Aims: To compare outcomes between Asian and non-Asian patients with type 2 diabetes (T2D) inadequately controlled on oral antidiabetic drugs (OADs) initiating insulin glargine 100 units (U)/mL (Gla-100) in randomised controlled clinical trials.

Methods: Post hoc analysis of patient-level data (Asian n = 235; non-Asian n = 3351) from 16 trials.

Results: At baseline, Asian patients were younger with lower body mass index (BMI), fasting C-peptide, and fasting plasma glucose (FPG) than non-Asian patients (all \(P\) < .001). Asian patients had a higher mean glycosylated haemoglobin (HbA1c) at Week 24 and less reduction in HbA1c from baseline (7.4% vs. 7.2%; \(-1.3\)% vs. \(-1.6\)%), respectively, \(P\) = .0001), and were less likely to achieve HbA1c <7.0% (40% vs. 47%; \(P\) = .002) than non-Asian patients. Reductions in FPG and rates of hypoglycaemia were similar between Asian and non-Asian patients. Asian patients had less weight gain than non-Asian patients (+1.3 vs. +1.9 kg, respectively, \(P\) = .013).

Conclusions: In our post hoc meta-analysis, Gla-100 effectively lowers HbA1c and FPG in Asian patients with T2D uncontrolled on OADs with similar incidence of hypoglycaemia and less absolute weight gain compared with non-Asian patients. At a similar FPG reduction, fewer Asian patients achieved HbA1c target <7.0%, suggesting that prandial glucose needs to be addressed.
1. Introduction

Diabetes represents one of the most significant global health crises. Its impact is particularly acute in Asia which, based on 2013 estimates, is home to more than 55% of people with diabetes worldwide [1]. The acceleration in the prevalence of type 2 diabetes (T2D) in Asia has occurred principally over recent decades. Asian individuals develop T2D at a lower mean body mass index (BMI) and a younger age than Europeans [2,3] with a propensity for developing renal disease in addition to cardiovascular diseases [4,5]. Type 2 diabetes in Asians is characterised by early decline in β-cell function rather than insulin resistance [6,7], which may influence their response to anti-hyperglycaemic treatment [8,9]. In the real-world First Basal Insulin Evaluation (FINE)-Asia study, Asian patients (69.8% with combination oral antidiabetic drugs [OAD] therapy) required a mean basal insulin dose of 0.22–0.24 units (U)/kg to achieve a 2% reduction in glycosylated haemoglobin (HbA1c) [10]. In comparison, the Treat-to-Target study of North American patients showed that doses of 0.42 U/kg and 0.48 U/kg (for NPH insulin and insulin glargine, respectively) were required for a mean change in HbA1c of ~1.6% over a 6-month period [9], which is much higher than the mean basal insulin doses required in the Asian population.

In this post hoc patient-level analysis, we compared the clinical outcomes (HbA1c, fasting plasma glucose [FPG], insulin dose, hypoglycaemia event rate and body weight) between Asian and non-Asian insulin-naïve patients with T2D, inadequately controlled on OADs who were initiated on insulin glargine 100 U/mL (Gla-100) in randomised controlled clinical trials.

2. Material and methods

2.1. Study and patient selection

Studies included in the analysis were randomised controlled trials of Gla-100 lasting for at least 24 weeks with a treatment target of FPG ≤100.0 mg/dL (5.6 mmol/L) and where individual patient-level data were available. All patients were insulin-naïve adults with inadequately controlled T2D with a HbA1c range of >7.0–10.0% (>53.0–86.0 mmol/mol) and were given Gla-100 in addition to their current OAD therapy. Ethnicity (Asian vs. non-Asian) was based on investigator classification and reported in each individual trial. The pooled analysis was performed for the overall population initiating Gla-100 therapy at bedtime, regardless of OAD therapy. In addition, a sub-analysis of patients using concomitant metformin (MET) and sulfonylurea (SU) therapy (Gla-100 + MET + SU) was performed. Asian patient characteristics for each study are reported in the supplementary appendix.

2.2. Endpoints

The main efficacy endpoints included change from baseline HbA1c and FPG, and achievement of target HbA1c (<7.0% [53.0 mmol/mol]) and FPG ≤100.0 mg/dL [5.6 mmol/L]). The main safety endpoint was hypoglycaemia (event rate/patient-year). Hypoglycaemia was defined as overall (i.e. events with confirmed plasma glucose [PG] <70.0 mg/dL [3.9 mmol/L] or requiring third-party assistance), nocturnal (i.e. events with PG <70.0 mg/dL [3.9 mmol/L] occurring between 00:01 AM and 05:59 AM), and severe (i.e. any event requiring third-party assistance). In addition to overall hypoglycaemia rates, we also examined the incidence of clinically significant hypoglycaemic events with confirmed PG <56.0 mg/dL (3.1 mmol/L). Insulin dose (U/kg) and body weight (kg) at Week 24 were also assessed.

2.3. Statistical analyses

Standardised patient-level data were pooled from the identified studies. HbA1c, FPG, body weight and insulin dose (U/kg) at baseline and Week 24 were summarised descriptively for Asian and non-Asian patients. Between-group comparisons of HbA1c, FPG, body weight and insulin dose (U/kg)
were performed using analysis of covariance (ANCOVA). The factors and covariates were age, sex, duration of diabetes, baseline values of BMI, HbA1c and FPG, and Asian/non-Asian group and concomitant OAD group and corresponding baseline values. Studies were included in the model for analysis by OAD categories. The percentage of patients achieving targets of HbA1c <7.0% (53.0 mmol/mol) or FPG ≤100.0 mg/dL (5.6 mmol/L) at Week 24 were summarised for Asian and non-Asian patients and compared by logistic regression (PROC GENMOD, binomial distribution, logit link) using the same factors and covariates as previously described. Adjusted hypoglycaemia event rates (events/patient-year) were derived from a negative binomial regression including baseline BMI, duration of diabetes and Asian group as factors.

3. Results

3.1. Studies and patients

Sixteen studies with available patient-level data [11,12] met the inclusion criteria (supplementary appendix). Overall, 3586 patients were included in the analysis (235 Asian and 3351 non-Asian). Patient demographics and clinical characteristics are presented in Table 1. Asian patients were younger, had a lower mean baseline body weight, BMI, C-peptide, FPG and a lower daily Gla-100 dose (U/day) than non-Asian patients (all \( P < .001 \)).

![Fig. 1 - Mean HbA1c at baseline and Week 24 (A) and proportion of patients achieving HbA1c <7.0% (53.0 mmol/mol) (B) in Asian and non-Asian patients with T2D treated with Gla-100. P values for change from baseline data from an ANCOVA model. ANCOVA, analysis of covariance; Gla-100, insulin glargine 100 units/mL; HbA1c, glycosylated haemoglobin; T2D, type 2 diabetes.](image1)

![Fig. 2 - Mean FPG at baseline and Week 24 (A) and proportion of patients achieving FPG ≤100 mg/dL (5.5 mmol/L) (B) in Asian and non-Asian patients with T2D treated with Gla-100. P values for change from baseline data from an ANCOVA model. ANCOVA, analysis of covariance; Gla-100, insulin glargine 100 units/mL; HbA1c, glycosylated haemoglobin; NS, not significant; T2D, type 2 diabetes.](image2)
3.2. **Efficacy**

Both groups had similar baseline HbA1c values. At Week 24, Asian patients had higher HbA1c and smaller reduction from baseline compared to non-Asian patients (−1.3% vs. −1.5%, *P* < .001) (Fig. 1A). Similarly, fewer Asian patients achieved target HbA1c <7.0% (53.0 mmol/mol) (Fig. 1B). Mean reductions in FPG at Week 24 were similar in both groups with a tendency towards a lower baseline FPG in Asian patients (Fig. 2A) and increased likelihood of achieving a target FPG <100.0 mg/dL (5.6 mmol/L) than non-Asian patients, albeit not significant (Fig. 2B). Numerically more Asian (48.5%) than non-Asian patients (37.4%) with FPG <100.0 mg/dL (5.6 mmol/L) at Week 24 had HbA1c values above 7.0% (53.0 mmol/mol) (*P* = .26).

3.3. **Insulin dose**

Overall, Week 24 insulin dose and change from baseline were similar between Asian and non-Asian patients (Fig. 3). In patients receiving MET + SU combination therapy, Asian patients required a lower insulin dose at Week 24 than patients in the non-Asian subgroup (adjusted endpoint for Asian vs. non-Asian: 0.36 vs. 0.41 U/kg, *P* = .045, change from baseline to endpoint: 0.22 vs. 0.27 U/kg, respectively, *P* = .045).

3.4. **Hypoglycaemia event rates**

Overall, Asian and non-Asian patients experienced similar hypoglycaemia event rates (PG <70.0 mg/dL [3.9 mmol/L]) (Fig. 4A) although all events were numerically lower in the Asian patients, reaching significance for severe hypoglycaemia (PG <56.0 mg/dL, 3.1 mmol/L) (Fig. 4B).

3.5. **Body weight**

Mean body weight increased in both groups with greater change in non-Asian than Asian patients (adjusted endpoint for non-Asian vs. Asian patients: 88.1 vs. 87.4 kg, *P* = .013, change from baseline to endpoint: 1.9 vs. 1.3 kg, respectively, *P* = .013).

4. **Discussion**

In this pooled data analysis of 16 randomised clinical trials, Asian patients with T2D uncontrolled by OADs and initiating basal insulin therapy with Gla-100 were 4 years younger, and leaner with a BMI 3–4 kg/m² lower than their non-Asian counterparts. They also had lower baseline C-peptide levels, FPG and starting insulin dose (U/day). Overall, Asian and non-Asian patients received similar dosage of insulin but Asian patients had less reduction in mean HbA1c with less weight gain. They were also less likely to achieve target HbA1c despite having a lower FPG, suggesting that Asian patients may need additional treatment to optimise prandial blood glucose. Overall, there were low hypoglycaemia event rates in both groups, with Asians having a tendency for lower event rates reaching significance for clinically significant hypoglycaemia (PG <56.0 mg/dL [3.1 mmol/L]) than non-Asian patients.

In line with other reports [2,3], Asian patients with T2D in our cohort had lower BMI and C-peptide than their non-Asian counterparts, despite having similar disease duration. Apart from insulin resistance occurring at a younger age and lower BMI compared to Caucasians and Hispanic Americans [13], β-cell dysfunction is an important culprit in the rising prevalence of young-onset diabetes in Asia [6,7]. In our cohort, the C-peptide level was 20% lower in Asian than non-Asian patients (0.95 vs. 1.18 nmol/L). Similar findings have also been reported in Japanese T2D patients compared to Caucasian patients [2,14]. Given this intrinsic insulin secretory defect, basal insulin alone may not correct postprandial glucose (PPG) levels which might explain the higher mean HbA1c in Asian patients despite their lower FPG. However, PPG response was not systematically assessed in these trials.

In support of this notion, some researchers have reported that PPG might be a more important contributory factor to dysglycaemia in Asian patients with uncontrolled T2D than in those of other ethnicities [8,9]. In addition, PPG had better correlation to HbA1c in lean patients with diabetes, as also seen in our Asian cohort [15]. In the real-world FINE-Asia registry, despite a wide range of baseline factors and glycaemic control, Asian patients appeared to have a better response to early initiation of basal insulin than other ethnic groups [16]. On the other hand, meta-analyses also support the favourable effects of incretin therapy in Asian patients [17,18]. Taken together, these data suggest that a combination of early initiation of basal insulin and use of a prandial glucose regulator such as incretin mimetics and/or prandial insulin might be particularly beneficial to Asian T2D patients uncontrolled on OADs.

There are conflicting data on the influence of ethnicity on the relationship between FPG and HbA1c levels. A number of studies have indicated that higher HbA1c levels occurred with lower overall and fasting glucose in some ethnic groups,
which is in line with the lower mean baseline FPG in our study [19,20]. Although a sub-analysis of the large ORIGIN study did not show any effect of ethnicity on the relationship between FPG and HbA1c, the issue of prandial glucose was not addressed [21]. In a Singapore multi-ethnic study [22], HbA1c values were lower in Malays and Indians than Chinese at low FPG levels; in contrast, when FPG levels were >90.0 mg/dL (5.0 mmol/L), HbA1c values were higher in Malays and Indians than Chinese. However, given the many determinants for blood glucose including lifestyle, environmental and cultural factors as well as access to care, these inter-ethnic differences in less controlled settings must be interpreted with caution.

In our pooled analysis, the mean starting Gla-100 dose based on U/kg body weight was numerically higher in Asian patients than their non-Asian counterparts. At Week 24, both groups had similar insulin dosage by weight. Although Asian
patients had less absolute weight gain than Caucasian patients (least squares [LS] mean change [standard error (SE)]: 2.6 [6.3] kg vs. 3.6 [6.2] kg, respectively; \( P < .05 \)), the percentage change compared to baseline body weight was similar between both groups as reported by other researchers [23]. Since cardiovascular risk factors occur at lower BMIs in Asian than non-Asian patients, the small effect of Gla-100 on absolute weight gain is desirable [24].

The main strength of this analysis lies in its relatively large number of patients from multiple sites worldwide with patient-level data. Apart from limitations associated with post hoc analyses, the generalisability of our data collected in a controlled setting to the wider population remains unclear.

In summary, in this pooled analysis, Gla-100 effectively lowers HbA1c and FPG in both Asian and non-Asian patients with T2D uncontrolled onOADs, with a similar incidence of hypoglycaemia but less weight gain in Asian than non-Asian patients. However, the lower number of Asian patients achieving HbA1c goals despite a higher achievement of target FPG suggests that some Asian patients may benefit from an alternative intensification strategy with additional prandial therapy, such as incretin mimetics or rapid-acting insulin, alongside basal insulin therapy.

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Conflict of interest

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.diabres.2017.11.025.

REFERENCES


