Diabetes Ther (2017) 8:1197–1214
DOI 10.1007/s13300-017-0322-z

REVIEW

Optimizing Glycemic Control Through Titration of Insulin Glargine 100 U/mL: A Review of Current and Future Approaches with a Focus on Asian Populations

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Received: July 19, 2017 / Published online: November 1, 2017

ABSTRACT

Various data have demonstrated inadequate glycemic control amongst Asians with type 2 diabetes mellitus (T2DM), possibly on account of suboptimal titration of basal insulin—an issue which needs to be further examined. Here we review the available global and Asia-specific data on titration of basal insulin, with a focus on the use of insulin glargine 100 U/mL (Gla-100). We also discuss clinical evidence on the efficacy and safety of titrating Gla-100, different approaches to titration, including some of the latest technological advancements, and guidance on the titration of basal insulin from international and local Asian guidelines. The authors also provide their recommendations for the initiation and titration of basal insulin for Asian populations. Discussion of the data included in this review and in relation to the authors' clinical experience with treating T2DM in Asian patients is also included. Briefly, clinical studies demonstrate the achievement of adequate glycemic control in adults with T2DM through titration of Gla-100. However, studies investigating approaches to titration, specifically in Asian populations, are lacking and need to be conducted. Given that the management of insulin therapy is a multidisciplinary team effort involving endocrinologists, primary care physicians, nurse educators, and patients, greater resources and education targeted at

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Electronic supplementary material The online version of this article (doi:10.1007/s13300-017-0322-z) contains supplementary material, which is available to authorized users.

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these groups are needed regarding the optimal titration of basal insulin. Technological advancements in the form of mobile or web-based applications for automated dose adjustment can aid different stakeholders in optimizing the dose of basal insulin, enabling a larger number of patients in Asia to reach their target glycemic goals with improved outcomes.

Keywords: Asia; Basal insulin; Dose optimization; Dose titration; Insulin glargine 100 U/mL; Type 2 diabetes mellitus

INTRODUCTION

Asians show a strong ethnic association and genetic predisposition for developing type 2 diabetes mellitus (T2DM) at a younger age, and a lower body mass index than their Caucasian counterparts [1–3]. Consequently, Asian populations demonstrate higher rates of morbidity and early mortality [4, 5]. Only 37.3% of Asian patients from the International Diabetes Management Practice Study (IDMPS) [6] and 35.3% from the Joint Asia Diabetes Evaluation (JADE) program [7] had adequately controlled T2DM, with glycated hemoglobin (HbA_{1c}) levels < 7%, as recommended by the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) [8, 9].

T2DM is a progressive disease, and early treatment intensification has been shown to aid in the achievement of glycemic targets [6, 7, 10–12]. Benefits of intensive glycemic control include a reduction in the risk of microvascular complications and the impact of macrovascular problems [13, 14]. Studies have illustrated that patients on basal insulin are often able to achieve $HbA_{1c} < 7\%$ [15–17], and early intervention with basal insulin has been shown to maintain glycemic control in the long term [10]. Evidence, therefore, indicates that early initiation of basal insulin should be considered for patients with T2DM.

However, data indicate that Asian patients are poorly controlled for approximately 6–10 years, with average HbA_{1c} levels of 8.7–9.8% at the point of basal insulin initiation [11, 18–20]. The prospective, observational First Basal Insulin Evaluation (FINE) study examined the initiation of basal insulin in insulin-naïve patients with T2DM, uncontrolled ($HbA_{1c} \geq 8\%$) with oral antidiabetic drugs (OADs), in real-world clinical practice from 11 different Asian countries [19]. The study showed that in countries where the delay in initiation of basal insulin was > 9 years, patients were less likely to reduce their HbA_{1c} levels and meet glycemic targets [21]. Also of interest is a pooled analysis of 724 Asian patients for whom data were extracted from seven randomized clinical trials (RCTs) that investigated the initiation and titration of insulin glargine 100 U/mL (Gla-100). The pooled analysis demonstrated, through multivariate analysis, that a higher baseline HbA_{1c} at initiation of treatment with Gla-100 is associated with a smaller reduction in HbA_{1c} ($p < 0.0001$) [22]. This finding reinforces the importance of early initiation of basal insulin in Asian patients.

Once basal insulin is initiated, dose titration is an important factor affecting the patient's ability to achieve their target glycemic control [23]. Several studies have demonstrated the attainment of HbA_{1c} levels < 7% in patients with T2DM titrating Gla-100 toward well-defined physiologic targets, known as the treat-to-target (TTT) method [16, 17, 24–26].

There is a difference in insulin needs between Asian and Caucasian populations on account of ethnic and genetic differences, as demonstrated by a pooled analysis of 16 RCTs [1]. In this analysis, at similar doses of Gla-100, non-Asian patients were able to achieve better HbA_{1c} control than Asian patients, indicating that higher daily basal insulin doses may be required by Asian patients to achieve adequate glycemic control [1]. Differences in the pathophysiology of T2DM mean that the findings from clinical trials in Caucasian populations cannot necessarily be extrapolated to Asian populations, as noted in a publication where this was cited to be one of the potential reasons for insufficient dose adjustments in Japanese patients with T2DM [27]. Additionally, there is a lack of data on the titration of basal insulin in

Asian populations compared with that available for Caucasian populations.

Asian patients with diabetes are generally leaner than Caucasian patients and are therefore perceived to have an increased risk of hypoglycemia (although this has been demonstrated to be an incorrect assumption [1]), which leads to conservative treatment goals [28] and a cautious approach to the titration of insulin in Asia [19]. Real-world data from the Observational Registry of Basal Insulin Treatment (ORBIT) study conducted in China demonstrates suboptimal titration of basal insulin [29]. In the study, titration of basal insulin was in accordance with the provider's recommendation and the patient's willingness [20], and the dose of basal insulin was increased by only 0.03 units/kg/day over a period of 6 months [29].

These challenges demonstrate the difficulty of managing dose titration in Asian patients (a possible reason for the inadequate glycemic control seen amongst Asians), and highlight the need for further education and examination of the titration of basal insulin in Asia.

Of the several basal insulin analogs available, this review will focus on Gla-100 (Lantus®, Sanofi, France), a long-acting recombinant human insulin analog indicated for the treatment of adults and pediatric patients with type 1 diabetes mellitus, and adults with T2DM [30]. Newer basal insulin analogs, such as insulin glargine 300 U/mL (Gla-300), will not be discussed in this review. Gla-100, by virtue of having been available for more than 10 years [30, 31], has amassed a large volume of RCT and real-world data that warrants standalone discussion, especially since titration is still suboptimal in Asia [19, 29]. Despite the availability of newer basal insulins, in the opinion of the authors Gla-100 remains an integral part of the diabetes treatment paradigm in Asia, and discussion of approaches to the titration of Gla-100 is therefore still relevant. In this review, global and—where possible—Asian data on the efficacy and safety of titrating Gla-100 will be explored, and opinion on these data from the authors and their experiences with treating T2DM in Asian patients are also included. Where possible, approaches specific to the titration of Gla-100 have been reviewed; however, due to the lack of data, approaches to the titration of other basal insulins have also been included. This article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

TITRATING GLA-100

Meta-analyses published in 2014 by DeVries et al. [32] and Owens et al. [33] examined efficacy and safety outcomes across 15 TTT trials with once-daily Gla-100 added to different combinations of OADs at bedtime in insulin-naïve individuals with T2DM uncontrolled on OADs. The analysis included data derived from Sanofi-sponsored phase IIIb and IV TTT RCTs with protocol-driven titration algorithms for a duration $\geq$ 24 weeks [32, 33]. Overall, 2837 patients were analyzed, with efficacy assessed in terms of reduction in HbA_{1c} and fasting plasma glucose (FPG) [32, 33]. Safety outcomes assessed included hypoglycemia, as well as change in insulin dose and body weight [32, 33]. Safety and efficacy outcomes were calculated for weeks 0–12, referred to as the "titration period," as well as for weeks 12–24, referred to as the "maintenance period" [33]. All outcomes were assessed for each of the different treatment combinations, which included Gla-100 with metformin, Gla-100 with sulfonylurea, as well as Gla-100 in combination with metformin and sulfonylurea [32, 33].

Glycemic control improved following the initiation and subsequent titration of Gla-100, with HbA_{1c} and FPG decreasing from baseline to week 12, and this decrease was sustained or further improved at week 24 in participants receiving all three treatment combinations [32, 33]. The combination of Gla-100 and metformin demonstrated the greatest efficacy, with a mean reduction in HbA_{1c} from 8.7% at baseline to 7% at week 24 [32]. Of the patients receiving Gla-100 and metformin, 56.8% achieved an HbA_{1c} target of $< 7.0\%$ at week 24, the largest proportion of patients amongst the three treatment combinations [32]. Of the total HbA_{1c} reduction achieved at week 24, $> 80\%$

was achieved by week 12, demonstrating that Gla-100 can aid in the achievement of early and satisfactory treatment outcomes [33].

With regard to the safety outcomes, the combination of Gla-100 and metformin demonstrated the lowest incidence of overall, daytime, and nocturnal hypoglycemia, as well as the lowest weight gain compared with the other treatment groups [32, 33]. This was despite the greatest increase in the insulin dose taken by those on Gla-100 and metformin compared with patients who received sulfonylurea in their treatment regimen [32, 33]. The incidence of hypoglycemia was similar during the titration and maintenance periods for all of the treatment groups [33].

Overall, the meta-analyses concluded that initiation and subsequent titration of Gla-100 can lead to improved early (> 80% reduction in HbA_{1c} by week 12) and sustained glycemic control, with a low incidence of hypoglycemic events and minimal changes in weight [32, 33]. Patients receiving Gla-100 and metformin had a significantly shorter duration of diabetes at initiation compared with patients who received sulfonylurea in their treatment regimen—a possible reason for the greater efficacy and safety outcomes achieved by these individuals [32, 33].

In the past decade, several clinical trials have applied and investigated uniform titration algorithms, often referred to as TTT algorithms [34, 35]. TTT is a therapeutic concept that takes into consideration and works toward well-defined and specific physiological targets for controlling the pathophysiology of a disease [35]. The TTT approach is particularly suitable for the treatment of diabetes, as it can be measured by "gold-standard" quantitative measures such as HbA_{1c} and fasting blood glucose (FBG), clinical thresholds which have been determined by multiple international and national diabetes organizations [35]. Multiple TTT algorithms have been investigated in clinical studies. These algorithms are designed to produce equal degrees of glycemic control and are therefore able to reveal differences in safety, tolerability, and clinical utility between different treatment regimens when insulin dosing and efficacy is maximized [36]. An overview and the intervention details of several key TTT clinical trials involving patients with T2DM with inadequate glycemic control on OADs alone are shown in Table S1 in the Electronic supplementary material (ESM). The studies listed show consistent and substantial improvements in glycemic control, as well as a low incidence of hypoglycemic episodes with Gla-100.

APPROACHES TO THE TITRATION OF BASAL INSULIN

It is often considered too difficult and time-consuming for those in a primary care environment to initiate patients with T2DM on basal insulin [34, 37]. A primary care physician has an average consultation time of 5–20 min to oversee and assess the large amount of clinical information that must be reviewed before initiating and titrating basal insulin for each individual patient [38]. Various approaches to the titration of Gla-100 and other basal insulins, using TTT algorithms, have been investigated in order to help improve this situation. Some of those that have been investigated in clinical studies are discussed below, and others will be highlighted in the section "Strategies for optimal titration of basal insulin in Asian populations."

Titration in Groups Versus Individuals

The Initiate Insulin by Aggressive Titration and Education (INITIATE) study investigated the initiation and self-titration of Gla-100 using a TTT algorithm in insulin-naïve patients with T2DM [26]. Patients enrolled in the study were educated either individually or in groups of between four to eight on a variety of factors in relation to the treatment of T2DM, including self-adjustment of the dose of Gla-100. Educational sessions were held prior to, as well as throughout, the 24-week treatment period. Over the 24 weeks, mean HbA_{1c} levels decreased from 8.7 ± 0.2 to $6.9 \pm 0.1\%$ ($p < 0.001$) in those educated individually, and from 8.8 ± 0.2 to $6.8 \pm 0.1\%$ ($p < 0.001$) in those educated in groups, showing that providing support to

groups of patients who are initiating Gla-100 treatment can be as effective at achieving glycemic control as providing support on an individual basis [26]. The frequency of hypoglycemic events between both groups was similar, as was the dose of Gla-100. The total time spent on educating patients in groups on self-titration, monitoring, and injection of Gla-100 was 48% less than in those educated individually [26]. This study demonstrated that providing education on the dose titration of Gla-100 in groups is a viable option, and could help to overcome the resource and time constraints often faced by primary care physicians [34, 37, 38], enabling a higher number of patients to receive and optimize their insulin therapy [26].

Patient-Led Versus Physician-Led Titration

Greater awareness of the principle of patient self-titration has been aided by several TTT trials of insulins [36]. One of these is the Canadian Implementing New Strategies with Insulin Glargine for Hyperglycemia Treatment (INSIGHT) study, which investigated self-titration with Gla-100 using a TTT algorithm in 206 patients with T2DM. The study found improved glycemic control and greater increases in treatment satisfaction in those who self-titrated Gla-100 compared with those who received physician-adjusted conventional therapy with OADs [16].

Similarly, a study conducted by the AT.LANTUS (A Trial Comparing Lantus Algorithms to Achieve Normal Glucose Targets in Subjects with Uncontrolled Blood Sugar) study group compared two TTT treatment algorithms for the initiation and titration of Gla-100, the first being physician-led dose titration and the second self-management of dose adjustments [39]. The study concluded that a simple patient-administered titration algorithm significantly improves glycemic control with a low incidence of severe hypoglycemia compared with physician-led titration. It should be noted, however, that Asian patients were underrepresented in the AT.LANTUS study [18, 39].

In order to address this, the randomized multinational Asian Treat to Target Lantus Study (ATLAS) compared the relative effectiveness of patient-led versus physician-led titration of Gla-100 using TTT algorithms in insulin-naïve Asian patients with T2DM [18]. A greater decrease in HbA_{1c} values approaching the target was achieved by those who self-titrated their insulin dose compared with physician-led titration [18]. Severe hypoglycemia was rare in both treatment groups. Thus, when guidance is provided, Asian patients are able to effectively self-titrate their basal insulin to improve glycemic control [18].

Mobile and Web-Based Technologies

Advances in mobile and web-based technologies provide the potential for new models of collaborative care between patients and healthcare providers (HCPs) [40]. This includes capabilities for the real-time sharing of data, as well as improved communication between HCPs and patients between medical visits [40]. Whilst the outpatient-based face-to-face care model is suitable for managing acute illnesses, this approach may be inadequate for managing chronic diseases such as diabetes [40]. Patients with diabetes often need continuous advice on managing their glucose levels and on the risk of hypoglycemia (especially for patients on insulin) [40, 41], particularly as they are sensitive to many factors such as change in diet, physical activity, and stress [40]. In particular, basal insulin titration by way of face-to-face visits with a clinician can be time-consuming as well as logistically and financially burdensome for patients, especially those of low socioeconomic status (SES), as it often requires multiple appointments with the physician before dose optimization and adequate glycemic control are achieved [41, 42]. Research has consistently shown that diabetes management is an area where mobile and web-based technologies can improve the glycemic control of patients and empower them with the confidence to self-manage their disease to a greater extent [40, 43]. Some of the mobile and web-based technologies used for the titration of basal

insulin in patients with T2DM are reviewed below.

Mobile Technology Applications

Several studies have investigated the clinical efficacy and safety of the titration of basal insulin using an application, visualized via a tablet or a smart phone, in patients with T2DM [40, 44, 45]. The applications are guided by established basal insulin titration algorithms, and work by providing patients with the dosage of basal insulin they need to administer to achieve optimum glycemic control, based on their blood glucose (BG) level, which is required to be inputted into the application [40, 44]. The applications offer several self-tracking and streamlined communication tools. These tools include text message and virtual visit capabilities (audio, video, and shared screen control), charts demonstrating a correlation between medication adherence and glycemic level, BG readings that can be automatically integrated into the application via wireless glucometers, daily reminders for BG testing, alerts to warn patients if their BG is low, and information on diabetes medications. Both patients and their clinicians can also have the application synchronized to allow HCPs to remotely monitor their patients. These tools allow for in-depth co-exploration of data and collaborative decision-making between patients and clinicians [40, 44]. In Singapore, doctors from the Singapore General Hospital (SGH) Department of Endocrinology and Integrated Health Information Systems have developed a smart phone application named SGH Diabetes Pal that can guide patients with T2DM to self-titrate their basal insulin by providing recommended daily doses [46]. The application allows each patient's maximum dose to be inputted into the application as a safety feature [44].

A 24-week study has been conducted in Singapore to determine the effectiveness of the SGH Diabetes Pal application. The study enrolled insulin-naïve patients with T2DM with suboptimal glycemic control despite the use of two or more OADs. Patients either used the application (interventional group) or written instructions (control group) to self-titrate their doses of insulin detemir. Although not statistically significant, the reduction in HbA_{1c} from the baseline was numerically greater in the intervention group than in the control group. A steeper increase in the daily dose of basal insulin was observed in the intervention group. There were no episodes of severe hypoglycemia in either group [44].

A 14-week study by Hsu et al. considered whether a cloud-based diabetes management program, implemented through a tablet computer application, could help poorly controlled individuals with T2DM who were starting treatment with basal insulin therapy achieve better glycemic control (HbA_{1c}) compared with standard clinical practice involving interim face-to-face visits as well as telephone/fax communication between patients and HCPs [40]. At the end of the study, patients using the application achieved a statistically greater mean HbA_{1c} decrease than those receiving standard care. Additionally, an improvement in BG levels was observed within only a few days post-initiation for some patients using the application. On average, the amount of time required to instruct patients on use of the application was generally less than 1 h, and patients using the application reported a higher satisfaction of care. The mean virtual visit time per patient using the application was much lower than the mean clinician visit time of patients receiving standard care. Communication between the patients and HCPs through the application also decreased over time as patients gained the confidence to make their own clinical decisions. Overall, patients using the application reported that connectivity with their clinician through the application helped them feel more confident and motivated, that the collaboration with the HCP helped empower them to make their own decisions, and that they could, through the application's visualization capabilities, understand the connection between their BG levels and insulin intake [40].

A study by Spat et al. demonstrated that a tablet computer application aiding basal/bolus insulin titration can reduce the risk of human error [45]. This was done through a simulation of HCP decisions made in a paper-based clinical trial with the application. The simulation included 1190 decisions made by HCPs during

the paper-based clinical trial. From the simulation, four errors associated with the application were identified regarding the calculation of the daily insulin dose adjustment. However, the simulation also detected 144 calculation errors by physicians and nurses from the paper-based clinical study. The most common errors identified in the paper-based clinical trial were associated with basal/bolus insulin dose calculation, daily insulin dose calculation, and daily insulin dose adjustment. This highlights the potential of an electronic application to improve the accuracy of the implementation of a basal insulin titration protocol [45].

Although the above studies demonstrate the advantages of mobile technologies, in a review of a diverse number of diabetes mobile applications, Chomutare et al. noted that only 20% have educational content and fewer still have the ability to provide personalized feedback, indicating that there are still unmet needs that mobile technologies have not addressed [47].

Web-Based Technology

The internet provides a readily accessible platform for real-time communication between patients and HCPs, exchange of information, and remote health monitoring [48–50]. Patients can upload their BG readings to secure web-based platforms for the clinician to review and subsequently send back suggested changes in insulin dose and self-monitoring of blood glucose (SMBG) frequency, or even to provide feedback [41]. Alternatively, platforms can be built to provide insulin titration advice directly to the patient, based on a built-in titration algorithm [51]. Web-based platforms can reduce the need for appointments with a physician solely for the purpose of insulin titration, and can be a more cost-effective method of follow-up, especially for patients who live in rural areas [41].

A study showed significant improvements in glycemic control for patients with T2DM using an internet-based glucose monitoring system (IBGMS) for insulin titration compared with standard care (i.e., face-to-face appointments with the endocrinologist). Patients in the standard care group were required to keep a record of their SMBG readings in a diary between visits to the endocrinologist. Patients in the IBGMS group had statistically significant HbA_{1c} improvements after 3 months that were sustained over 6 months, which was not observed in patients in the standard care group. Biweekly communication with the endocrinologist through the IBGMS system allowed patients to have more accurate adjustments of their insulin dose. In addition, SMBG testing reminders and ease of data tracking and analysis through the system's tables/graphs were all hypothesized to aid patients in the IBGMS group to achieve greater glycemic control than those receiving standard care [41].

Cross-Platform Mobile and Web-Based Technologies

In the past year, several basal insulin dose calculators have been approved by the US Food and Drug Administration. These are Insulia (Gla-100, Gla-300, and insulin detemir) [52, 53], iSage Rx (Gla-100, Gla-300, insulin detemir, and insulin degludec) [54, 55], and My Dose Coach (any once-daily long-acting basal insulin) [56, 57]. These systems utilize both mobile and web-based platforms to automate the dose adjustment of basal insulin for patients with T2DM. While these systems are not replacements for HCPs, they do provide optimized and personalized suggestions for daily doses of basal insulin in between patient–HCP visits. In general, the HCP registers a patient and creates an individualized titration algorithm through a website portal, which can be accessed by the patient via a smart phone application. Patients input their daily FPG values into the smart phone application which provides them with real-time dose recommendations as per the HCP's treatment plan. HCPs can remotely track their patients' progress and make changes to the titration algorithm depending on treatment response [52, 54, 56].

Cell-Phone-Based Support

Cell phones are a part of daily life for most adults of all age groups and different cultural and socioeconomic backgrounds [43], and are increasingly being used to deliver health services [58].

A study by Levy et al. aimed to investigate whether the remote titration of Gla-100 was feasible by using only the basic features of a cell phone, namely short message service (SMS) text messaging and phone calls (including voicemail) between patients and HCPs. This could be particularly beneficial for patients of low SES, who find it challenging to attend multiple follow-ups with physicians and own a cell phone without advanced features (i.e., not a smart phone). The 12-week study aimed to investigate whether SMS and phone calls could assist patients to optimize their insulin dose, as well as determine the feasibility of this type of intervention, and whether there are cost savings and improved patient satisfaction compared with standard care (control group). In the study, a web-based platform automatically sent text messages to patients each weekday, to which they had to respond through SMS citing their BG level. A diabetes nurse educator would in turn log on to the web platform daily to view the patients' BG reading and flag any alarming values with the patients by phone. Titration of Gla-100 was performed once weekly by the nurse through phone calls or voicemails. A significantly greater number of patients in the intervention group achieved their optimal insulin dose in a median of just 3 weeks compared with patients receiving standard care, for whom it took a median of 7.07 weeks. The patients in the intervention group were highly interactive, and the majority of SMS text messages sent to the patients received a reply. Additionally, nurses were able to contact patients on the first or second attempt, or by voicemail, 91% of the time. The median duration of titration-related interactions in the clinic was 30.0 min, whereas the median for phone/voicemail interactions was 6.0 min ($p = 0.008$). Patients in the intervention group also saved travel time to and from the clinic, as well as time spent in the waiting room, and were shown to be more satisfied with their treatment [42]. The findings of this study are in line with previous studies that have demonstrated the effectiveness of SMS text messaging in assisting general and low-SES patients with diabetes to manage their disease [59–61].

Although the above studies indicate that advances in mobile and web-based technologies have the potential to enable successful collaboration between patients and HCPs for the titration of basal insulin and management of diabetes as a whole, further research is still needed to assess patient acceptability, attitudes toward these platforms, and their cost-effectiveness [62].

INTERNATIONAL GUIDELINE RECOMMENDATIONS FOR THE INITIATION AND TITRATION OF BASAL INSULIN

Recommendations on the initiation and titration of basal insulin can be found in several international clinical practice guidelines. The 2017 American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) comprehensive diabetes management algorithm specifies that basal insulin can be initiated in patients with T2DM with an entry HbA_{1c} level $< 7.5\%$ when either monotherapy with metformin or other OADs, or dual therapy with metformin and other agents, fails to achieve the glycemic target ($HbA_{1c} < 7\%$) [63]. The guidelines also indicate that basal insulin can be initiated as a part of dual therapy with metformin in patients with entry $HbA_{1c} \geq 7.5\%$, or when a patient presents with a HbA_{1c} level $> 9.0\%$ (dual or triple therapy with metformin) and symptomatic hyperglycemia at entry [63]. The 2015 diabetes clinical practice guidelines from the AACE/ACE acknowledged that the traditional postponement of insulin therapy after prolonged failure of lifestyle management and OADs to achieve glycemic control has been revised in the past decade, and recommended that basal insulin therapy should be initiated much sooner, and often in combination with OADs [64]. The ADA's updated Standards of Medical Care in Diabetes 2017 states the importance of dose titration of any insulin regimen once initiated, and that dose adjustments should be based on prevailing BG levels, together with knowledge of the pharmacodynamic profile of the insulin used [23]. The ADA recommends that if the HbA_{1c} target ($< 7\%$) is not achieved after

3 months of monotherapy with metformin, combination therapy of basal insulin with metformin, amongst other options, should be considered [23]. The 2015 position statement from the ADA/EASD emphasizes that insulin has the advantage of being effective where other agents may not be, and should be considered a part of any combination regimen when hyperglycemia is severe, particularly if the patient is symptomatic [9]. The International Diabetes Federation (IDF) recommends the initiation of basal insulin after the failure of combination therapy with metformin and other OADs, and the titration of insulin using a self-titration regimen, or with at least biweekly contact with a HCP [65]. Table 1 highlights key recommendations regarding the initiation and titration of basal insulin from several international guidelines.

COUNTRY-SPECIFIC RECOMMENDATIONS FOR THE INITIATION AND TITRATION OF BASAL INSULIN IN ASIA

Most countries in Asia have developed diabetes treatment guidelines that closely reflect international guidelines. For example, recommendations in the 2015 Indonesian Clinical Practice Guideline of Insulin Therapy in Diabetes Mellitus Patients reflect guidelines issued by the ADA/EASD and AACE/ACE, and contain guidance on the initiation and titration of insulin [66]. Recommendations from Hong Kong's Department of Health regarding the treatment of hypergylcemia in primary care settings also closely follow guidelines from the ADA/EASD, AACE/ACE and IDF, amongst others, with different treatment options for different baseline HbA_{1c} levels, as well as information on the titration of insulin [67]. The Philippine Practice Guidelines on the Diagnosis and Management of Diabetes Mellitus are aimed at educating all physicians involved in the management of diabetes. The guidelines include recommendations on the screening and diagnosis of diabetes mellitus, the screening and prevention of complications associated with diabetes, as well as information on the management of diabetes, particularly for special populations such as the elderly [68]. In Malaysia, the Ministry of Health's endocrinologists developed a practical guide for insulin therapy in 2010 that outlines a clear and concise approach for all HCPs to initiate insulin safely, optimize doses effectively, and intensify insulin regimens promptly [69]. The release of the guidelines was followed by nationwide education on the guidelines for primary care physicians, the result of which was an increase in the rates of insulin initiation in primary care practice. The Clinical Practice Guidelines for Diabetes Care 2015 from the Diabetes Association of the Republic of China (Taiwan) emphasizes that treatment goals should be individualized based on the patient's condition, similar to recommendations from the 2015 ADA/EASD position statement [70]. The 2014 Clinical Practice Guideline for Diabetes from Thailand was adapted from the IDF, ADA/EASD, and the National Institute for Health and Care Excellence (NICE) guidelines, and recommends starting basal insulin in patients with T2DM after the failure of dual or triple therapy with OADs [71]. Table 2 provides an overview of key recommendations regarding the initiation and titration of basal insulin from several Asian-country-specific guidelines.

In alignment with international guidelines, the majority of the recommended titration algorithms in Asia follow the TTT approach (Table 2), wherein basal insulin is initiated at a low dose to avoid hypoglycemia and subsequently adjusted based on pre-defined physiologic targets, meaning that patients may eventually end up on different doses of insulin. The TTT approach has proven to be an effective approach for initiating and adjusting the dose of basal insulin for non-Asian and Asian patients with T2DM [16–18, 32, 33, 39].

AUTHOR RECOMMENDATIONS FOR THE INITIATION AND TITRATION OF BASAL INSULIN IN ASIAN POPULATIONS

Based on their clinical experience, the authors have provided recommendations for the

Table 1 Recommendations from international guidelines for the initiation and titration of basal insulin for the treatment of T2DM

Guidelines	Starting dose (U/kg/day)	Dose titration	Glycemic targets	Controlling hypoglycemia
IDF 2012 [65]	For safety reasons, starting doses of insulin should be low	Self-titration regimen: insulin dose increase of 2 units every 3 days Physician-led: biweekly or more frequent contact with a healthcare professional	HbA_{1c}: < 7.0% FPG: < 6.5 mmol/L	NR
ADA 2017 [23]	0.1–0.2	Increase dose by 2–4 units once or twice weekly	HbA_{1c}: < 7.0% FPG: 4.4–7.2 mmol/L	Decrease dose by 4 units
AACE/ACE 2017 [63]	HbA_{1c} < 8%: 0.1–0.2 HbA_{1c} > 8%: 0.2–0.3	Fixed regimen: increase TDD of basal insulin by 2 units every 2–3 days Adjustable regimen: titrate insulin every 2–3 days according to: FBG 6.1–7.7 mmol/L: increase dose by 1 unit FBG 7.8–10 mmol/L: add 10% of TDD FBG > 10 mmol/L: add 20% of TDD	HbA_{1c}: < 7.0% FPG: < 6.1 mmol/L	BG < 3.9 mmol/L: decrease TDD by 10–20% BG < 2.2 mmol/L: decrease TDD by 20–40%

AACE American Association of Clinical Endocrinologists, *ACE* American College of Endocrinology, *ADA* American Diabetes Association, *BG* blood glucose, *FBG* fasting blood glucose, *FPG* fasting plasma glucose, *HbA_{1c}* glycated hemoglobin, *IDF* International Diabetes Federation, *NR* not reported, *T2DM* type 2 diabetes mellitus, *TDD* total daily dose

initiation and titration of basal insulin specific to the Asian population in Fig. 1 and Table 3, respectively.

The algorithm in Fig. 1 is in accordance with those provided by the ADA, AACE/ACE, and IDF [23, 63, 65], and indicates the optimal time for initiation of basal insulin; namely, following failure of treatment with metformin along with lifestyle modifications for a period of 3 months. However, the reality is that this algorithm is often not followed in clinical practice in Asia. In the authors' clinical experience, basal insulin is often initiated following failure with dual or triple OAD therapy (in addition to lifestyle modifications). Although patient-specific factors must be taken into consideration, in general there needs to be a push for earlier initiation of basal insulin in Asia, and the authors hope to encourage this.

The titration algorithm in Table 3 is closely aligned with other algorithms given in Asian-country-specific guidelines [66, 67, 69, 71], and involves a low dose of basal insulin for initiation to avoid hypoglycemia, and subsequent dose adjustments based on predefined physiologic targets; that is, the TTT approach. When choosing this algorithm, it is important that other patient- and disease-specific factors are also taken into consideration, as well as any dose adjustments to OADs that might be required.

STRATEGIES FOR THE OPTIMAL TITRATION OF BASAL INSULIN IN ASIAN POPULATIONS

Consistent and substantial improvements in glycemic control, as well as a low incidence of hypoglycemic episodes, have been observed in insulin-naïve patients with T2DM titrating Gla-100 using a TTT algorithm. Of these studies,

Table 2 Recommendations from Asian-country-specific guidelines for the initiation and titration of basal insulin

Country	Starting dose (U/kg/day)	Dose titration	Glycemic targets	Controlling hypoglycemia
Hong Kong [67]	0.1–0.2	According to latest average of 3 or more FBG values taken at specific times: FBG 4.0–7.0 mmol/L: maintain current dose FBG 7.1–10 mmol/L: increase insulin dose by 2 units FBG > 10 mmol/L: increase insulin dose by 4 units	HbA_{1c}: < 7.0% FPG: 4–6 mmol/L	FBG < 4.0 mmol/L: decrease insulin dose by 2 units
Malaysia [69]	0.1–0.2	Based on 3 consecutive BG values obtained every 3–7 days: BG 4–6 mmol/L: maintain current dose BG > 6 mmol/L: increase insulin dose by 2 units	HbA_{1c}: < 6.5% FPG: 4.4–6.1 mmol/L	BG < 4 mmol/L: Reduce dose by 2 units
Indonesia [66]	0.1–0.2	FBG 5–7.2 mmol/L: maintain current dose FBG > 7.2 mmol/L: increase dose by 2–4 units, once–twice weekly	HbA_{1c}: < 7% FPG: 4.4–6.1 mmol/L	FBG < 5 mmol/L: decrease insulin dose by 4 units or 10–20%
Philippines [68]	0.2	NR	HbA_{1c}: < 7% FPG: 4–7 mmol/L	NR
Thailand [71]	0.1–0.2	FBG > 6.7 mmol/L: increase insulin dose by 2–4 units per injection every 3–7 days	HbA_{1c}: < 7%	NR
Singapore [72]	NR	NR	HbA_{1c}: ≤ 7.0%	NR
Taiwan [70]	0.1–0.2	NR	HbA_{1c}: < 7%	NR

BG blood glucose, *FBG* fasting blood glucose, *FPG* fasting plasma glucose, *HbA_{1c}* glycated hemoglobin, *NR* not reported

only a handful have been conducted specifically in Asian populations [18, 28]. Thus, there is a lack of information and guidance on the appropriate frequency of titration, safe dose increments, and the maximal dose of basal insulin for Asian populations. Studies need to be conducted to enable an adequate understanding of the pathophysiology of Asian patients and therefore how insulin requirements, treatment goals, and the risk of hypoglycemia differ from those for Caucasian patients.

In order to provide some guidance, based on their own clinical experience, the authors recommend that with careful monitoring, the presence of hypoglycemia may be taken as an indication that the basal insulin dose is too high. Consideration should be given to any

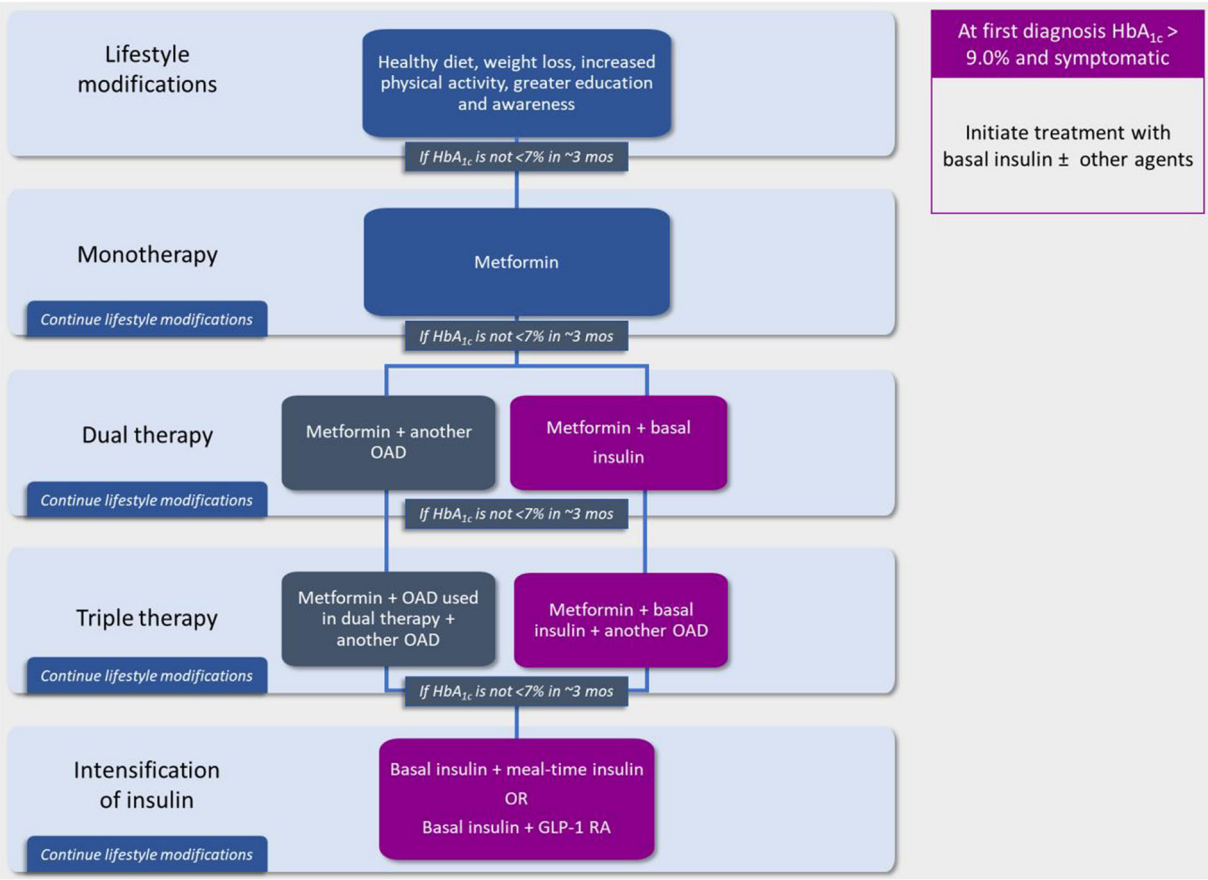

Fig. 1 Author recommendations for the initiation of basal insulin for the treatment of T2DM in Asian populations. *GLP-1 RA* glucagon-like peptide-1 receptor agonist, *HbA$_{1c}$* glycated hemoglobin, *mos* months, *OAD* oral antidiabetic drug, *T2DM* type 2 diabetes mellitus

dose adjustments to OADs that might be required with basal insulin initiation and titration. The authors recommend, despite current real-world practices in Asia, that the optimal time for initiation of basal insulin should follow approximately 3 months of failure of metformin monotherapy and lifestyle modifications, as summarized in Fig. 1. The recommended titration algorithm given in Table 3 involves a low dose of basal insulin for initiation to avoid hypoglycemia, and subsequent dose adjustments based on predefined physiologic targets. When choosing this algorithm, it is important that other patient- and disease-specific factors are also taken into consideration.

The management of insulin therapy is a multidisciplinary team effort that involves specialists, primary care physicians, nurse educators, and patients. Due to the high prevalence of T2DM in Asia [5], it is vital that primary care providers, patients, and other HCPs are able to adequately manage insulin therapy; to achieve this, greater education and resources on the optimal titration of basal insulin need to be targeted at these groups.

The time and resource constraints that primary care physicians face [34, 37, 38] could potentially be relieved through the use of modern technology, including web-based tools, mobile applications, cell-phone-based support, glucometers capable of uploading data to the web, and telephone hotlines [40–42, 44, 45, 48, 49, 73]. As an example, one of the authors of this paper has implemented the titration of insulin through the medium of

Table 3 Author recommendations for the titration of basal insulin for the treatment of T2DM in Asian populations

Starting dose (U/kg/day)	Dose titration	Glycemic targets	Controlling hypoglycemia
0.1–0.2	Based on the lowest FPG reading of the previous 3 days, adjust the dose of basal insulin weekly: FPG 4.0–6.0 mmol/L: maintain current dose FPG 6.1–8.9 mmol/L: increase dose by 2 units FPG > 8.9 mmol/L: increase dose by 4 units	$HbA_{1c} < 7\%$ FPG 4.0–6.0 mmol/L	FPG < 4.0 mmol/L: reduce dose by 2 units

FPG fasting plasma glucose, *HbA_{1c}* glycated hemoglobin, *T2DM* type 2 diabetes mellitus

SMS in his clinical practice in Indonesia. Patients send their SMBG readings by SMS every 3–7 days to their clinician (author) and receive advice via a return SMS regarding changes in their insulin dose. The author has reported that patients are satisfied with this method of communication because of its efficiency and the amount of attention from the physician that it affords. In another author's clinical practice in the Philippines, patients relay their SMBG readings through SMS or by phone call and accordingly receive advice on their readings through phone calls. Patients have reported satisfaction with this method as it saves on travel time to the clinic and circumvents the need to take time off work to attend clinic appointments.

With regard to technology-based methods, care should be taken to implement these in the right settings. Other approaches to titration, for example group titration and education, may be effective for elderly patients who may not be comfortable with the use of technology. Titrating and providing education in groups not only reduces the amount of time needed with each patient but also creates an environment that allows patients to discuss and share their problems as well as support each other [26].

To reduce the burden on primary care physicians, diabetes nurse educators should be empowered to provide patients with guidance on titration. Nurse-led care is a practical and cost-effective model, and is effective in maintaining optimal glycemic control of patients as well as enhancing their adherence to treatment [74]. One example of facilitating nurse-led care could be to set up nurse-led titration clinics. Technology could also be taken advantage of to support nurse-led titration. A study has demonstrated that patients can effectively titrate their doses of Gla-100 and improve their glycemic control through SMS/phone call contact with their diabetes nurse educators. This method also reduced travel time, time spent in the waiting room, and the overall cost of treatment for patients [42].

Despite an increasing drive for patients to be more involved in the management of their disease [9, 75, 76], physicians often are of the opinion that patients are unable or unprepared to effectively self-titrate and manage their insulin dose. The ATLAS study has demonstrated that patients in Asia are able to effectively titrate their dose of Gla-100 when provided with guidance [18]; however, only a few clinical studies investigating the self-titration of basal insulin amongst patients with T2DM have been conducted [18, 39]. To increase awareness of self-titration, as well as provide specialists and primary care physicians with evidence that patients are able to effectively self-titrate their insulin, further studies investigating patient-led titration specifically in Asian populations should be conducted. Supporting patients is also vital, and can be achieved through various measures, such as by setting up insulin titration clinics as well as enrolling patients into patient support programs that encourage self-titration. Mobile and web-based technologies can also empower patients with the confidence to self-manage their disease to a greater extent, and various studies have demonstrated that by using these technologies, patients are able to effectively

titrate their basal insulin for improved glycemic control. Patients are often frustrated with the time it takes to attain adequate glycemic control [77], and involving them in their own treatment can potentially help to resolve this.

The ultimate goal of the research and recommendations outlined in this article is to enable patients with T2DM to achieve optimal glycemic control. The authors acknowledge that achieving this requires patients to control their postprandial BG in addition to their FPG, possibly requiring a prandial insulin. Dose optimization of basal and prandial insulin analogs together is therefore a subject for future consideration.

CONCLUSIONS

We have reviewed the efficacy and safety of titrating Gla-100, and highlighted the importance of optimal dose titration in supporting Asian patients with T2DM to achieve glycemic control. Specific challenges exist within Asia that impact basal insulin titration and therefore affect treatment outcomes. These include the strong ethnic association with and genetic predisposition to diabetes among Asians [4, 78], as well as the relatively long delays incurred before insulin initiation and suboptimal dose titration, which have been reported in several countries [11, 18–21]. Current treatment guidelines recommend early initiation of basal insulin therapy, and subsequent effective patient- or physician-led dose titration regimens to facilitate dose optimization [9, 63, 65–67, 69, 71]. In the past decade, various studies have illustrated that titration of Gla-100 using the TTT method has been able to aid patients in achieving $HbA_{1c} < 7\%$ [32, 33], and early intervention with basal insulin has been shown to maintain glycemic control in the long term [10]. Early initiation and optimal titration of basal insulin is therefore key to improving patient outcomes. Given the success with patient-led dose titration observed in several studies [16, 18, 39], this method could prove to be an effective means of optimizing treatment. Thus, future initiatives in Asia should embrace educational support to promote patient-led approaches so as to empower individuals with T2DM to take control of their treatment [18]. Additionally, the use of mobile and web-based technologies has the potential to facilitate successful collaboration between patients and HCPs [40–44] and therefore improve the titration of basal insulin and the management of diabetes as a whole, and should be further used and encouraged.

ACKNOWLEDGEMENTS

The authors did not receive funding to participate in the development of this article. Editorial assistance in the preparation of this manuscript was provided by Priya Shreedhar of MediTech Media Singapore, funded by Sanofi Singapore. In addition to medical writing support, article processing charges were funded by Sanofi Singapore. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published. Dr. Tran Quang Khanh, an endocrinologist at Nguyen Tri Phuong Hospital in Ho Chi Minh City, Vietnam, contributed to the initial discussion of this review paper. Information from the Indonesian Clinical Practice Guideline of Insulin Therapy in Diabetes Mellitus Patients was verified by Pratidina Paramita and Ratna Indah Widyasari, employees of Sanofi. Information from the 2014 Clinical Practice Guideline for Diabetes from Thailand was verified by Soamrutai Boonsuepsakul, an employee of Sanofi.

Compliance with Ethics Guidelines. This article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

Disclosures. Maria Aileen Mabunay is an employee of Sanofi and contributed in their capacity as diabetes subject matter experts. Shailendra Bajpai is an employees of Sanofi and contributed in their capacity as diabetes subject matter experts. They did not exercise selective influence over the opinions expressed by other

authors in this article. Chaicharn Deerochanawong has been a consultant and speaker for Sanofi, Takeda, Novo Nordisk, Eli Lilly, Boehringer Ingelheim, Astra Zeneca, and Abbott. I. Made Pande Dwipayana has served on an advisory board for Sanofi. Reynaldo Rosales is a member of the Medical Advisory Board of Sanofi Philippines, and has received honoraria for speaker services from Sanofi and Novo Nordisk. Man Wo Tsang has received honoraria for speaker services from Sanofi, served on advisory boards for Eli Lilly, MSD, Astra Zeneca, and Abbott Nutrition, and received a research grant from Johnson & Johnson. Shih-Tzer Tsai has been a consultant and has received honoraria for speaker services from Sanofi, Novo Nordisk, Eli Lilly, Astra Zeneca, and Boehringer Ingelheim. Zanariah Hussein has received honoraria for speaker services from Sanofi, Eli Lilly, and Novo Nordisk.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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