<110*	<110	72–126
Prandial algorithm				
Initial dose	4 units	5 units	Not specified	Total daily dose of 0.3–0.5 units/kg† 40% of total = basal 20% of total = bolus (3 times/day)
Titration	2 units every 3 days	2–3 units every 2–3 days	2 units every 3 days	Not available
Target A1C (%)	<7.0	≤6.5	≤6.5	≤7.0
Target PPG (mg/dL)	<180	≤140‡	<145	90–180§

*FPG target recommendations from the AACE 2011 guidelines

†For initiation of intensive basal bolus therapy.

‡PPG target recommendations from AACE 2011 guidelines

§Adjust to 90–144 mg/dL if A1C targets are not being met.

AACE, American Association of Clinical Endocrinologists; ACE, American College of Endocrinology; ADA, American Diabetes Association; CDA, Canadian Diabetes Association; EASD, European Association for the Study of Diabetes; FPG, fasting plasma glucose; IDF, International Diabetes Federation; PPG, postprandial glucose.

dec allows for flexible timing of day-to-day dosing, and flexible dosing (at intervals of 8–40 hours) results in glycemic control and overall and nocturnal hypoglycemia rates similar to those resulting from fixed dosing (44,45,51). The flexible timing of once-daily insulin degludec administration may improve acceptance of insulin therapy among patients who prefer one injection per day and may also help to alleviate the concerns of PCPs regarding complex injection regimens.

Gla-300 and degludec are the only new basal insulins currently approved in the United States.

Basal Insulin Peglispro

The insulin analog basal insulin peglispro LY2605541 (BIL), is a novel, long-acting insulin that consists of insulin lispro modified with a 20-kDa polyethylene glycol moiety. The large hydrodynamic size of BIL delays insulin absorption and reduces renal clearance, resulting in a prolonged duration of action (52).

Experience with BIL in diabetes to date comes from two phase 2 studies (41,42). Currently, BIL is being investigated in the phase 3 IMAGINE development program with studies being conducted in type 1 diabetes (ClinicalTrials.gov identifiers NCT01481779, NCT01454284, NCT01769404, and NCT01792284) and type 2 diabetes (NCT01468987 and NCT01435616). Initial analyses of the IMAGINE 2, 4, and 5 trials demonstrated a noninferior reduction in A1C, a lower rate of nocturnal hypoglycemia, and comparable or significantly less weight gain (53). Increased liver enzymes and unfavorable lipid profiles have been reported and need to be further explored (52).

BIL may provide patients with diabetes with a lower risk of nocturnal hypoglycemia, reduced glycemic variability, and a weight advantage for a similar degree of glycemic control compared to insulin glargine. Such characteristics may help to counter some of the concerns of patients and

PCPs regarding the efficacy and tolerability of insulin.

Novel Insulin Delivery Systems

When considering treatment with insulin, many patients are concerned about the need for multiple injections and the hassle of carrying around vials and syringes (29,32). Pen devices are an alternative to vials and syringes, providing convenience, ease of use, accurate dosing, and dose titrations via an almost painless 32-gauge needle (12).

Whether real or perceived, patients' and PCPs' concerns regarding needle anxiety may be addressed by several new oral, transdermal, and inhaled insulin delivery options that are currently in development for both basal and nonbasal insulins. The oral insulins include ORMD-0801 (Oramed Ltd.; ClinicalTrials.gov identifier NCT01889667), rapid-acting IN-105 (Biocon Ltd.; NCT01035801), and long-acting NN1954 (Novo Nordisk; NCT01597713). Other options include the transdermal patch U-Strip (54)

and insulin patch pumps that provide insulin at a continuous basal rate with the option for on-demand bolus dosing (55). Furthermore, Technosphere inhaled ultra-rapid acting insulin (Afrezza; MannKind Corp.) appears to offer glycemic control comparable to injectable insulins (56,57) and has recently been approved in the United States for the treatment of both type 1 and type 2 diabetes (58). Once inhaled, this form of insulin dissolves on contact with the surface of the lungs, allowing for rapid absorption. The quick onset of action and short duration period (12–17 minutes) are sufficient for countering postprandial increases in blood glucose levels (59).

Novel Insulin Initiation Strategies

Randomized, controlled clinical trials have demonstrated that insulin treatment can be readily initiated and successfully intensified for many patients in the primary care setting (60–62). Several algorithms have been proposed for basal insulin initiation and treatment intensification (Table 2) (63). Such algorithms provide a pragmatic and simple approach that minimizes the need for primary care resources and allow patients to take control of their treatment through self-monitoring of blood glucose.

Insulin-naïve patients have been found to be as adept as physicians at titrating their insulin regimens (60), and, among patients with an A1C >7.0% despite insulin glargine therapy, the addition of insulin glulisine using a simple patient-managed titration algorithm has been proven to be as effective as a physician-managed algorithm (62). Simple, easy-to-learn algorithms are essential if patients are to take control of their blood glucose measurements and insulin titration. Furthermore, technological advances (e.g., telephone-based support [64], Web-based programs [65], and mobile phone health apps [66]) can help patients with type 2 diabetes feel educated, supported, and empowered

to take an active role in ensuring their own long-term health (67,68).

It is crucial that the insulin regimen is personalized for individual patients, taking into account their eating, sleeping, and exercise patterns; work or daily schedule; need for flexibility; level of engagement; and ability and willingness to take insulin. Appropriate insulin formulations can then be selected, and treatment schedules can be designed in collaboration with patients (12). It is also essential to assess and address patients' fears, worries, and barriers to maximize their ability and desire to initiate and maintain insulin therapy (32). Minimizing the number of hypoglycemia events during the first 8 weeks of treatment—the time when the greatest insulin dose titration occurs—may also increase patients' confidence to increase their insulin dosage when necessary.

To help overcome practice-level barriers to insulin initiation, PCPs can consider the potential roles of other HCPs—as well as patients—in managing type 2 diabetes (69). Integrating pharmacists, diabetes educators, and diabetes specialists into the primary care setting may also prove beneficial (70–73). As the increasing diversity of treatment options further complicates therapeutic choices, PCPs should take full advantage of multidisciplinary HCP team members to ensure that their own job in treating patients with diabetes is made easier rather than more complicated.

Conclusions

Numerous novel insulin products and delivery systems now in development have the potential to provide important benefits for patients with type 2 diabetes and to help PCPs initiate insulin more comfortably and earlier in the disease process. For example, new basal insulins provide targeted, practical solutions to specific barriers that currently limit the uptake of insulin by patients with type 2 diabetes and their PCPs. Once-daily injections of

Gla-300, insulin degludec, and BIL provide more constant PK profiles than Gla-100 and may reduce less nocturnal or overall hypoglycemia. For patients who require multiple daily injections or worry about the association between insulin and hypoglycemia, these new basal insulins may allay fears and become a viable option in the future.

At the same time, PCPs who are concerned about the intensity of training required to enable their patients to use insulin, or those who feel their patients would not be able to use insulin, may be convinced by the availability of a simpler treatment regimen. For PCPs, the future will include new, simple, and pragmatic treatment algorithms that place individual patients in control of their own insulin titration, as well as improved team-led approaches to patient management. It is acknowledged, however, that the diversity of existing and emerging treatment options may also complicate therapeutic choices. Therefore, it is imperative that the wider multidisciplinary health care team be involved in better educating, supporting, and engaging patients in managing type 2 diabetes, including determining the most appropriate treatment options.

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Duality of Interest

Dr. Brunton serves on advisory boards or speaker's bureaus for Abbott Pharmaceuticals, AstraZeneca, Becton Dickinson, Boehringer-Ingelheim, Eli Lilly and Company, Janssen Pharmaceuticals, Novo Nordisk, and Sanofi. Ms. Kruger serves on advisory boards or speaker's bureaus for Eli Lilly and Company, Novo Nordisk, and Sanofi. Ms. Funnell serves on advisory boards for Eli Lilly and Company and Novo Nordisk and receives

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References

1. Klein R. Hyperglycemia and microvascular and macrovascular disease in diabetes. *Diabetes Care* 1995;18:258–268
2. U.K. Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837–853
3. Chen HS, Wu TE, Jap TS, Hsiao LC, Lee SH, Lin HD. Beneficial effects of insulin on glycemic control and beta-cell function in newly diagnosed type 2 diabetes with severe hyperglycemia after short-term intensive insulin therapy. *Diabetes Care* 2008;31:1927–1932
4. Asche CV, Bode B, Busk AK, Nair SR. The economic and clinical benefits of adequate insulin initiation and intensification in people with type 2 diabetes mellitus. *Diabetes Obes Metab* 2012;14:47–57
5. American Diabetes Association. Standards of medical care in diabetes—2015. *Diabetes Care* 2015;38(Suppl. 1):S1–S92
6. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2015;38:140–149
7. Costi M, Dilla T, Reviriego J, Castell C, Goday A. Clinical characteristics of patients with type 2 diabetes mellitus at the time of insulin initiation: INSTIGATE observational study in Spain. *Acta Diabetol* 2010;47(Suppl. 1):169–175
8. Davis TM, Davis WA, Bruce DG. Glycaemic levels triggering intensification of therapy in type 2 diabetes in the community: the Fremantle Diabetes Study. *Med J Aust* 2006;184:325–328
9. Jones S, Benroubi M, Castell C, et al. Characteristics of patients with type 2 diabetes mellitus initiating insulin therapy: baseline data from the INSTIGATE study. *Curr Med Res Opin* 2009;25:691–700
10. Peyrot M, Rubin RR, Lauritzen T, et al. Resistance to insulin therapy among patients and providers: results of the cross-national Diabetes Attitudes, Wishes, and Needs (DAWN) study. *Diabetes Care* 2005;28:2673–2679
11. Nichols GA, Koo YH, Shah SN. Delay of insulin addition to oral combination therapy despite inadequate glycemic control: delay of insulin therapy. *J Gen Intern Med* 2007;22:453–458
12. Unger J. Insulin initiation and intensification in patients with T2DM for the primary care physician. *Diabetes Metab Syndr Obes* 2011;4:253–261
13. DeFronzo RA, Simonson D, Ferrannini E. Hepatic and peripheral insulin resistance: a common feature of type 2 (non-insulin-dependent) and type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 1982;23:313–319
14. DeFronzo RA, Tripathy D. Skeletal muscle insulin resistance is the primary defect in type 2 diabetes. *Diabetes Care* 2009;32(Suppl. 2):S157–S163
15. Piatt GA, Valerio MA, Nwankwo R, Lucas SM, Funnell MM. Health literacy among insulin-taking African Americans: a need for tailored interventions in clinical practice. *Diabetes Educ* 2014;40:240–246
16. Peters A. Incretin-based therapies: review of current clinical trial data. *Am J Med* 2010;123(3 Suppl.):S28–S37
17. Ilag LL, Kerr L, Malone JK, Tan MH. Prandial premixed insulin analogue regimens versus basal insulin analogue regimens in the management of type 2 diabetes: an evidence-based comparison. *Clin Ther* 2007;29:1254–1270
18. Emerging Risk Factors Collaboration, Sarwar N, Gao P, Seshasai SR, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010;375:2215–2222
19. Yakubovich N, Gerstein HC. Serious cardiovascular outcomes in diabetes: the role of hypoglycemia. *Circulation* 2011;123:342–348
20. Currie CJ, Johnson JA. The safety profile of exogenous insulin in people with type 2 diabetes: justification for concern. *Diabetes Obes Metab* 2012;14:1–4
21. Mellbin LG, Malmberg K, Norhammar A, Wedel H, Rydén L; DIGAMI 2 Investigators. Prognostic implications of glucose-lowering treatment in patients with acute myocardial infarction and diabetes: experiences from an extended follow-up of the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) 2 Study. *Diabetologia* 2011;54:1308–1317
22. Shaefer CF, Reid TS, Dailey G, et al. Weight change in patients with type 2 diabetes starting basal insulin therapy: correlates and impact on outcomes. *Postgrad Med* 2014;126:93–105
23. ORIGIN Trial Investigators. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med* 2012;367:319–328
24. Becker RH, Dahmen R, Bergmann K, Lehmann A, Jax T, Heise T. New insulin glargine 300 units/mL provides a more even activity profile and prolonged glycemic control at steady state compared with insulin glargine 100 units/mL. *Diabetes Care* 2015;38:637–643
25. Steintraesser A, Schmidt R, Bergmann K, Dahmen R, Becker RH. Investigational new insulin glargine 300 U/ml has the same metabolism as insulin glargine 100 U/ml. *Diabetes Obes Metab* 2014;16:873–876
26. Brod M, Kongsø JH, Lessard S, Christensen TL. Psychological insulin resistance: patient beliefs and implications for diabetes management. *Qual Life Res* 2009;18:23–32
27. Karter AJ, Subramanian U, Saha C, et al. Barriers to insulin initiation: the translating research into action for diabetes insulin starts project. *Diabetes Care* 2010;33:733–735
28. Ratanawongsa N, Crosson JC, Schillinger D, Karter AJ, Saha CK, Marrero DG. Getting under the skin of clinical inertia in insulin initiation: the Translating Research Into Action for Diabetes (TRIAD) Insulin Starts Project. *Diabetes Educ* 2012;38:94–100
29. Polonsky WH, Fisher L, Guzman S, Villa-Caballero L, Edelman SV. Psychological insulin resistance in patients with type 2 diabetes: the scope of the problem. *Diabetes Care* 2005;28:2543–2545
30. Phillips LS, Branch WT, Cook CB, et al. Clinical inertia. *Ann Intern Med* 2001;135:825–834
31. Hayes RP, Fitzgerald JT, Jacober SJ. Primary care physician beliefs about insulin initiation in patients with type 2 diabetes. *Int J Clin Pract* 2008;62:860–868
32. Funnell MM. Lessons from DAWN: implementing effective insulin therapy. *Internet J Adv Nurs Pract* 2008;Vol. 10
33. Furler J, Spitzer O, Young D, Best J. Insulin in general practice: barriers and enablers for timely initiation. *Aust Fam Phys* 2011;40:617–621
34. Riddle MC, Bolli GB, Ziemien M, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using basal and mealtime insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 1). *Diabetes Care* 2014;37:2755–2762
35. Riddle MC, Bolli GB, Yki-Järvinen H, et al. Sustained glycemic control and less hypoglycemia with new insulin glargine 300 U/mL compared with 100 U/mL: one-year results in people with T2DM using basal + mealtime insulin (EDITION 1) [Abstract 81-LB]. *Diabetes* 2014;63(Suppl. 1):LB20
36. Yki-Järvinen H, Bergenstal R, Ziemien M, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using oral agents and basal insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 2). *Diabetes Care* 2014;37:3235–3243
37. Yki-Järvinen H, Bergenstal RM, Bolli GB, et al. Less nocturnal hypoglycaemia and weight gain with new insulin glargine 300 U/ml vs 100 U/ml: 1-year results in people with type 2 diabetes using basal insulin and OADs (EDITION 2) [abstract 946]. *Diabetologia* 2014;57(Suppl. 1):S387
38. Bolli GB, Riddle MC, Bergenstal RM, et al. New insulin glargine 300 U/ml

- compared with glargine 100 U/ml in insulin-naïve people with type 2 diabetes on oral glucose-lowering drugs: a randomized controlled trial (EDITION 3). *Diabetes Obes Metab* 2015;17:386–394
39. Home PD, Bergenstal RM, Riddle MC, et al. Glycaemic control and hypoglycaemia with new insulin glargine 300 U/mL in people with type 1 diabetes (EDITION 4) [Abstract 148]. *Diabetologia* 2014;57(Suppl. 1):S69–S70
40. Ritzel R, Roussel R, Bolli GB, Vinet L, Yki-Järvinen H. New insulin glargine 300 U/mL: glycemic control and hypoglycemia in a meta-analysis of phase 3a EDITION clinical trials in people with T2DM [Abstract 90-LB]. *Diabetes* 2014;63(Suppl. 1):LB23
41. Rosenstock J, Bergenstal RM, Blevins TC, et al. Better glycemic control and weight loss with the novel long-acting basal insulin LY2605541 compared with insulin glargine in type 1 diabetes: a randomized, crossover study. *Diabetes Care* 2013;36:522–528
42. Bergenstal RM, Rosenstock J, Arakaki RF, et al. A randomized, controlled study of once-daily LY2605541, a novel long-acting basal insulin, versus insulin glargine in basal insulin-treated patients with type 2 diabetes. *Diabetes Care* 2012;35:2140–2147
43. Garber AJ, King AB, Del Prato S, et al. Insulin degludec, an ultra-long acting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. *Lancet* 2012;379:1498–1507
44. Meneghini L, Atkin SL, Gough SC, et al. The efficacy and safety of insulin degludec given in variable once-daily dosing intervals compared with insulin glargine and insulin degludec dosed at the same time daily: a 26-week, randomized, open-label, parallel-group, treat-to-target trial in individuals with type 2 diabetes. *Diabetes Care* 2013;36:858–864
45. Mathieu C, Hollander P, Miranda-Palma B, et al. Efficacy and safety of insulin degludec in a flexible dosing regimen vs insulin glargine in patients with type 1 diabetes (BEGIN: Flex T1): a 26-week randomized, treat-to-target trial with a 26-week extension. *J Clin Endocrinol Metab* 2013;98:1154–1162
46. Zinman B, Philis-Tsimikas A, Cariou B, et al. Insulin degludec versus insulin glargine in insulin-naïve patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN Once Long). *Diabetes Care* 2012;35:2464–2471
47. Becker RH, Nowotny I, Teichert L, Bergmann K, Kapitza C. Low within- and between-day variability in exposure to new insulin glargine 300 U/ml. *Diabetes Obes Metab* 2015;17:261–267
48. Jeandidier N, Riddle MC, Bolli GB, et al. New insulin glargine 300 U/ml: efficacy and safety of flexible vs fixed dosing intervals in people with type 2 diabetes mellitus [Abstract 961]. *Diabetologia* 2014;57(Suppl. 1):S393–S394
49. Heise T, Nosek L, Böttcher SG, Hastrup H, Haahr H. Ultra-long-acting insulin degludec has a flat and stable glucose-lowering effect in type 2 diabetes. *Diabetes Obes Metab* 2012;14:944–950
50. Vora J, Christensen T, Rana A, Bain SC. Insulin degludec versus insulin glargine in type 1 and type 2 diabetes mellitus: a meta-analysis of endpoints in phase 3a trials. *Diabetes Ther* 2014;5:435–446
51. Josse RG, Woo V. Flexibly timed once-daily dosing with degludec: a new ultra-long-acting basal insulin. *Diabetes Obes Metab* 2013;15:1077–1084
52. Madsbad S. LY2605541: a preferential hepato-specific insulin analogue. *Diabetes* 2014;63:390–392
53. Eli Lilly and Company. Lilly's basal insulin peglispro shows superiority in HbA1c reduction compared to insulin glargine in three phase III trials in patients with type 2 diabetes. Available from <https://investor.lilly.com/releasedetail.cfm?releaseid=847123>. Accessed 18 March 2015
54. Transdermal Specialties. The U-Strip – insulin patch. Available from <http://www.transdermalspecialties.com/u-strip-patch.html>. Accessed 18 March 2015
55. Skladany MJ, Miller M, Guthermann JS, Ludwig CR. Patch-pump technology to manage type 2 diabetes mellitus: hurdles to market acceptance. *J Diabetes Sci Technol* 2008;2:1147–1150
56. Rosenstock J, Lorber DL, Gnudi L, et al. Prandial inhaled insulin plus basal insulin glargine versus twice daily biphasic insulin for type 2 diabetes: a multicentre randomised trial. *Lancet* 2010;375:2244–2253
57. Boss AH, Petrucci R, Lorber D. Coverage of prandial insulin requirements by means of an ultra-rapid-acting inhaled insulin. *J Diabetes Sci Technol* 2012;6:773–779
58. MannKind Corporation. Briefing document. AFREZZA® (insulin human [rDNA origin]) inhalation powder: an ultra-rapid acting insulin treatment to improve glycaemic control in adult patients with diabetes mellitus. Available from <http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm390865.pdf>. Accessed 18 March 2015
59. Zisser H, Jovanovic L, Markova K, et al. Technosphere insulin effectively controls postprandial glycaemia in patients with type 2 diabetes mellitus. *Diabetes Technol Ther* 2012;14:997–1001
60. Meneghini L, Koenen C, Weng W, Selam JL. The usage of a simplified self-titration dosing guideline (303 Algorithm) for insulin detemir in patients with type 2 diabetes: results of the randomized, controlled PREDICTIVE 303 study. *Diabetes Obes Metab* 2007;9:902–913
61. Davies M, Evans R, Storms F, Gomis R, Khunti K. Initiation of insulin glargine in suboptimally controlled patients with type 2 diabetes: sub-analysis of the AT.LANTUS trial comparing treatment outcomes in subjects from primary and secondary care in the UK. *Diabetes Obes Metab* 2007;9:706–713
62. Harris SB, Yale JF, Berard L, et al. Does a patient-managed insulin intensification strategy with insulin glargine and insulin glulisine provide similar glycemic control as a physician-managed strategy? Results of the START (Self-Titration with Apidra to Reach Target) study: a randomized noninferiority trial. *Diabetes Care* 2014;37:604–610
63. LaSalle JR, Berria R. Insulin therapy in type 2 diabetes mellitus: a practical approach for primary care physicians and other health care professionals. *J Am Osteopath Assoc* 2013;113:152–162
64. Chan JC, Sui Y, Oldenburg B, et al. Effects of telephone-based peer support in patients with type 2 diabetes mellitus receiving integrated care: a randomized clinical trial. *JAMA Intern Med* 2014;174:972–981
65. van Vugt M, de Wit M, Cleijne WH, Snoek FJ. Use of behavioral change techniques in web-based self-management programs for type 2 diabetes patients: systematic review. *J Med Internet Res* 2013;15:e279
66. Goyal S, Cafazzo JA. Mobile phone health apps for diabetes management: current evidence and future developments. *Q J Med* 2013;106:1067–1069
67. White RD. Patient empowerment and optimal glycemic control. *Curr Med Res Opin* 2012;28:979–989
68. Spollett GR. Insulin initiation in type 2 diabetes: what are the treatment regimen options and how can we best help patients feel empowered? *J Am Acad Nurse Pract* 2012;24(Suppl. 1):249–259
69. Peyrot M, Rubin RR, Khunti K. Addressing barriers to initiation of insulin in patients with type 2 diabetes. *Prim Care Diabetes* 2010;4(Suppl. 1):S11–S18
70. Harris SB, Gerstein HC, Yale JF, et al. Can community retail pharmacist and diabetes expert support facilitate insulin initiation by family physicians? Results of the AIM@GP randomized controlled trial. *BMC Health Serv Res* 2013;13:71
71. Brown SA. Effects of educational interventions in diabetes care: a meta-analysis of findings. *Nurs Res* 1988;37:223–230
72. Brown SA. Meta-analysis of diabetes patient education research: variations in intervention effects across studies. *Res Nurs Health* 1992;15:409–419
73. Shah BR, Hux JE, Laupacis A, Zinman B, Austin PC, van Walraven C. Diabetic patients with prior specialist care have better glycaemic control than those with prior primary care. *J Eval Clin Pract* 2005;11:568–575