

Hypoglycemia with New-Generation Basal Analog Insulins: A Descriptive Critical Review

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Abstract

Optimizing the treatment of people with diabetes relies on balancing the benefits of glycemic control with the risk of hypoglycemia. Although insulin is essential for treating patients with type 1 diabetes mellitus, patient and physician concerns regarding an increased risk of hypoglycemia can lead to delays in initiating insulin treatment in patients with type 2 diabetes mellitus. This clinical inertia contributes to reduced glycemic control and poorer outcomes for patients. Advances in insulin agents have reduced the risk of hypoglycemia. In particular, the introduction of insulin glargine, the first basal analog insulin with a 24-hour glucose-lowering profile with no pronounced peak, represented a significant step towards achieving this goal.

To further improve patient management, a number of insulin formulations and molecules are in development and are designed to have pharmacokinetic/pharmacodynamic (PK/PD) profiles allowing closer mimicking of normal physiologic insulin release. Here we review these new agents, and discuss their hypoglycemic risk as reported in clinical trials. In addition, the difficulties in making comparative evaluations from studies with different patient populations and definitions of hypoglycemia are discussed. Solutions to improve future clinical trials are suggested. In general, the improved PK/PD profiles of new-generation insulins appear to result in better clinical outcomes in terms of hypoglycemia. What is needed are head-to-head trials using standardized methods and criteria to allow clinicians to compare hypoglycemia rates between insulins, and help them to discuss appropriate choices of therapy with their patients.

Keywords: Hypoglycemia; Insulin; Type 1 diabetes; Type 2 diabetes

Introduction

Insulin treatment is essential for individuals with type 1 diabetes mellitus (T1DM). As a result of progressive beta-cell deterioration in type 2 diabetes mellitus (T2DM), most patients with T2DM eventually require insulin to achieve and maintain optimal glycemic targets. Usually, basal insulin is initiated before adding prandial therapy to maintain glycemic control [1]. Optimizing diabetes treatment depends on balancing glycemic control and the risk of hypoglycemia.

As plasma glucose levels decrease, there is a hierarchy of physiologic counterregulatory responses aimed at preventing further decreases and restoring normal plasma glucose levels (Figure 1) [2,3]. When plasma glucose levels decrease to <70 mg/dl (3.8 mmol/l), activation of counterregulation mechanisms begins; i.e., an increase in the secretion of glucagon, catecholamines, cortisol, and growth hormone, and a decrease in insulin secretion. These changes occur before there are any signs or symptoms related to hypoglycemia. As a consequence of these counterregulatory changes, there is an initial increase in hepatic and renal glucose release into the circulation (approximately equal amounts of glucose are released from the liver and kidneys), followed by a decrease in removal of glucose from the circulation. Decreases in plasma glucose to ~60 mg/dl (3.3 mmol/l) usually evoke the so-called autonomic warning symptoms (hunger, anxiety, palpitations, sweating, nausea). If interpreted correctly, these lead the patient to eat and thus prevent more serious hypoglycemia. If plasma glucose levels decrease to ~55 mg/dl (3.0 mmol/l), neuroglycopenic signs and symptoms of brain dysfunction (blurred vision, slurred speech, glassy eyed appearance, confusion) occur. Concentrations of plasma glucose below 30 mg/dl (1.6 mmol/l) - if prolonged - can cause seizures, permanent neurologic deficits, and death [4].

Within a few years of diabetes onset, people with T1DM develop

impaired counterregulatory hormone responses, which are manifested first by decreased or absent glucagon responses to hypoglycemia [3]. This is followed by decreased catecholamine responses, and later by variable decreases in growth hormone and cortisol responses. Defective glucose counterregulation plays a major role in the susceptibility to severe hypoglycemia of people with T1DM. In contrast, people with T2DM experience more modest impairment in glucose counterregulation [5].

In addition to impaired glucose counterregulation, people with T1DM and T2DM may suffer from hypoglycemia unawareness [4]. These patients have an often transient loss of the autonomic symptoms warning them of developing hypoglycemia; these symptoms would normally have prompted them to take appropriate action (i.e., food intake before occurrence of severe hypoglycemia with neuroglycopenia). Hypoglycemia unawareness can be reversed in most cases by instigating a management plan that includes strict avoidance of hypoglycemia [6,7].

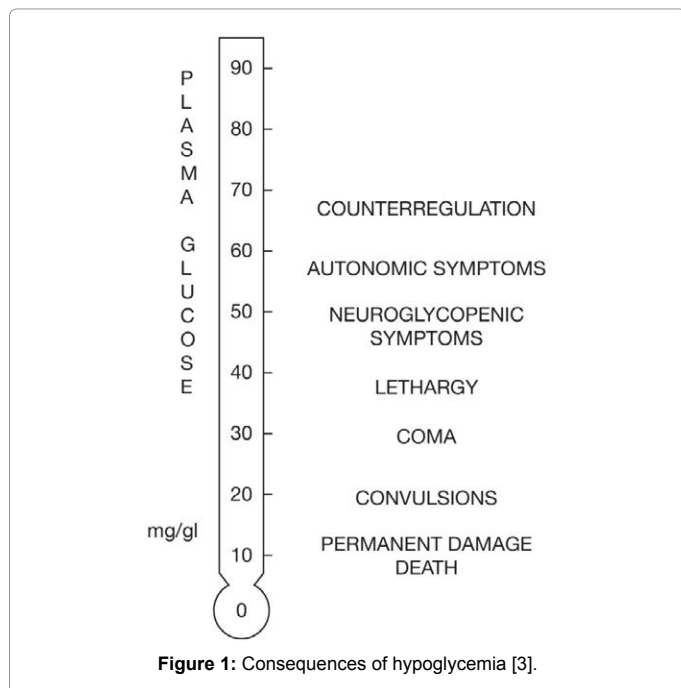
Although long-term studies suggest that tight glycemic control can reduce diabetes complications [8,9], this tight control increases the risk of hypoglycemia [9-11]. Concerns regarding hypoglycemia can lead to clinical inertia among physicians and barriers to initiating insulin

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Received June 05, 2015; Accepted June 29, 2015; Published July 03, 2015

Citation: Alsahli M, Thrasher JR, Gerich JE (2015) Hypoglycemia with New-Generation Basal Analog Insulins: A Descriptive Critical Review. J Diabetes Metab 6: 576. doi:10.4172/2155-6156.1000576

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among patients. These have clinical consequences, as hypoglycemic events and the fear of future hypoglycemia are associated with reduced adherence to and persistence with treatment [12-15]. In turn, lower adherence is associated with the reduced likelihood to intensify treatment [16], and contributes to suboptimal glycemic control [17].

The majority of people with T2DM will progress to basal insulin therapy when oral antidiabetes drugs (OADs) fail to maintain adequate glycemic control. The relative simplicity of basal insulin regimens alongside the concept of “fix fasting first” makes basal insulin a desirable choice when intensifying treatment. However, as the disease progresses, this is usually insufficient for maintaining glycemic control and postprandial control is generally also required [18]. Various insulin therapies are available, but the introduction of the long-acting basal analog insulin glargine 100 units/ml (Gla-100) resulted in a reduction in rates of hypoglycemia compared with NPH insulin [19,20]. Diabetes treatment is an evolving field of medicine, with new-generation therapies in development.

The efficacy and safety of investigational insulins have been compared with standardized insulin in treat-to-target trials [21]. In these trials, insulin dosages are titrated in patients according to a specific algorithm so they can achieve a determined treatment glycemic goal [22]. At the same time, clinicians are able to determine differences in other treatment effects, like weight gain and hypoglycemia. It should be noted that the results of treat-to-target trials are sensitive to sample size [23]. For this reason, treat-to-target trials are subject to bias, unless a specific algorithm is rigorously enforced.

In this paper, we review the new generation of basal analog insulins in terms of their effect on hypoglycemia rates in clinical trials. A review of current literature and recent conference abstracts was undertaken to gather evidence. PubMed was searched with the search term: “basal insulin” OR “long-acting insulin” OR “ultra-long insulin” OR “long-acting basal” OR “ultra-long acting basal”. Furthermore, abstracts from the annual conferences of the European Association for the Study of Diabetes (EASD) of 2013 and 2014 were searched. Results were taken for any novel long-acting basal insulins with hypoglycemia data.

Pharmacokinetic/Pharmacodynamic Profiles of Novel Basal Analog Insulins

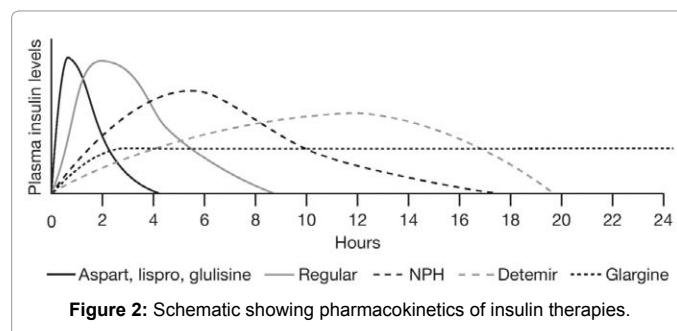
A key goal of insulin therapy is replicating physiologic basal insulin release: the release of insulin averages around 1.3 U/h under normoglycemic physiologic conditions [24]. As the first basal analog insulin with a 24-hour glucose-lowering profile with no pronounced peak [25], Gla-100 represented a significant step towards achieving this goal. Gla-100’s pharmacokinetic (PK) and pharmacodynamic (PD) profile resulted in the first opportunity for basal insulin coverage with once-daily (QD) dosing. Insulin detemir (IDet) has a similar glucose-lowering profile to Gla-100, often allowing basal coverage from a single daily dose, although twice-daily injections are required in up to 57% of patients (Figure 2) [26].

Advances in insulin therapy have included developing new agents or evolving established therapies. Increasing half-lives and improving peak-trough dynamics have provided a number of agents with therapeutic potential in treating hyperglycemia that more closely mimic physiologic insulin release patterns with fewer injections.

Insulin degludec (IDeg) is a new basal analog insulin with a PK/PD profile that extends glucose lowering beyond 24 hours. Upon injection, IDeg di-hexamers assemble to form stable multi-hexamers. These form a soluble depot in the subcutaneous tissue from which IDeg monomers slowly dissociate. Studies to determine the PK/PD profile of IDeg demonstrate an evenly distributed glucose-lowering profile, with a terminal half-life of more than 25 hours under steady state conditions [27] and a duration of action reported to be over 40 hours [28].

A new formulation of Gla-100 is in development (insulin glargine 300 units/ml [Gla-300]), in which the same number of insulin units as Gla-100 is delivered, but in a third of the injection volume. Gla-100 forms crystals at neutral pH when injected subcutaneously; Gla-300 forms a more compact depot of crystals resulting in a lower depot surface area and a slower rate of dissolution. In patients with T1DM, PK/PD studies of Gla-300 have demonstrated a longer, smoother glucose-lowering profile compared with Gla-100, with a terminal half-life of approximately 19 hours and activity up to 36 hours, resulting in tighter glucose control [29-31]. The peak-trough ratio of Gla-300 is low at ~1.7 versus 2.3 for Gla-100, and this helps to minimize glycemic variability [32]. Theoretically, the less pronounced peak of action could result in a more gradual drop in blood glucose, with a reduced risk of hypoglycemia; this would need to be confirmed clinically in phase 3 trials.

Other basal insulins are in development that also have extended terminal half-lives and activity profiles. A PEGylated form of the fast-acting basal insulin lispro LY2605541 (basal insulin peglispro [BIL]) has a functional size of approximately 75 kDa due to the hydrodynamic properties of the polyethylene glycol chain linked to the insulin lispro



molecule. This results in slowed absorption and possible preferential hepatic activity [33]. BIL is approximately four times larger than un-PEGylated lispro, which contributes to the PK/PD profile of BIL. Data from patients with T2DM suggest that a relatively long time is required to achieve steady state: 7-10 days versus 2-4 days for IDeg and Gla-300, respectively [27,29]. BIL has a terminal half-life of 45-76 hours and low peak-trough fluctuation [34]. In a recent PK/PD study in patients with T2DM, the new insulin glargine LY2963016 was shown to have a similar profile to Gla-100, with a duration of action of approximately 24 hours [35].

In earlier-stage clinical development, HM12470 is a long-acting basal analog insulin produced by conjugating an insulin analog to the constant region of a human immunoglobulin fragment using a non-peptidyl linker [36]. Animal studies in rats showed an approximately 43-hour half-life for HM12470 compared with 2.9 hours for IDeg [36]. Animal studies in mice, rats, and dogs showed a predicted half-life of HM12470 of approximately 132 hours and a low peak-trough ratio of 1.6 in humans [36]. This long half-life may allow once-weekly dosing.

BIOD-531 is a concentrated formulation of recombinant human insulin (400 units/ml) with a high dose:volume ratio and more rapid

absorption, owing to the addition of EDTA, citrate, and MgSO₄ [37]. Data suggest that BIOD-531 has a rapid onset of action and a duration of action of around 18 hours in non-diabetic obese subjects [38].

New basal analog insulins and hypoglycemia

As noted above, the clinical use of Gla-100 is associated with a lower risk of hypoglycemia than NPH insulin; this is a result of its longer, more constant PK/PD profile and a reduction in the variability of glucose-lowering effects [19,20]. Data from clinical trials suggest that the newer generation of basal analog insulins, with their extended, smoother PK/PD profiles, may also result in improved rates of hypoglycemia compared with currently available insulins. In this section, we summarize data from clinical trials with these agents in patients with T2DM and T1DM (trials are summarized in Tables 1 and 2, respectively). Data reviewed are restricted to head-to-head phase 3 clinical trials. Note that data on hypoglycemia rates for BIOD-531 and HM12470 are not yet available.

Hypoglycemia in T2DM

Hypoglycemia is a frequent adverse effect of the treatment of T2DM, with hypoglycemic events commonly occurring at night. As

Study	Investigational vs comparator	Population	n	Hypoglycemia category	Result	RR ^{ab} (95% CI)	P value
BEGIN Once Long [46]	Insulin degludec vs insulin glargine	Adults with T2DM (A1C 7.0-10.0%) taking OADs only	1030	- Confirmed hypoglycemia (PG \leq 54 mg/dl or severe*)	1.52 vs 1.85 episodes/PYE	RR ^a 0.82 (0.64-1.04)	0.106
				- Nocturnal confirmed hypoglycemia	0.25 vs 0.39 episodes/PYE	RR ^a 0.64 (0.42-0.98)	0.038
				- Severe*	0.003 vs 0.023 episodes/PYE	RR ^a 0.14 (0.03-0.70)	0.017
BEGIN Once Asia [49]	Insulin degludec vs insulin glargine	Asian adults with T2DM (A1C 7.0-10.0%) taking OADs only	435	- Confirmed hypoglycemia (PG \leq 54 mg/dl or severe*)	3.0 vs 3.7 episodes/PYE	RR ^a 0.82 (0.60-1.11)	0.2
				- Nocturnal confirmed hypoglycemia	0.8 vs 1.2 episodes/PYE	RR ^a 0.62 (0.38-1.04)	0.07
				- Severe*	-	-	-
BEGIN Basal-Bolus [47]	Insulin degludec + insulin aspart vs insulin degludec + insulin aspart	Adults with T2DM (A1C 7.0-10.0%) on any insulin regimen with or without OADs	1006	- Confirmed hypoglycemia (PG \leq 54 mg/dl or severe*)	11.1 vs 13.6 episodes/PYE	RR ^a 0.82 (0.69-0.99)	0.0359
				- Nocturnal confirmed hypoglycemia	1.39 vs 1.84 episodes/PYE	RR ^a 0.75 (0.58-0.99)	0.0399
				- Severe*	0.06 vs 0.05 episodes/PYE	-	-
BEGIN Flex [48]	Insulin degludec flexible [†] vs insulin degludec fixed vs insulin glargine	Adults with T2DM taking OADs (A1C 7.0-11.0%) or basal insulin + OADs (A1C 7.0-10.0%)	687	- Confirmed hypoglycemia (PG \leq 54 mg/dl or severe*)	3.6 vs 3.6 vs 3.5 episodes/PYE	RR ^a 1.03 (0.75-1.40) flexible vs glargine RR ^a 1.10 (0.79-1.52) flexible vs fixed	NS NS
				- Nocturnal confirmed hypoglycemia	0.6 vs 0.6 vs 0.8 episodes/PYE	RR ^a 0.77 (0.44-1.35) flexible vs glargine RR ^a 1.18 (0.66-2.12) flexible vs fixed	NS NS
				- Severe*	-	-	-
EDITION 1 [54]	Gla-300 vs Gla-100	Adults with T2DM (A1C 7.0-10.0%) using \geq 42 U/day basal insulin + mealtime insulin	807	- Confirmed hypoglycemia (PG \leq 70 mg/dl or severe*)	81.9% vs 87.8%	RR ^b 0.93 (0.88-0.99)	-
				- Nocturnal confirmed hypoglycemia	44.6% vs 57.5%	RR ^b 0.78 (0.68-0.89)	-
				- Severe*	5.0% vs 5.7%	RR ^b 0.87 (0.48-1.55)	-
EDITION 2 [55]	Gla-300 vs Gla-100	Adults with T2DM (A1C 7.0-10.0%) using \geq 42 U/day basal insulin + OADs	811	- Confirmed hypoglycemia (PG \leq 70 mg/dl or severe*)	70.0% vs 77.3%	RR ^b 0.90 (0.83-0.98)	-
				- Nocturnal confirmed hypoglycemia	28.3% vs 39.9%	RR ^b 0.71 (0.58-0.86)	-
				- Severe*	1.0% vs 1.5%	-	-

EDITION 3 [56]	Gla-300 vs Gla-100	Adults with T2DM (A1C 7.0-11.0%) on OADs	878	- Confirmed hypoglycemia (PG ≤70 mg/dl or severe*)	46.2% vs 52.5%	RR ^b 0.88 (0.77-1.01)	-
				- Nocturnal confirmed hypoglycemia	17.9% vs 23.5%	RR ^b 0.76 (0.59-0.99)	-
				- Severe*	0.9% vs 0.9%	-	-
EDITION JP 2 [57]	Gla-300 vs Gla-100	Asian adults with T2DM basal insulin + OADs	241	- Confirmed hypoglycemia (PG ≤70 mg/dl or severe*)	65.0% vs 76.7%	RR ^b 0.86 (0.73-1.01)	-
				- Nocturnal confirmed hypoglycemia	28.3% vs 45.8%	RR ^b 0.62 (0.44-0.88)	-
				- Severe*	-	-	-
Bergenstal et al., 2012 [58]	peglispro vs insulin glargine	Adults with T2DM (A1C ≤10.5%) on basal insulin and OADs	289	- Total hypoglycemia (BG ≤70 mg/dl or symptoms)	1.34 vs 0.34 events/30 days	-	0.804
				- Nocturnal hypoglycemia	0.25 vs 0.39 events/30 days	-	0.178
ELEMENT 2 [61]	LY2963016 vs insulin glargine	Adults with T2DM on OADs (A1C 7.0-11.0%) or insulin glargine + OADs (A1C ≤11.0%)	756	- Total hypoglycemia (BG ≤70 mg/dl or symptoms)	21.3 vs 22.3	-	0.995

*Requiring assistance; †dosing schedule creating 8-40 hours between injections. A1C, glycated hemoglobin; BG, blood glucose; CI, confidence interval; NS, not significant; PG, plasma glucose; PYE, patient year of exposure; OADs, oral antidiabetic drugs; RR^a, rate ratio; RR^b, relative risk; T2DM, type 2 diabetes mellitus.

Table 1: Hypoglycemia in randomized clinical trials of novel basal analog insulins in T2DM [46-49,54-58,61].

Study	Investigational vs comparator	Population	n	Hypoglycemia category	Result	RR ^{ab} (95% CI)	P value
BEGIN Basal-Bolus Type 1 [28]	Insulin degludec + insulin aspart vs insulin degludec + insulin aspart	Adults with T1DM (A1C ≤10%) on basal-bolus therapy	629	- Confirmed hypoglycemia (PG <54 mg/dl or severe*)	42.54 vs 40.18 events/PYE	RR ^a 1.07 (0.89-1.28)	0.48
				- Nocturnal confirmed hypoglycemia	4.41 vs 5.86 events/PYE	RR ^a 0.75 (0.59-0.96)	0.021
				- Severe*	0.21 vs 0.16 events/PYE	RR ^a 1.38 (0.72-2.64)	0.34
BEGIN Flex T1 [62]	Insulin degludec flexible [†] + insulin aspart vs insulin degludec fixed + insulin aspart vs insulin glargine+insulin aspart	Adults with T1DM (A1C ≤10%) on basal-bolus therapy	493	- Confirmed hypoglycemia (PG <54 mg/dl or severe*)	82.4 vs 88.3 vs 79.7 events/PYE	RR ^a 1.03 (0.85-1.26) flexible vs glargine	NS
					RR ^a 0.92 (0.76-1.12) flexible vs fixed	NS	
				- Nocturnal confirmed hypoglycemia	6.2 vs 9.6 vs 10.0 events/PYE	RR ^a 0.60 (0.44-0.82) flexible vs glargine	0.001
					RR ^a 0.63 (0.46-0.86) flexible vs fixed	0.003	
				- Severe*	0.3 vs 0.4 vs 0.5 events/PYE	RR ^a 0.89 (0.40-1.99) flexible vs glargine	NS
					RR ^a 1.09 (0.48-2.48) flexible vs fixed	NS	
EDITION 4 [63]	Gla-300 vs Gla-100	Adults with T1DM basal insulin + prandial insulin	549	- Confirmed hypoglycemia (PG ≤70 mg/dl or severe*)	78.4 vs 72.5 events/PYE	RR ^a 1.09 (0.94-1.25)	-
				- Nocturnal confirmed hypoglycemia	8.0 vs 8.9 events/PYE	RR ^a 0.90 (0.71-1.14)	-
				- Severe*	6.6% vs 9.5%	-	-
Edition 4 JP 1 [64]	Gla300 vs Gla-100	Adults with T1DM basal insulin + prandial insulin	243	- Confirmed hypoglycemia (PG ≤70 mg/dl or severe*)	96.7% vs 97.5%	RR ^b 0.99 (0.95-1.04)	-
				- Nocturnal confirmed hypoglycemia	68.9% vs 81.0%	RR ^b 0.85 (0.73-0.99)	-
				- Severe*	-	-	-

Rosenstock et al., 2013 [65]	LY2605541 + prandial insulin vs insulin glargine + prandial insulin	Adults with T1DM (A1C ≤10.5%) on basal-bolus insulin	137	- Total hypoglycemia (BG ≤70 mg/dl or symptoms)	8.74 vs 7.36 events/PME	RR ^a 1.12 (1.03-1.23)	0.037
				- Nocturnal hypoglycemia	0.88 vs 1.13 events/PME	RR ^a 0.75 (0.62-0.90)	0.012
				- Severe	6 events in both arms (in 5 vs 3 patients)	-	-
ELEMENT 1 [66]	LY2963016 + insulin lispro vs insulin glargine + insulin lispro	Adults with T1DM (A1C ≤11%) on basal-bolus insulin	535	- Total hypoglycemia (BG ≤70mg/dl or symptoms)	86.5% vs 89.2%	-	0.717

*Requiring assistance; †dosing schedule creating 8-40 hours between injections. A1C, glycated hemoglobin; BG, blood glucose; CI, confidence interval; NS, not significant; PG, plasma glucose; PME, patient month of exposure; PYE, patient year of exposure; RRA, rate ratio; RRb, relative risk; T1DM, type 1 diabetes mellitus.

Table 2: Hypoglycemia in randomized clinical trials of novel basal analog insulins in T1DM [28,62-66].

well as accidents and physical injury, the sequelae of hypoglycemia involve neurologic and cardiovascular complications discussed above [39]. Although reported rates of hypoglycemia in clinical trials vary considerably because of differences in study design, definitions used, and population included (among other factors) [40], a recent non-randomized retrospective study using real-world outcomes from patients treated with Gla-100 or IDet in the United States suggested a rate of hypoglycemia of ~8% [41]. Treatment regimen and a history of hypoglycemia are the most important predictors of future hypoglycemic events, but renal insufficiency, older age, and history of hypoglycemia-associated autonomic failure are also important risk factors [42].

Insulin degludec: IDeg is currently licensed for use in the European Union, Japan, Mexico, and India. However, to date the US Food and Drug Administration (FDA) has declined to approve IDeg following a possible signal of an increased risk of major adverse cardiovascular events, and has requested additional cardiovascular outcomes data from a dedicated trial [43,44].

In common with the other novel basal analog insulins, head-to-head trials of IDeg have concentrated on Gla-100 as a comparator, as this is the most widely used and extensively studied basal analog insulin. A meta-analysis of results from phase 3 trials suggests that the efficacy, in terms of lowering glycated hemoglobin (A1C), of IDeg and Gla-100 was similar in patients with T2DM [45]. Hypoglycemia event outcomes with IDeg compared with Gla-100 have been reported from the BEGIN series of phase 3 trials, in which confirmed hypoglycemia was defined as a composite of episodes with a recorded self-monitored blood glucose (SMBG) value of less than ~54 mg/dl (3.1 mmol/l) and severe episodes were defined as those requiring assistance. Statistical comparisons of hypoglycemia between patient groups primarily used rate ratios in the trials.

The BEGIN Once Long trial was a 52-week, parallel-group, open-label, head-to-head trial of Gla-100 or IDeg QD with treat-to-target titration to achieve pre-breakfast plasma glucose of ~70-90 mg/dl (3.9-4.9 mmol/l) [46]. In this trial, rates of confirmed hypoglycemia were similar between patient groups, and rates of confirmed nocturnal hypoglycemia (events occurring between 00:01 and 5:59 hours) were significantly lower with IDeg (Table 1). Although severe hypoglycemic episodes were rare in both groups, there was a statistical advantage for patients treated with IDeg (Table 1).

The BEGIN Basal-Bolus trial was a 52-week, parallel-group, open-label trial of patients treated with IDeg or Gla-100 QD plus mealtime insulin aspart, in which basal analog insulins were titrated with an aim of achieving blood glucose ~70-90 mg/dl (3.9-5.0 mmol/l) [47]. In this study, both confirmed hypoglycemia and confirmed nocturnal hypoglycemic events were significantly fewer with IDeg (Table 1). The incidence of severe episodes of hypoglycemia appeared to be similar

between groups; however, rates were too low to assess statistically (Table 1).

The BEGIN series of studies also included trials with a 26-week duration. BEGIN FLEX was a 26-week, open-label, three-arm, parallel-group trial, in which patients received IDeg QD flexibly dosed to a pre-specified rotating morning and evening dosing schedule (IDeg FLEX), creating 8-40 hour intervals between doses [48]. IDeg QD was dosed at the evening meal, or Gla-100 dosed at the same time each day. This trial had a treat-to-target design aimed at achieving blood glucose ~70-90 mg/dl (3.9-5.0 mmol/l) [48]. There were no significant differences in terms of confirmed hypoglycemia, confirmed nocturnal hypoglycemia, and/or severe hypoglycemia between the three treatment groups (Table 1).

In the 26-week, open-label BEGIN Once Asia study, patients were treated with either IDeg or Gla-100 QD, with a titration target of blood glucose ~70-90 mg/dl (3.9-5.0 mmol/l) [49]. There were no significant differences in rates of confirmed overall or nocturnal hypoglycemia over the trial period (Table 1).

Insulin glargine 300 units/ml: In February 2015, the FDA approved Gla-300 based on data from the EDITION series of 26-week, phase 3 clinical trials [50]. Around the same time, the European Medicines Agency (EMA) adopted a positive opinion towards Gla-300 [51]. A meta-analysis of the currently available data from the EDITION trials of Gla-300 versus Gla-100 showed similar reductions in A1C (least square [LS] mean change -1.02%) for both formulations [52].

The main secondary outcome in the EDITION 1, 2, and 3 trials was the percentage of participants with one or more confirmed nocturnal hypoglycemic events, defined as a composite of events with an SMBG value ≤70 mg/dl (3.9 mmol/l) [53] or a severe event (requiring assistance) occurring between 00:00 and 05:59 hours from Week 9 to Week 26 of treatment. Confirmed or severe hypoglycemia events at any time of the night were also assessed over the full 26-week study period and for the first 8 weeks of the study.

EDITION 1 was a randomized, open-label, parallel-group trial in which patients using high daily doses of basal insulin (≥42 U/day) alongside mealtime insulin received Gla-300 or Gla-100 QD titrated to achieve fasting plasma glucose (FPG) ~80-100 mg/dl (4.4-5.6 mmol/l) [54]. There was a significantly lower incidence of confirmed (plasma glucose ≤70 mg/dl) or severe nocturnal hypoglycemic events in the Gla-300 group compared with the Gla-100 group between Week 9 and Week 26 (36% vs 46%, respectively; $P=0.0045$) as well as over the full 26-week trial period (Table 1) [54]. Over the full 26-week trial period, the incidence of confirmed hypoglycemia (plasma glucose ≤70 mg/dl) was also lower in the Gla-300 group, while there was no statistically significant difference in the incidence of severe hypoglycemic events (Table 1).

In the EDITION 2 trial, a randomized, open-label, parallel-group study, adults treated with high-dose basal insulin (≥ 42 U/day) and OADs received either Gla-300 or Gla-100 QD titrated to an FPG target of ~ 80 -100 mg/dl (4.4-5.6 mmol/l) [55]. The incidence of confirmed (plasma glucose ≤ 70 mg/dl) or severe nocturnal hypoglycemic events was significantly lower in the Gla-300 group than the Gla-100 group between Week 9 and Week 26 (21.6% vs 27.9%, respectively; $P=0.038$), as was the incidence over the full study period (Table 1) [55]. The incidence of confirmed (plasma glucose ≤ 70 mg/dl) or severe hypoglycemic events occurring at any time was lower in the Gla-300 group than the Gla-100 group during the full 26-week study period, similarly to EDITION 1 (Table 1). The incidence of severe hypoglycemia was low in both groups over the 26-week period (Table 1).

In the open-label EDITION 3 trial, insulin-naïve participants on OADs were randomized to receive Gla-300 or Gla-100 titrated to an FPG target of ~ 80 -100 mg/dl (4.4-5.6 mmol/l). There was no significant difference in the incidence of confirmed (plasma glucose < 70 mg/dl) or severe nocturnal hypoglycemia between Week 9 and Week 26 ($P=0.45$) [56]. Over the full 26-week period, the incidence of confirmed (plasma glucose < 70 mg/dl) or severe nocturnal hypoglycemia was lower in the Gla-300 group than the Gla-100 group, and the incidence of confirmed (plasma glucose < 70 mg/dl) or severe hypoglycemia at any time was numerically lower in the Gla-300 group (Table 1). There was no difference in the incidence of severe hypoglycemia over the whole treatment period between groups (Table 1).

Gla-300 has also been compared with Gla-100 in the EDITION JP 2 trial, an open-label study in Japanese patients using basal insulin and OADs [57]. In this study, no main secondary endpoint was defined. However, although not powered to identify statistical differences in hypoglycemia, the incidence of confirmed (plasma glucose < 70 mg/dl) or severe nocturnal hypoglycemia was lower in the Gla-300 group than in the Gla-100 group (25.4% vs 43.7%; relative risk 0.58, 95% CI 0.40-0.85) [57]. Confirmed (plasma glucose < 70 mg/dl) or severe nocturnal hypoglycemia was also lower over the full 26-week study period; confirmed (plasma glucose < 70 mg/dl) or severe hypoglycemia at any time was numerically lower in the Gla-300 group (Table 1), and severe hypoglycemia was low in both groups (2.5% and 1.7% with Gla-300 and Gla-100, respectively).

A meta-analysis of the EDITION 1, 2, and 3 trials showed a reduction in overall confirmed or severe hypoglycemia when using Gla-300 compared with Gla-100, which was not consistently observed in the individual clinical trials included in the meta-analysis [52].

LY2605541, basal insulin pегlispro: Data on hypoglycemia in patients receiving BIL are available only from a single phase 2 trial in T2DM [58]. In this 12-week, open-label, three-arm, parallel-group study, patients were treated with basal insulin and OADs and randomized to receive either BIL or Gla-100 QD. Hypoglycemia was defined as any event with a blood glucose measurement ≤ 70 mg/dl (3.9 mmol/l), and severe hypoglycemia was defined as that requiring assistance from another person with prompt recovery in response to carbohydrate intake. Insulin dose was titrated to a blood glucose target of ≤ 100 mg/dl (≤ 5.6 mmol/l). The efficacy of BIL was similar to that of Gla-100 in terms of A1C reduction and there were no significant differences in terms of incidence of total or nocturnal hypoglycemia events (Table 1). However, when results were adjusted for baseline hypoglycemia, a significant 48% reduction favoring BIL was detected for nocturnal hypoglycemia ($P=0.021$) [58]. There were no severe hypoglycemic events reported during the study period.

Four phase 3 trials comparing BIL to Gla-100 or NPH have been completed as part of the IMAGINE trial series; reporting of results is expected shortly (NCT01582451, NCT01790438, NCT01435616, NCT01468987; <https://clinicaltrials.gov>)

New insulin glargine LY2963016: The EMA recommended approval of LY2963016 as a biosimilar in June 2014 [59], and the FDA tentatively approved the New Drug Application for LY2963016 in August 2014 [60].

In the ELEMENT 2 trial, a 26-week, phase 3, double-blind, parallel-group study, insulin-naïve patients treated with OADs received either LY2963016 or Gla-100 QD. The insulin dose was titrated to achieve blood glucose ≤ 100 mg/dl (≤ 5.6 mmol/l). The efficacy of both agents in terms of A1C reduction was similar [61]. With regard to rate of total hypoglycemia (defined as blood glucose ≤ 70 mg/dl [3.9 mmol/l]), where measures were available, there was no statistically significant difference between LY2963016 and Gla-100 (Table 1).

Hypoglycemia in T1DM

The incidence of hypoglycemia in patients with T1DM is generally higher than among those with T2DM. Adults with T1DM have ~ 2 episodes of mild hypoglycemia per week; the annual prevalence of severe hypoglycemia is $\sim 30\%$, with several factors, such as long disease duration, increasing its incidence [39,40].

Insulin degludec: In their meta-analysis of phase 3 trials of IDeg versus Gla-100, Vora et al. reported that the two agents had similar efficacy in terms of reduction of A1C in T1DM patients [45].

In the BEGIN Basal-Bolus Type 1 study, a 52-week, parallel-group, phase 3 study, T1DM patients previously treated with basal-bolus insulin for ≥ 1 year received either IDeg or Gla-100 QD with mealtime insulin aspart [28]. Both basal and mealtime insulin were titrated to achieve blood glucose ~ 70 -90 mg/dl (3.9-5.0 mmol/l). In this study, rates of confirmed hypoglycemia were similar between patient groups, confirmed nocturnal hypoglycemia was significantly lower with IDeg than with Gla-100, and a similar rate of severe hypoglycemia was observed for both treatment groups (Table 2).

In the BEGIN FLEX T1 trial, patients received mealtime insulin aspart alongside basal analog insulin treatment. The trial had a treat-to-target design with basal analog insulin titrated to achieve blood glucose ~ 70 -90 mg/dl (4.0-5.0 mmol/l) and mealtime insulin titrated to achieve ≤ 90 mg/dl (≤ 5.0 mmol/l), based on the preceding day's pre-lunch, pre-dinner, and bedtime SMPG values [62]. After 26 weeks, confirmed hypoglycemia rates were similar and rates of severe events were low in all groups (Table 2). Confirmed nocturnal events were significantly lower with the IDeg FLEX dosage compared with either IDeg (37%, $P=0.003$) or Gla-100 (40%, $P=0.001$) [62].

Insulin glargine 300 units/ml: Two phase 3 studies have been conducted in otherwise healthy patients with T1DM as part of the EDITION series of clinical trials. Study designs, definitions of hypoglycemia, and titration targets were consistent throughout the series in patients with T2DM and T1DM.

The EDITION 4 trial was a 26-week, open-label study in which participants were randomized to Gla-300 (morning or evening) or Gla-100 (morning or evening) while continuing their mealtime insulin [63]. Gla-300 showed similar efficacy to Gla-100 in terms of lowering A1C. Confirmed (plasma glucose < 70 mg/dl) or severe nocturnal hypoglycemia was similar between the two groups (Table 2). The rate of confirmed (plasma glucose < 70 mg/dl) or severe nocturnal

hypoglycemia was lower in the Gla-300 group than in the Gla-100 group during the first 8 weeks of the study (rate ratio 0.69, 95% CI 0.53-0.91) [63]. Over the whole study period, the incidence of confirmed or severe hypoglycemia at any time was similar between treatment groups (Table 2). Severe hypoglycemia was seen in 6.6% and 9.5% of patients in Gla-300 and Gla-100 groups, respectively. Neither glycemic control nor hypoglycemia differed between insulins or times for morning and evening injection.

Similarly to the EDITION JP 2 trial, EDITION JP 1 was a 26-week, randomized, open-label study conducted with Japanese participants who received either Gla-300 or Gla-100 alongside continued use of mealtime insulin [64]. Gla-300 showed similar efficacy to Gla-100 in terms of lowering A1C. The incidence of confirmed or severe nocturnal hypoglycemia was not significantly different between groups from Week 9 to Week 26; however, the incidence was lowest during the first eight weeks of the study in the Gla-300 group compared with the Gla-100 group, and was lower in the Gla-300 group over the full 26-week study period (Table 2). Severe hypoglycemia was low in both groups (5.7% and 9.9% with Gla-300 and Gla-100, respectively). There was no difference in the incidence of confirmed or severe hypoglycemia experienced at any time between groups (Table 2).

LY2605541, basal insulin peglispro: There are data from one 8-week, phase 2, open-label, randomized, two-arm, cross-over study in patients with T1DM who received either BIL or Gla-100 QD while continuing mealtime insulin [65]. In this study, BIL demonstrated greater improvements compared with Gla-100 in terms of glycemic control. The rate of total hypoglycemia was higher in the BIL group than in the Gla-100 group (Table 2). However, the rate of nocturnal hypoglycemia was lower in the BIL group than in the Gla-100 group (Table 2). The incidence of severe hypoglycemia was similar between the two treatment groups (five patients with six events in the BIL group and three patients with six events in the Gla-100 group).

Two phase 3 trials comparing BIL to Gla-100 or NPH have been completed as part of the IMAGINE trial series, with reporting of results expected shortly (NCT01481779, NCT01454284; <https://clinicaltrials.gov>).

New insulin LY2963016: The ELEMENT 1 trial was a 52-week, phase 3, open-label, parallel-group study in which patients received either LY2963016 or Gla-100 in combination with mealtime insulin lispro [66]. Insulin doses were titrated to achieve blood glucose \geq or \sim 110 mg/dl (\leq 6.0 mmol/l). LY2963016 had similar efficacy to Gla-100 in terms of lowering A1C, and the rate of total hypoglycemia was similar between patient groups (Table 2).

Summary

The longer, more constant PK/PD profiles of the new basal analog insulins appear to confer advantages over previous basal analog insulins with respect to reduced hypoglycemia, particularly nocturnal hypoglycemia. However, interpretation of the data is limited by a lack of head-to-head comparisons between these agents and the fact that all data published to date are from trials sponsored by the pharmaceutical company producing the insulin, with no independent meta-analyses currently available. In addition, the trials have been designed to evaluate efficacy outcomes and are thus powered to detect differences in A1C rather than hypoglycemia. Hence, they might be underpowered to detect differences in hypoglycemia. Indeed, a meta-analysis of three T2DM trials showed a reduction in overall confirmed or severe hypoglycemia when using Gla-300 compared with Gla-100, which was

not consistently observed in the individual clinical trials included in the meta-analysis [52].

There remains a lack of consistent definitions and outcome measures for hypoglycemia and patient selection criteria in trials of insulin therapies, which adds an unwelcome layer of complexity for clinicians wishing to make descriptive comparisons of hypoglycemia rates between trials. Lack of standardized reporting underlines the need for head-to-head trials and subsequent meta-analyses of data. Trials designed specifically to assess the effect of novel basal analog insulins in patients with a history of hypoglycemia unawareness or at high risk for severe hypoglycemia should also be undertaken. The difficulty in performing double-blind assessments in insulin trials, due to the different appearances of formulations, is a perennial issue in randomized trials comparing basal analog insulins. However, two of the upcoming phase 3 studies of BIL have a double-blind design (NCT01435616, NCT01454284; <http://clinicaltrials.gov/>). Whether this represents a crossing of the Rubicon for the design of insulin trials remains to be seen.

Conclusion

The development of the new generation of basal analog insulins represents an additional step towards patients achieving physiologic glycemic control. Improved PK/PD profiles appear to be associated with better clinical outcomes in terms of hypoglycemia. Future head-to-head trials, studies in specific patient populations, and pharmacoeconomic analyses - many of which are already underway - will be key for clinicians and patients to determine appropriate, individualized treatment courses.

Acknowledgments

The contents of this paper and the opinions expressed within are those of the authors, and it was the decision of the authors to submit the manuscript for publication. The authors contributed to the writing of this manuscript, including critical review and editing of each draft, and approval of the submitted version. The authors received writing/editorial support in the preparation of this manuscript provided by Pim Dekker, PhD, of Excerpta Medica, funded by Sanofi US, Inc.

Conflicts of Interest

Alsahli: None

Thrasher: Research grant support from Amgen, Aventis, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Janssen, Gilead Sciences, GlaxoSmithKline, Medtronic, Merck & Co, Novartis, Novo Nordisk, Pfizer, Sanofi, Speedel Pharma Ltd, and Yamanouchi Pharma America; has served on the speaker bureau for Amylin, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, GlaxoSmithKline, Janssen, Lilly, Medtronic, Novo Nordisk, Pfizer, Sanofi, Takeda, and Virus, and is on advisory boards for Medtronic, Pfizer Pharmaceuticals, and Sanofi-Aventis; and has received editorial/publication support from Boehringer Ingelheim and Eli Lilly.

Gerich: Consultant/member of the speaker bureau for Bristol-Myers Squibb, AstraZeneca, Merck, Janssen Pharmaceuticals, Eli Lilly, and Boehringer Ingelheim.

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Citation: Hypoglycemia with New-Generation Basal Analog Insulins: A Descriptive Critical Review. *J Diabetes Metab* 6: 576. doi:[10.4172/2155-6156-1000576](https://doi.org/10.4172/2155-6156-1000576)

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