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REVIEW ARTICLE

Basal insulin therapy: Unmet medical needs in Asia and the new insulin glargine in diabetes treatment

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ABSTRACT

Diabetes remains a global epidemic and a tremendous health challenge, especially in the Asian population. Dramatic increases in the prevalence of diabetes across different countries or areas in Asia have been reported in recent epidemiological studies. Although clinical guidelines have strengthened appropriate antihyperglycemic medications and lifestyle modifications for optimal diabetes management, inadequate glycemic control still occurs in many patients with an increased risk of developing microvascular and macrovascular complications. Insulin administration is the main therapy for diabetes in response to the inability to secrete insulin, and is recommended in current guidelines to treat patients with type 2 diabetes after failure of oral antidiabetic drugs. Clinical studies have shown that long-acting insulin analogs improve basal glycemic control with reduced risk of hypoglycemia. In the present review, we discuss previous challenges with basal insulin therapy in Asia, the pharmacological development of insulin analogs to overcome the unmet medical needs and recent clinical studies of the new ultra-long-acting insulin analog, insulin glargine U300. Furthermore, relevant findings of current real-world evidence are also included for the comparison of the efficacy and safety of different insulin formulations. Based on the accumulating evidence showing a low incidence of hypoglycemia and technical benefits of dose titration, treatment with glargine U300 can be a promising strategy for Asian diabetes patients to achieve glycemic targets with favorable safety.

INTRODUCTION

The prevalence of diabetes mellitus has continuously increased worldwide[1,2]. There are two main types of diabetes, type 1 diabetes (formerly called insulin-dependent diabetes) and type 2 diabetes (formerly called non-insulin-dependent diabetes). Type 2 diabetes is more common in adults and constitutes the majority (90–95%) of all diabetes cases[3]. Epidemiological studies estimate that globally, the number of diabetes patients is expected to rise from 415 million in 2015 to 642 million by 2040[4]. Diabetes is considered a serious public health challenge in developing countries following the epidemiological transition[5]. Asia has become the epicenter of the current diabetes epidemic after having undergone drastic socioeconomic changes in the past decades. In Asian populations, particularly East Asians, diabetes tends to develop at a younger age and a lower body mass index, with the characteristic of visceral obesity[5,6]. Under the influence of nutrition transition, rapid urbanization and increased adoption of Western lifestyles, Asian patients have accounted for 60% of the world's diabetic population. In

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1980, <1% of Chinese adults had the disease; and by 2008, the prevalence had soared to nearly 10%[7]. A Taiwanese study also showed an upward trend in the prevalence of type 2 diabetes during 2000–2007 among adults in Taiwan[8]. China and India are projected to be among the top 10 countries in the world, with the highest number of estimated cases by 2040[9,10].

Diabetes can develop acute and chronic complications in response to inadequate glycemic control. The former includes hypoglycemia diabetic ketoacidosis and hyperosmolar hyperglycemic state[11], and the latter occurs mainly as a result of a mix of microangiopathy (causing nephropathy, neuropathy and retinopathy) and macrovascular disease (causing stroke, coronary heart disease and peripheral vascular disease)[12]. The long-term health problems have a significant impact on quality of life and increase the risk of premature death, posing a heavy economic and social burden in all nations[13]. Early intervention to achieve and maintain glycemic control is essential to reduce the risk of diabetes-related chronic complications[14]. However, despite the evidence for the benefit of optimal glycemic control, there are many individuals in Asia whose diabetes remains uncontrolled[15]. For example, previous studies reported that <40% of diabetes patients achieved adequate glycemic control in China and Taiwan after treatment[16,17]. The present review article points out the unmet medical needs of diabetes treatment, as well as the existing clinical challenges associated with basal insulin therapy in Asia, and brings the new generation basal insulin into the scope for effective glycemic control with better blood glucose stability, improved tolerability and convenience advantages.

INSULIN THERAPY FOR DIABETES

Diabetes management requires appropriate glycemic control to prevent acute and chronic complications associated with the disease[14,18]. Measurement of glycated hemoglobin, predominantly HbA1c, is integral to the management of diabetes[15]. The HbA1c level reflects a combined exposure to both fasting plasma glucose (FPG) and postprandial glucose (PPG)[19], which can be used as an indicator of long-term glycemic control and a basis for adjustment of diabetes treatment plans[20]. Current treatment guidelines often recommend that patients achieve and maintain an HbA1c level that is <7%[21]. An ideal range or target HbA1c level might vary from person to person, depending on the clinical and demographic characteristics of the individual patient, such as age and sex[20]. To minimize the risk of long-term vascular complications, the National Institute for Health and Care Excellence has recommended a tighter target level of ≤6.5% in adult patients with type 1 diabetes[22]. American Association of Clinical Endocrinologists and American College of Endocrinology also recommended an HbA1c target of <6.5% for adult patients with recent type 2 diabetes onset and no clinically significant cardiovascular disease[23]. In addition, the Japan Diabetes Society set the main objective value of HbA1c to <7% for patients with diabetes to prevent microvascular complications[24].

Insulin is the mainstay of therapy for type 1 diabetes patients due to insulin deficiency[25]. Almost all people with type 1 diabetes should be treated with multiple-dose insulin injections or continuous subcutaneous insulin infusion. In patients choosing multiple-dose insulin injections, it is the current standard of care to use long-acting basal insulin analogs. For type 2 diabetes patients, most should begin with diet and lifestyle changes. When these modification efforts do not achieve or maintain glycemic targets, metformin is usually the preferred initial pharmacological agent[25,26]. Although insulin is the most potent agent against hyperglycemia, it is still applied to type 2 diabetes patients in response to elevated HbA1c after failure on oral antidiabetic drugs (OADs)[18,27]. Owing to the progressive loss of pancreatic β-cell function in type 2 diabetes, insulin therapy is eventually indicated for most patients[25].

Basal insulin therapy after metformin treatment was recommended in clinical guidelines, such as 2015 American Diabetes Association/European Association for the Study of Diabetes guidelines, 2018 American Diabetes Association standards of medical care in diabetes, and 2018 American Association of Clinical Endocrinologists and American College of Endocrinology consensus statement for type 2 diabetes management[18,23,28]. In Taiwan, taking effect nowadays, the health insurance authorities agree that insulin could be considered for type 2 diabetes treatment at an early stage[29]. Injected basal insulin alone is the most convenient initial regimen to supplement a patient's endogenous basal insulin level, which can be used in combination with metformin and sometimes an additional non-insulin agent. If HbA1c remains uncontrolled despite normalization of the FPG, we could consider proceeding to the combination of injectable therapy to address PPG excursions. Options include the addition of one injection of a rapid-acting insulin analog administered before the largest meal, or a glucagon-like peptide 1 receptor agonist. Recent research showed that combining glucagon-like peptide 1 receptor agonists with basal insulin demonstrated comparable or slightly better efficacy versus the addition of prandial insulin, with less hypoglycemia and no weight gain[25,30]. As an alternative, in selected patients, a simpler but somewhat less flexible approach is transitioning from basal insulin to premixed formulations containing an intermediate or long-acting basal insulin mixed with short/rapid-acting prandial insulins in fixed ratios[26,31]. If patients still do not respond adequately to these regimens, the basal–bolus strategy, which adds more than two rapid-acting insulin injections before meals to basal insulin, might be required[32]. Dose titration is important once an insulin regimen is initiated. Adjustments should be made in both mealtime and basal insulins based on the prevailing blood glucose levels and an understanding of the pharmacodynamic profile of each formulation[25].

CHALLENGES WITH BASAL INSULIN THERAPY IN ASIA

Although comprehensive guidelines for the treatment of type 2 diabetes patients emphasized the importance of glycemic control with appropriate antihyperglycemic medications and

lifestyle modifications, inadequate glycemic control still occurs in many patients because of the delayed insulin initiation or intensification[33,34]. A retrospective longitudinal analysis of 40,627 type 2 diabetes patients from five European countries and the USA showed poor glycemic control in patients initiating basal insulin[35]. It was found that the proportion of patients for short-term and long-term optimal glycemic control increased after the initiation of basal insulins with or without OADs. However, almost half of the patients in France, Italy and Spain, and 62.9% of the patients in the UK, initiated basal insulin with very high HbA1c levels (>9.0%), and >70% of patients still failed to reach HbA1c target (≤7.0%) in the first 3 months and 2 years after the insulin therapy. Approximately 9% of patients reported hypoglycemia experiences according to the electronic medical records[35].

The issue of delayed insulin therapy also exists in Asian countries. The First Basal Insulin Evaluation Asia study, a prospective, observational registry follow-up study performed in 11 Asian countries, was carried out to evaluate the initiation of basal insulins (neutral protamine Hagedorn [NPH] insulin, glargine or detemir) in patients with type 2 diabetes inadequately controlled by OADs. This study showed that in a real-world setting, insulin initiation is delayed in Asian patients by approximately 9 years[36]. The efficacy and safety of basal insulin therapy by country was further investigated, and the results showed large variation of glycemic control in type 2 diabetes patients among the country cohorts[37]. Nevertheless, type 2 diabetes patients in Korea and Taiwan represented the smallest reduction in HbA1c and the lowest proportion of patients reaching the treatment goals of HbA1c and FPG, which was closely correlated to a delay of insulin initiation with prolonged OAD use (9.2 and 11.1 years, respectively) after diabetes duration of >10 years. In addition, hypoglycemia rates also varied in different countries, where 7.1% (India) to 27.3% (China) of patients had experienced hypoglycemia at least once[37].

According to a Taiwanese study comprising 836 patients with poorly controlled type 2 diabetes (duration of diabetes: 11.6 ± 7.0 years; duration of OAD therapy: 10.7 ± 6.6 years), the mean HbA1c value had reached as high as 10.1% when basal insulin therapy was initiated. Most of the patients were insulin-naïve, with just 6.9% of them having received insulin therapy before participation. In this study, glycemic control was significantly improved after the treatment of basal insulin for 6 months, with reductions in both HbA1c and FPG[38]. An earlier Japanese study found that 83.4% of Japanese patients had microvascular complications at the time of initiating insulin treatment[39]. In a subgroup analysis of the observational, non-interventional Add-on Lantus® to Oral Hypoglycemic Agents study, Japanese insulin-naïve patients without microvascular complications showed better response to basal supported oral therapy with higher chances of achieving HbA1c <7.0% than those with complications[40].

Technical difficulty of insulin therapy, such as subcutaneous injection, dose titration and regular SMBG, might affect patients' willingness to accept insulin therapy[38]. Once insulin therapy is initiated, dose titration should be taken into account to achieve optimal glycemic control. Real-world evidence from the Observational Registry of Basal Insulin Treatment study showed that the initiation of basal insulins was delayed in the majority of patients with type 2 diabetes in China[41]. A suboptimal titration of basal insulins was also shown, as Asian patients with diabetes might have delayed insulin initiation and a higher risk of hypoglycemia. Such ethnic and genetic differences between Asians and Caucasians pose a clinical challenge to deal with the dose adjustment for different insulin needs[42,43].

Furthermore, it was found that one-quarter of type 2 diabetes patients treated with basal insulin had difficulties attaining the recommended HbA1c goal despite adequate FPG levels[44]. In that case, further interventions to control PPG might become necessary with the introduction of rapid-acting bolus (mealtime) insulin in a basal–bolus regimen or glucagon-like peptide 1 receptor agonist. For patients with type 1 diabetes, multiple injections of mealtime insulin are also required. Furthermore, patients might be required to calculate the mealtime insulin doses to match the amount of carbohydrate in the meal[45]. Maintenance of glycemic control thereby can be achieved by intensification of insulin therapy, either adding another type of insulin or increasing the number of injections per day. However, the additional task could make insulin therapy more cumbersome, and greater injection frequency might restrict patients' daily activities with a negative impact on quality of life[46,47].

Hypoglycemia is widely regarded as a critical barrier to insulin therapy initiation and adherence[48–50]. Hypoglycemia is associated with acute short-term symptoms related to either glucose counter-regulatory responses, such as tachycardia and shakiness, or to neuroglycopenia, such as irritability and confusion, that in severe cases that might lead to increased mortality[51]. Repeated hypoglycemia might reduce working capacity and quality of life, increase a fear of recurrent hypoglycemic episodes with insulin therapy, and eventually result in deterioration of glycemic control[51]. In Taiwan's nationwide population-based study, symptomatic hypoglycemia was found to be strongly associated with major cardiovascular events that increased hospitalization and all-cause mortality[52]. Nocturnal hypoglycemia is likely to be underreported, because patients might not awaken or recognize the symptoms during sleep[53,54].

Severe hypoglycemia is recognized as one of the strongest predictors of macrovascular events in patients with type 1 diabetes and type 2 diabetes, which was also noted by studies from Taiwan and Japan[55–57]. The increased risk of cardiovascular diseases is associated with long-term hypoglycemia, either as a result of weight gain related to defensive food intake, or through activation of the sympathoadrenal response[51,55]. According to the Action to Control Cardiovascular Risk in Type 2 Diabetes study, intensive glycemia control increased the occurrence of severe hypoglycemia in type 2 diabetes patients at high risk of cardiovascular events, but might not directly account for the increased death[58]. However, improved glycemic

control for the long term, which was investigated in the Cardiovascular Risk Evaluation in People with Type 2 Diabetes on Insulin Therapy study over 4 years, facilitated the reduction of cardiovascular events[59].

Another barrier to insulin therapy is glycemic variability[60]. Variable glucose readings generate difficulties to adjust insulin dosage. Furthermore, the variability in glucose levels is, to some extent, a reflection of variability in the glucose-lowering action of the insulin therapy itself. The scope for insulin-induced glucose variability is particularly great with basal insulin because of its prolonged absorption resulting from high-dose subcutaneous depots[61]. Although rapid/short-acting insulin might reduce post-meal glucose excursions in multiple daily injection[62], as will be discussed later, long-acting insulin analogs can more effectively mimic the constitutive secretion of endogenous insulin than NPH, the conventional basal insulin, thereby reducing glycemic variability[34,63].

TACKLING BARRIERS TO INSULIN THERAPY

The goal of effective insulin therapy for diabetes patients is to mimic the normal insulin secretion in order to achieve tight glycemic control without the risk of hypoglycemia[26,34]. Various approaches have been made to develop insulin analogs with different pharmacokinetic (PK)/pharmacodynamics (PD) profiles, including basal and ultra-long-acting basal insulins (Figure 1)[64,65]. NPH insulin was originally produced in 1946, could be mixed with soluble insulin and became the predominant basal insulin in clinical use throughout the 20th century[64,66]. As an intermediate-acting formulation, NPH displays time-action profiles that differ considerably from the physiological dynamics of endogenous basal insulin secretion.

The advent of recombinant DNA technology in the 1980s enabled optimization of the properties of insulin through modification of the amino acid sequence[67]. New long-acting insulin analogs, such as glargine and detemir, showed fairly flat PK profiles, a duration lasting >24 h and little day-to-day variation, thus allowing once-daily dosing[68]. The first long-acting basal insulin analog to be approved for clinical use was insulin glargine 100 units/mL (Gla-100), and it is usually taken as a once-daily subcutaneous injection in the evening[69]. The pharmacological characteristics of insulin glargine allow for greater physiological basal glycemic control with a reduced risk of hypoglycemia than current intermediate- and long-acting insulin preparations[70–73].

Although the mean PK/PD and variability profiles of Gla-100 represent substantial improvements, it still does not completely mimic physiological insulin secretion[64]. Administration of high-dose Gla-100 might show a peak on the PK/PD profile[74]. In contrast, a low dose might not be sufficient to last a 24-h period, and there is still intra- or interindividual variations after injections[75]. To address these limitations, ultra-long-acting basal insulin regimens were developed, such as insulin glargine U300 (Gla-300) and insulin degludec, to provide comparable efficacy reaching the glycemic target with less bodyweight gain and reduced hypoglycemia[76]. Gla-300 is a threefold more concentrated formulation as compared with Gla-100, which is designed for once-daily administration. Injection of Gla-300 leads to the formation of a smaller subcutaneous depot, resulting in a distinct PK profile with more consistent and prolonged insulin release[77]. Consequently, glucose control can remain up to 36 h after administration, resulting in decreased hypoglycemic episodes (overall and nocturnal) in patients[78].

CLINICAL STUDIES AND REAL-WORLD EVIDENCE OF INSULIN GLARGINE U300

The clinical efficacy of Gla-300 was evaluated in six phase III, multicenter, randomized, open-label, parallel-group, 6-month clinical trials known as the EDITION series (Table 1). The EDITION 1, 2 and 3 trials recruited patients with type 2 diabetes [79–82], and the EDITION 4 trial recruited patients with type 1 diabetes[83]. EDITION JP1 and EDITION JP2 were carried out in Japanese patients with type 1 diabetes and type 2 diabetes, respectively[84,85].

The EDITION 1 and 2 are studies related to regimen switching. Type 2 diabetes patients who had inadequate glycemic control on basal and mealtime insulin (Comparison of a New Formulation of Insulin Glargine With Lantus in Patients With Type 2 Diabetes Mellitus on Basal Plus Mealtime Insulin [EDITION 1]) or basal insulin and OADs (Comparison of a New Formulation of Insulin Glargine With Lantus in Patients

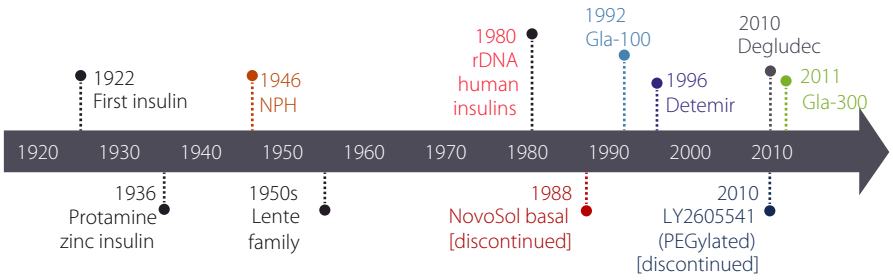

Figure 1 | Timeline for the development of basal insulins[64]. Gla, glargine; NPH, neutral protamine Hagedorn; PEG, polyethylene glycol; rDNA, recombinant deoxyribonucleic acid.

Table 1 | EDITION trials, comprehensive phase III studies to compare Gla-300 versus Gla-100 in several populations

Study	Diabetes type	Intervention	Covered region	Patient number
EDITION 1	T2D	Basal plus mealtime (bolus) insulin	North America, Europe, Japan	807
EDITION 2	T2D	Basal insulin plus OADs	North America, Europe, Japan	811
EDITION 3	T2D	Insulin naïve: basal insulin plus OADs	North America, Europe, Japan	878
EDITION 4	T1D	Basal plus mealtime (bolus) insulin	North America, Europe, Japan	549
EDITION JP1	T1D	Basal plus mealtime (bolus) insulin	Japan	243
EDITION JP2	T2D	Basal insulin plus OADs	Japan	241

EDITION 1, Comparison of a New Formulation of Insulin Glargine With Lantus in Patients With Type 2 Diabetes Mellitus on Basal Plus Mealtime Insulin; EDITION 2, Comparison of a New Formulation of Insulin Glargine With Lantus in Patients With Type 2 Diabetes Mellitus on Basal Insulin With Oral Antidiabetic Therapy; EDITION 3, Comparison of a New Formulation of Insulin Glargine With Lantus in Patients With Type 2 Diabetes Mellitus on Non-Insulin Antidiabetic Therapy; EDITION JP1, Comparison of a New Formulation of Insulin Glargine With Lantus in Japanese Patients With Type 1 Diabetes Mellitus; EDITION JP2, Comparison of a New Formulation of Insulin Glargine With Lantus in Combination With Oral Antihyperglycemic Drug(s) in Japanese Patients With Type 2 Diabetes Mellitus; OADs, oral antidiabetic drugs; T1D, type 1 diabetes; T2D, type 2 diabetes.

With Type 2 Diabetes Mellitus on Basal Insulin With Oral Antidiabetic Therapy [EDITION 2]) were randomly allocated to either the Gla-300 or the Gla-100 group. The results showed that Gla-300 controlled HbA1c as well as Gla-100, with a consistently lower risk of nocturnal hypoglycemia (EDITION 1), or a lower risk of hypoglycemia during the night and at any time of the day (EDITION 2)[79,80]. EDITION 3 (Comparison of a New Formulation of Insulin Glargine With Lantus in Patients With Type 2 Diabetes Mellitus on Non-Insulin Antidiabetic Therapy) was carried out in the treatment of insulin-naïve type 2 diabetes patients, the results being comparable with EDITION 1 and 2[81]. Extended follow up of the EDITION 3 participants showed that the efficacy of Gla-300 was maintained over 12 months[82]. Furthermore, it was noted in EDITION 2 and 3 that patients treated with Gla-300 consistently appeared to have less blood glucose variability, and lower risk in symptomatic and severe hypoglycemia, confirmed by the Low Blood Glucose Index[82,86,87]. In type 1 diabetes patients with long disease duration, EDITION 4 showed that Gla-300 achieved glucose control comparable with Gla-100, with a lower risk of hypoglycemia after transferring from other insulin regimens, irrespective of the time of injection, and with less weight gain[83].

EDITION JP1 (Comparison of a New Formulation of Insulin Glargine With Lantus in Japanese Patients With Type 1 Diabetes Mellitus) and EDITION JP2 (Comparison of a New Formulation of Insulin Glargine With Lantus in Combination With Oral Antihyperglycemic Drug[s] in Japanese Patients With Type 2 Diabetes Mellitus) were Asian studies, and their results suggesting racial differences in the efficacy and safety of Gla-300 were not an issue. Glycemic control did not differ between Gla-300 and Gla-100, but there were fewer hypoglycemic episodes at any time of the day observed with Gla-300 in Japanese type 1 diabetes patients pretreated with basal plus mealtime insulin (EDITION JP1) or in Japanese type 2 diabetes patients pretreated with basal insulin plus OADs (EDITION JP2)[84,85]. In particular, it was clinically relevant that the use of Gla-300 in Japanese patients with type 1 diabetes/type 2 diabetes was associated with a lower risk of nocturnal hypoglycemia during treatment for 6 months, including the first 8 weeks that titration of basal insulin was often required.

A meta-analysis of EDITION 1, 2 and 3 provides a comparison of the 6-month safety and efficacy profiles of Gla-300 and Gla-100 in a broader patient population with type 2 diabetes [88]. The mean change in HbA1c for Gla-300 was comparable with that for Gla-100. Annualized rates of confirmed (≤3.9 mmol/L, <3.0 mmol/L) or severe hypoglycemia were lower with Gla-300 than with Gla-100 during the night (31% difference in rate ratio over 6 months) and at any time (24 h, 14% difference; Figure 2). Bodyweight gain was lower in the Gla-300 group (0.49 kg) than the Gla-100 group (0.75 kg), with a trend towards significance ($P = 0.058$).

Although head-to-head clinical trials remain lacking, an indirect assessment of the efficacy and safety of Gla-300 relative to other basal insulins was carried out through a network meta-analysis on randomized controlled studies of intermediate-acting and ultra-long-acting basal insulins, including premixed insulins, NPH, glargine (Gla-100 and Gla-300), detemir and degludec[89,90]. The analyzed results suggest that Gla-300 in the treatment of patients with type 2 diabetes showed a comparable glycemic control versus other insulins, but the rate of nocturnal hypoglycemia was significantly lower than the treatment with premixed insulins and NPH. Change in bodyweight with Gla-300 was basically comparable with other basal insulins, except for more weight gain using premixed insulins. In addition, an indirect comparison between insulin degludec 100 U/mL (Deg-100) and Gla-300 relative to Gla-100 was carried out through trial-level meta-analyses, including the BEGIN and EDITION programs[91]. Overall, Deg-100 and Gla-300 shared more similarities than differences. Notably, Deg-100 was associated with less improvement in HbA1c, although a greater effect in FPG reduction and less nocturnal hypoglycemia was seen when compared with Gla-100. In contrast, Gla-300 showed a lower risk of hypoglycemia in both the whole day and night-time, and comparable HbA1c improvement.

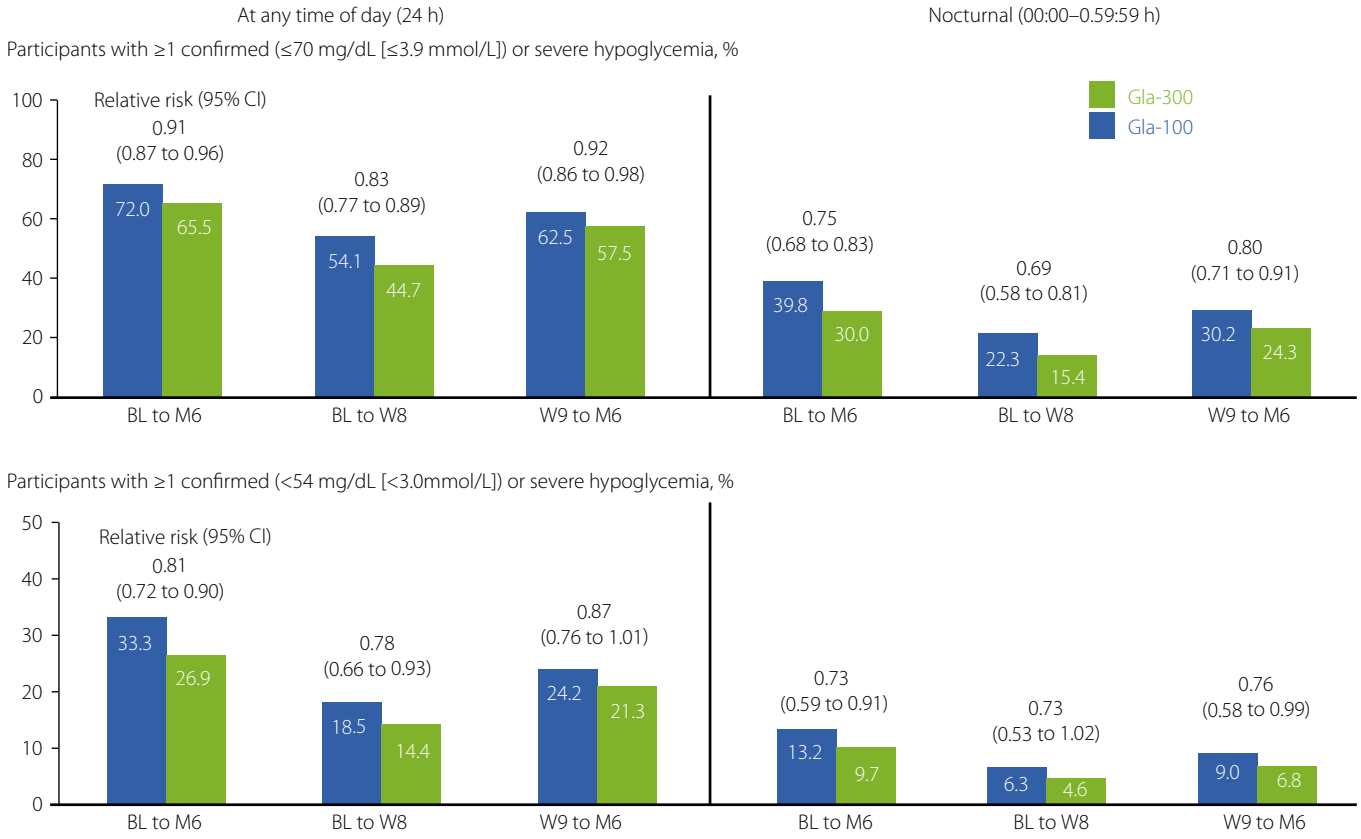

Figure 2 | Lower incidence of confirmed or severe hypoglycemia with Gla-300 versus Gla-100 at any time of day (24 h) and during the night from baseline to month 6[88]. BL, baseline; Gla, glargine; h, hour; M, month; RR, relative risk; W, week.

Real-world research increases the body of evidence on the use of Gla-300 in type 2 diabetes patients from observational studies. A new retrospective cohort study (Differentiate Gla-300 Clinical and Economic in Real-World Via EMR Data study [DELIVER 2]) analyzed the electronic medical records of 1,894 patients in two matched cohorts[92]. In the DELIVER 2 study, during the 6-month follow-up period, patients treated Gla-300 experienced less hypoglycemia versus patients treated with other basal insulins (15.9% vs 18.2%; $P = 0.01$; adjusted odds ratio 0.78), including Gla-100, insulin detemir and insulin degludec. After adjusting for the baseline hypoglycemia rate, patients who switched to Gla-300 experienced 33% fewer hypoglycemic events (adjusted mean 0.677 vs 0.902 events/per patient per year) versus those who switched to other basal insulins, without compromising blood sugar control (Figure 3). In addition, patients who switched to Gla-300 showed a lower risk of hypoglycemia-related inpatient or emergency department services versus patients who switched to other basal insulins (adjusted odds ratio inpatient 0.62, $P = 0.006$; emergency department 0.73, $P = 0.058$). The benefit for reduced hypoglycemia risk might represent an important advance of the new Gla-300 formulation to treat patients with type 2 diabetes, which can be a new option for elderly people, people with cardiovascular comorbidities or people with chronic kidney disease[90,93]. Additional studies and real-world evidence are important to compare the benefits and risks of Gla-300 relative to other basal insulin analogs for the treatment of people with comorbidities or even with very high HbA1c.

Research on dose titration with Gla-300 is also under way. TITRATION, a recent randomized clinical trial carried out in Canada, assessed a self-titration algorithm for Gla-300 injection to type 2 diabetes patients with an increase of 1 unit/day. The results indicated the glycemic response using this once-daily titration algorithm was effective and comparable with the EDITION algorithm, which was physician-driven titration at least once weekly. No differences were observed in the incidences of hypoglycemia between two algorithms. Furthermore, the rare frequency of severe hypoglycemia represented good safety in the dose adjustment of Gla-300[94].

CONCLUSION

Insulin replacement therapy is essential for patients with type 1 diabetes, and for many patients with type 2 diabetes. Achieving and maintaining glycemic control has great

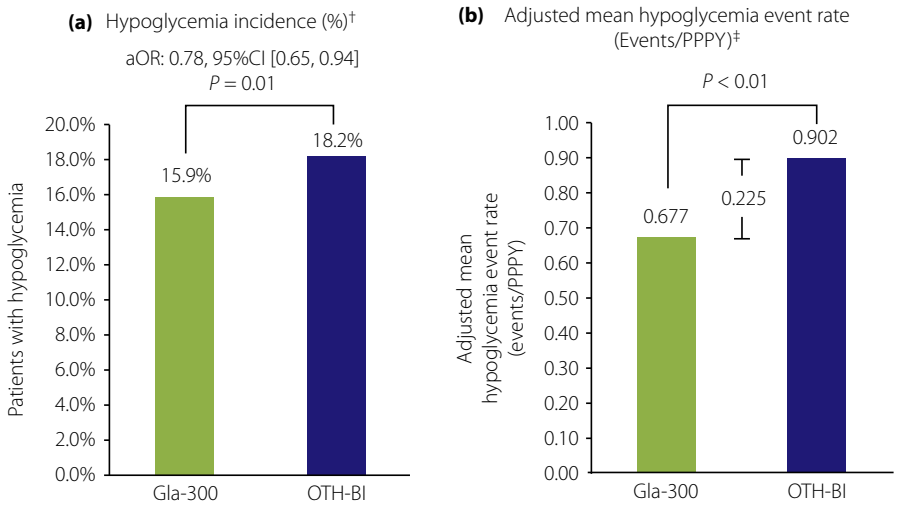

Figure 3 | Hypoglycemia occurrence with Gla-300 versus other basal insulins during the 6-month follow-up period[92]. (a) Hypoglycemia incidence. (b) Hypoglycemia event rate (events/per patient per year [PPPY]). †Adjusted odds ratio (aOR), adjusted for baseline hypoglycemia incidence. ‡Adjusted for baseline hypoglycemia event rate. CI, confidence interval; Gla, glargine; OTH-BI, other basal insulin; PPPY, per patient per year.

implications for preventing diabetes-related long-term complications, thus reducing the burden of mortality and disability. Ultra-long-acting basal insulin analogs overcome the major limitations of other intermediate- or long-acting insulin preparations currently used for basal insulin therapy, such as hypoglycemia and glycemic variability. Clinical trial findings in Western and Japanese populations support the use of Gla-300, administered as a once-daily subcutaneous injection, and Gla-300 can mimic physiological insulin secretion to a greater extent and satisfy the basal insulin requirements of patients with either type 1 diabetes or type 2 diabetes. Relevant results from a series of clinical trials, meta-analysis and accumulating real-world evidence highlight that this new-generation basal insulin might offer an alternative option for Asian patients who received OADs, but failed to achieve therapeutic targets, and facilitate a more stable and sustained glycemic control in long-term treatment.

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DISCLOSURE

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