



ORIGINAL RESEARCH

National Variations in Comorbidities, Glycosylated Hemoglobin Reduction, and Insulin Dosage in Asian Patients with Type 2 Diabetes: The FINE-Asia Registry

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ABSTRACT

Introduction: The First Basal Insulin Evaluation (FINE) Asia study was a prospective, observational registry evaluating basal insulin initiation in Asian patients with type 2 diabetes mellitus inadequately controlled by oral antihyperglycemic agents.

Methods: The objective of this post hoc analysis was to observe and report the findings from individual participating countries. The primary endpoint was change in glycosylated hemoglobin (HbA_{1c}) from baseline to month 6

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after basal insulin initiation. Secondary endpoints included change in fasting blood glucose (FBG), percent of patients achieving target HbA_{1c} and FBG levels, average insulin doses, and hypoglycemic events.

Results: The study included 2921 patients from 11 Asian countries at baseline, 2679 (92%) of whom had evaluable data. Following initiation of basal insulin (neutral protamine Hagedorn insulin, glargine, or detemir), there was a significant ($P < 0.001$) difference in HbA_{1c} reduction and proportions of patients meeting HbA_{1c} and FBG targets ($<7\%$ and <110 mg/dL, respectively) across all country cohorts by month 6. Glycemic control also varied greatly, with 7.4% (Taiwan) to 71.5% (China) of patients reaching target HbA_{1c} $<7\%$ levels. Mean (\pm standard deviation) insulin dose increases over the 6-month period ranged from 0.5 ± 3.1 U (Pakistan) to 6.0 ± 8.6 U (Thailand). Hypoglycemia rates also varied, with 7.1% (India) to 27.3% (China) of patients experiencing one or more events.

Conclusions: Data from the FINE-Asia registry study show widely varying degrees of baseline comorbidities and glycemic control in patients among the country cohorts observed. Countries

with >9 years of diabetes prior to insulin initiation had the lowest reductions in HbA_{1c} and proportions of patients achieving HbA_{1c} and FBG targets, suggesting that earlier basal insulin initiation may afford better glycemic control in these patients.

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Keywords: Asia; Basal insulin; Insulinization; Type 2 diabetes

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a progressive disease characterized by insulin resistance and decline of β -cell function [1, 2]. Tight glycemic control is one of the cornerstones of effective management of T2DM, as it significantly reduces the risk of microvascular complications and may reduce the impact of macrovascular problems, particularly when achieved early in the disease course [3–5].

Based on clinical and experimental studies, the International Diabetes Federation proposed a preferred glycosylated hemoglobin (HbA_{1c}) target of $\leq 6.5\%$ for the management of T2DM [3–6]; experts from the American Diabetes Association and the European Association for the Study of Diabetes issued a statement advocating HbA_{1c} levels of $< 7.0\%$, with stringency of control adapted according to patient-specific features such as age, disease duration, and comorbidities, among others [7]. This statement recognized that insulin can be an effective component of management strategies to achieve glycemic control, and early initiation of insulin is recommended in patients not meeting HbA_{1c} targets. The benefits of insulin therapy and the recommendations for its initiation in treatment guidelines have been demonstrated via observational studies and medical insurance

database analyses conducted in European and North American countries [8–10]. The translation of this to the Asian experience, however, has not specifically been reported. At the same time, the prevalence of T2DM continues to increase at higher rates among Asian countries than in other regions [11].

Available evidence suggests that insulin utilization in Asia has not markedly changed over the past 10 years [12–14], despite changes in treatment guidelines advocating the initiation and intensification of therapy to reach HbA_{1c} goals. The objective of the First Basal Insulin Evaluation (FINE)-Asia study was to provide details on the real-world initial insulinization in patients with T2DM across Asia, as well as to determine the tolerability and efficacy of basal insulin regimens in this region. This article provides information from post hoc analysis of the FINE-Asia study, which examined variations in baseline characteristics and efficacy and safety endpoints according to the country or region from which patients were enrolled.

METHODS

FINE-Asia was a multinational, prospective, observational study designed to assess the initiation of basal insulin in insulin-naïve patients with T2DM in a real-world clinical setting in Asia. Patients were enrolled from 195 centers/sites across 11 different Asian countries (Bangladesh, China, Hong Kong, India, Indonesia, Korea, Pakistan, Singapore, Taiwan, Thailand, and Vietnam) [15].

Study Objectives

The FINE-Asia study was designed to evaluate current clinical practice in the treatment of Asian patients with T2DM with inadequate

glycemic control on oral antidiabetic drugs (OADs) who have been initiated on basal insulin. The main objective of this post hoc analysis was to examine the baseline characteristics of the study population and to report the findings of the study according to the country or region from which patients were enrolled. The primary efficacy endpoint was the change in HbA_{1c} from baseline to month 6 after basal insulin initiation. Secondary endpoints included change in fasting blood glucose (FBG) from baseline to month 6, percent of patients achieving target HbA_{1c} and FBG levels, average insulin doses, and hypoglycemic events.

Patients

From the centers/sites participating in this registry study, male or female patients aged ≥ 20 years with T2DM inadequately controlled (HbA_{1c} $\geq 8\%$) by OADs, and who, in the opinion of their treating physician, required the initiation of a basal insulin, were eligible for inclusion in the registry.

Patients who received premixed insulin at the start of the registry period, who were prescribed insulin shortly before the start of the registry period (with the exception of acute rescue insulin therapy), or women who were either pregnant or of childbearing potential (not surgically sterile or postmenopausal for less than 2 years) and were not going to use a reliable contraceptive measure for the duration of the study were not included in this registry. In addition, patients with known hypersensitivity to insulin or any excipients of marketed insulin were also excluded from the study.

Study Treatment and Assessments

Basal insulin was initiated with or without concomitant OADs, and no specific protocol

on the type of basal insulin or OADs administered was recommended. The doses of basal insulin were based on the recommendation of locally approved package inserts and individually adjusted by the treating physicians based on individual patient profiles (e.g., comorbidities, tolerability/preference, etc.). Follow-up duration was 6 months; the registry involved three main visits scheduled according to physician routine practice, at which point effectiveness and safety data were collected (at inclusion, month 3 ± 7 days, and month 6 ± 7 days). Each visit included standard physical examinations (including body weight and blood pressure) and assessments of HbA_{1c}, FBG and self-monitoring of blood glucose (SMBG) profiles, adverse drug reactions (ADRs), and hypoglycemic episodes. It was recommended that patients perform SMBG using their own glucose monitors by their usual practice. In addition, SMBG was recommended when mild to moderate hypoglycemic events occurred. Safety was evaluated using the ADRs reported during the follow-up period, including all non-serious ADRs (especially hypoglycemic events), serious ADRs, overdoses, and changes in clinical and/or laboratory data. Severe hypoglycemia was defined as blood glucose (BG) <70 mg/dL (3.9 mmol/L) and requiring assistance.

Statistics

Statistical analyses were based on patients with HbA_{1c} data at both baseline and 6 months. All data were analyzed using SAS version 9.2 statistical software (SAS institute, Cary, NC) and summary statistics (mean, median, range, and standard deviation for continuous variables, and number and percent for categorical variables) were determined. Student's paired *t* test was used to compare

parameters before and after the treatment period, and qualitative variables and between-group comparisons were analyzed using Fisher's exact probability test or chi-square tests as appropriate. All statistical tests were performed using two-tailed tests at a 5% level of significance.

Compliance with ethics guidelines

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

RESULTS

Baseline Characteristics of the Study Population

The study included 2921 patients from 11 Asian countries at baseline; 2679 patients with both baseline and 6-month HbA_{1c} values were included in this post hoc analysis. Demographic characteristics and insulin regimen at baseline are shown in Table 1. Most patients initiated insulin therapy with insulin glargine. Mean (\pm standard deviation) insulin dose at baseline ranged from 9.5 ± 3.4 U/day in Thailand to 15.2 ± 6.3 U/day in Taiwan. Across the countries/region cohorts examined, mean duration of diabetes ranged from 6.3 ± 5.2 years (China) to 11.5 ± 7.1 years (Taiwan), and baseline HbA_{1c} ranged from $9.4\% \pm 1.2\%$ (India) to $10.5 \pm 1.9\%$ (SE Asia). Mean baseline HbA_{1c} ($10.5 \pm 1.9\%$) and FBG (230 ± 69.0 mg/dL [12.8 ± 3.8 mmol/L]) were highest in patients from South-East Asia (group defined

in this study as Bangladesh, Hong Kong, Indonesia, Singapore, and Vietnam). Patients from Taiwan had the longest duration of OAD use (11.1 ± 7.0 years; primarily sulfonylurea and/or biguanides) and were among those with the highest baseline HbA_{1c} level ($10.2 \pm 1.7\%$). Patients from China had the shortest duration of OAD use (5.8 ± 5.2 years) and were among those with the lowest baseline HbA_{1c} ($9.4 \pm 1.6\%$) and FBG (185 ± 47.2 mg/dL [10.3 ± 2.6 mmol/L]) levels. In contrast to patients from SE Asia (24.2 ± 3.8 kg/m²), patients from Pakistan (27.9 ± 6.3 kg/m²) had the highest body mass index. The prevalence of diabetic neuropathy or nephropathy ranged from 14.1% (SE Asia) to 39.2% (India), coronary artery disease from 7.0% (Pakistan) to 21.4% (China), and dyslipidemia from 48.8% (China) to 84.4% (Thailand) (Table 2).

Efficacy and Safety by Country at 6 Months

After the addition of basal insulin therapy, significant decreases in HbA_{1c} ($P < 0.001$) were observed from baseline to month 6 for each individual country/region, with decreases differing significantly between country cohorts ($P < 0.001$), ranging from -1.3% in Taiwan to -2.6% in China and Pakistan (Fig. 1; Table 3). After basal insulin initiation, significant reductions in FBG for each individual country cohort were also observed ($P < 0.001$). In addition, increases in the proportion of patients achieving FBG < 110 mg/dL (6.1 mmol/L) were observed at 6 months, although these proportions varied significantly ($P < 0.001$ between each country/region). Proportions (at 6 months) ranged from 24.7 to 27.6% among the patients in Taiwan, Korea, South-East Asia, and Thailand, and from 43.7 to

Table 1 Baseline characteristics of the study population

	China <i>n</i> = 491	India <i>n</i> = 681	Korea <i>n</i> = 291	Pakistan <i>n</i> = 139	SE Asia ^a <i>n</i> = 212	Taiwan <i>n</i> = 417	Thailand <i>n</i> = 448
Age* (years)	56.0 (12.0)	54.9 (10.0)	57.6 (10.5)	50.8 (9.5)	56.6 (10.3)	60.1 (11.9)	56.3 (11.5)
Sex* (%)							
Male	56.6	59.6	44.0	46.8	42.9	48.2	36.8
Female	43.4	40.4	56.0	53.2	57.1	51.8	63.2
Weight* (kg)	69.7 (12.3)	71.9 (11.9)	65.0 (11.4)	76.6 (11.6)	61.3 (11.3)	65.5 (12.3)	65.6 (12.9)
BMI*(kg/m ²)	25.5 (5.4)	27.6 (5.1)	25.0 (3.5)	27.9 (6.3)	24.2 (3.8)	25.4 (4.1)	26.4 (5.0)
Duration of diabetes* (years)	6.3 (5.2)	9.8 (6.4)	10.7 (6.4)	8.6 (5.2)	9.5 (6.1)	11.5 (7.1)	9.1 (6.5)
Duration of OAD use* (years)	5.8 (5.2)	9.2 (6.1)	9.2 (6.0)	7.8 (4.8)	8.4 (5.9)	11.1 (7.0)	9.0 (6.5)
OAD usage at baseline (% patients)							
Sulfonylureas	26.3	86.6	71.1	89.2	91.0	66.7	94.4
Biguanides	48.5	80.5	51.2	67.6	52.4	72.7	85.3
Thiazolidinediones	18.1	28.5	7.9	21.6	10.9	24.2	29.0
Other	67.6	9.7	26.5	1.4	11.8	23.7	8.3
Baseline HbA _{1c} * (%)	9.4 (1.6)	9.4 (1.2)	9.7 (1.6)	10.1 (1.3)	10.5 (1.9)	10.2 (1.7)	10.2 (1.9)
FBG* (mg/dL)	185 (47.2)	211 (61.0)	205 (63.7)	205 (61.2)	230 (69.0)	226 (71.4)	216 (64.2)
Insulin regimen (% patients)							
Glargine	61.9	94.3	90.7	100.0	53.3	73.6	55.1
NPH	37.5	5.0	9.3	0.0	42.9	12.5	44.9
Detemir	0.0	0.7	0.0	0.0	0.0	13.4	0.0
Other	0.6	0.0	0.0	0.0	3.8	0.5	0.0
Baseline insulin dose (U)	12.3 (5.8)	14.7 (5.9)	12.6 (5.4)	12.2 (4.5)	12.1 (6.8)	15.2 (6.3)	9.5 (3.4)

Values are mean (standard deviation), unless otherwise noted

SE Asia South-East Asia, BMI body mass index, OAD oral antidiabetic drug, HbA_{1c} glycosylated hemoglobin, FBG fasting blood glucose, NPH neutral protamine Hagedorn

* $P < 0.0001$ between countries/regions for all characteristics

^a Bangladesh, Hong Kong, Indonesia, Singapore, and Vietnam

Table 2 Baseline comorbidities of study population

	China <i>n</i> = 491	India <i>n</i> = 681	Korea <i>n</i> = 291	Pakistan <i>n</i> = 139	SE Asia ^a <i>n</i> = 212	Taiwan <i>n</i> = 417	Thailand <i>n</i> = 448
Diabetic retinopathy*	26.9	19.6	30.6	19.9	19.1	30.1	25.4
Diabetic neuropathy*	35.3	39.2	22.5	38.4	38.6	21.5	33.4
Diabetic nephropathy*	24.5	14.5	20.3	15.0	14.1	23.8	36.8
Coronary artery disease*	21.4	16.9	8.9	7.0	13.3	13.1	11.8
Stroke*	6.4	1.4	5.2	9.2	5.8	2.9	5.4
Other diab. vascular disease*	7.5	2.1	0.7	2.7	1.1	1.9	1.9
Hypertension*	49.0	72.1	65.6	67.7	59.4	69.8	73.4
Dyslipidemia*	48.8	62.6	53.6	62.1	58.7	64.2	84.4

All values are % patients

SE Asia South-East Asia

* $P < 0.0001$ between countries/regions for all characteristics

^a Bangladesh, Hong Kong, Indonesia, Singapore, and Vietnam

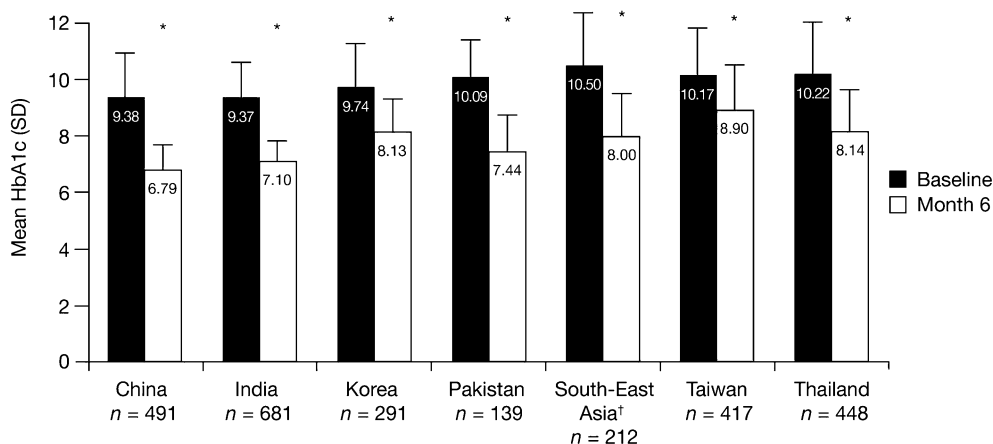


Fig. 1 Mean (standard deviation) glycosylated hemoglobin (HbA_{1c}) at baseline and month 6. * $P < 0.001$ compared with baseline. ^aSouth-East Asia: Bangladesh, Hong Kong, Indonesia, Singapore, and Vietnam. SD standard deviation

64.8% among those in India, China, and Pakistan (Fig. 2).

Wide variations between the cohorts in individual countries/regions were also observed in terms of the proportion of patients achieving HbA_{1c} < 7% at 6 months, with percentages ranging from 7.4% (Taiwan) to 71.5% (China) (Table 3). These variations were also observed with respect to mean insulin

dosing, where mean daily dose increases ranged from 0.5 ± 3.1 U/day for the patients in Pakistan to 6.0 ± 8.6 U/day in the Thailand cohort (Table 3).

After basal insulin initiation, significant differences were observed in the proportion of patients experiencing at least one hypoglycemic event during the 6 months of the study ($P < 0.001$), with the Indian cohort having the

Table 3 Mean national differences in glycemic control 6 months after initiation of basal insulin in patients with type 2 diabetes

	China <i>n</i> = 491	India <i>n</i> = 681	Korea <i>n</i> = 291	Pakistan <i>n</i> = 139	SE Asia ^a <i>n</i> = 212	Taiwan <i>n</i> = 417	Thailand <i>n</i> = 448
Δ HbA _{1c} from baseline (%)	-2.59 (1.5)	-2.27 (1.2)	-1.61 (1.8)	-2.64 (1.6)	-2.50 (2.2)	-1.27 (2.0)	-2.09 (2.0)
Patients with HbA _{1c} <7 (%)	71.5	43.0	13.1	46.0	26.4	7.4	15.2
Patients reaching FBG <110 mg/dL (6.1 mmol/L) (%)	49.9	43.7	24.8	64.8	25.2	24.7	27.6
Mean daily insulin dose (U)	13.66 (6.2)	16.35 (7.5)	13.38 (7.6)	12.70 (5.6)	16.54 (10.9)	17.68 (10.6)	15.52 (9.1)
Δ total daily insulin dose from baseline (U)	1.23 (4.6)	1.67 (5.1)	0.83 (4.8)	0.48 (3.1)	4.44 (9.1)	2.44 (9.0)	6.04 (8.6)
Mean daily insulin dose (U/kg)	0.20 (0.10)	0.23 (0.11)	0.20 (0.10)	0.17 (0.08)	0.27 (0.17)	0.27 (0.15)	0.24 (0.13)
Δ total daily insulin dose from baseline (U/kg)	0.016 (0.07)	0.023 (0.07)	0.005 (0.06)	0.005 (0.04)	0.07 (0.14)	0.03 (0.13)	0.09 (0.13)
Patients with hypoglycemia (%)	27.3	7.1	15.1	15.8	10.4	11.0	15.2

Values are mean (standard deviation) unless otherwise noted

SE Asia South-East Asia, HbA_{1c} glycosylated hemoglobin, FBG fasting blood glucose

P < 0.0001 between countries/regions for all characteristics

^a Bangladesh, Hong Kong, Indonesia, Singapore, and Vietnam

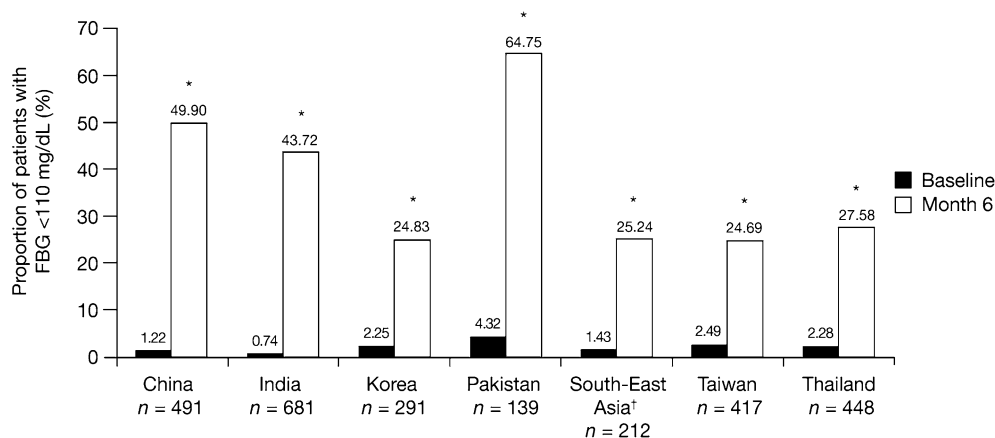


Fig. 2 Percentage of patients with a fasting blood glucose (FBG) level of <110 mg/dL at baseline and month 6. $P < 0.001$ between countries. * $P < 0.001$ compared with baseline. †Bangladesh, Hong Kong, Indonesia, Singapore, and Vietnam

lowest percentage (7.1%) and the Chinese cohort the highest (27.3%).

DISCUSSION

The Asia–Pacific region comprises more than half of the world’s population and has the largest diabetes burden in the world, with hypertension, dyslipidemia, and metabolic syndrome also highly prevalent [16]. India, China, and Pakistan make up three of the top 10 countries having the most people with diabetes, while the prevalence of T2DM in Thailand is 9.8%—double the number forecast by the World Health Organization [17, 18]. An increased risk of death associated with high HbA_{1c}, age, history of coronary artery disease, and cerebrovascular disease has been reported from the Thailand Diabetic Registry cohort [18]. As a result, establishing HbA_{1c} goals and treating patients in these countries, with the intent of rapidly and effectively achieving target HbA_{1c} levels, is crucial to successful glycemic control.

Data from this FINE-Asia study show widely varying degrees of glycemic control in patients with T2DM, depending on country of residence.

Of the country cohorts observed, the highest percentage of patients reaching target HbA_{1c} levels of <7.0% at study end (71.5%) was observed in Chinese patients. Along with India, China had the joint lowest mean HbA_{1c} levels (9.4%) at baseline, yet only 43.0% of Indian patients with T2DM reached target HbA_{1c} levels of <7.0% at study end. It should be noted that Chinese patients had the shortest duration of diabetes (6.3 years) and OAD use (5.8 years) of any country studied, including India. In line with findings from previous studies [19], as well as the Chinese Guidelines for Prevention and Treatment of Diabetes, Chinese patients with T2DM appear to benefit from earlier initiation of treatment. Rates of hypoglycemia, however, were highest (27.3%) in Chinese patients and lowest among those in India (7.1%). Although hypoglycemia is a well-reported side effect of insulin treatment [20], these findings highlight the importance of monitoring glucose levels upon initiation of basal insulin treatment, particularly when an early, aggressive approach to glycemic control is undertaken. While the reasoning for the disparity in hypoglycemia rates cannot be fully elucidated, duration of diabetes (6.3 vs.

9.8 years among the Chinese versus Indian cohort, respectively), duration of OAD usage (5.8 vs. 9.2 years), and neutral protamine Hagedorn usage (37.5% vs. 5.0% of patients), among other characteristics, are under consideration for further analysis.

Study cohorts from Korea and Taiwan had the longest duration of diabetes (10.7 and 11.5 years, respectively), as well as OAD use duration (9.2 and 11.1 years); baseline HbA_{1c} levels were also among the highest of all the countries analyzed. Interestingly, both countries had the smallest change in HbA_{1c} and the lowest proportion of patients achieving HbA_{1c} and FBG goals at 6 months. In these countries, patients did not receive insulin treatment until much later in the course of their disease, suggesting that earlier initiation of insulin treatment may result in more favorable glycemic control.

The concept of real-world clinical practice observational studies provides an expanded opportunity to observe and analyze therapeutic management strategies outside of more rigid, protocol-driven controlled clinical trials [21]. This is particularly important in diabetes, where both physician- and patient-based decisions and practice can impact outcomes. Multinational observational studies such as A1chieve (NCT00869908) [22], IMPROVE (NCT00659282) [23], PREDICTIVE (NCT00659295) [24], and PRESENT [25], among others, have utilized real-world clinical practice as the basis for observing and recommending management approach adjustments to optimize glycemic control in the context of insulin initiation. Many of these studies, such as A1chieve and CREDIT [26], are longer in duration and aim to analyze multifactorial aspects of long-term impact of treatments and treatment strategies. Our study, not unlike other studies mentioned above, was

limited to 6 months' duration. This was due to the fact that the study goal was to observe potential effects of insulin initiation; longer duration of observation, while informative, would potentially risk confounding the intent of the study with longer-term management adjustments.

As with the aforementioned observational studies, there are limitations and considerations that should be acknowledged. Lack of randomization, predefined visits, or protocol-driven care could potentially result in variations between patients and countries with respect to individual diabetes management.

Varied clinical practice between countries should be considered when interpreting these data. For example, in some Asian countries it is not unusual for physicians to discontinue OAD treatment when initiating basal insulin, either for cost- or patient-related reasons; as such, this may have influenced between-country differences in glycemic control. In general, country-specific approaches to insulin initiation (initial dosing, patient education, dietary behavior, procedural variation in management), as well as choice of OAD, may influence clinical response, yet it is important to note that this is reflective of real-world clinical practice, which was a key aspect of our study. There is a lack of available information regarding time of insulin administration, SMBG, and concomitant medications, which also may influence glycemic control. Since HbA_{1c}, FBG, and other clinical measurements were performed in different laboratories/hospitals and outside a rigid, protocol-driven setting, inconsistencies/errors may be possible.

Glycemic management differences between countries were directly observed, and other country-based factors likely warrant consideration as well. When considering basal insulin choice, no patients in any of the other

participating countries (with the exception of 0.7% of patients in India) were using insulin detemir, except for 13.4% of patients in Taiwan. Findings of recently published studies [27–29] suggest that the use of insulin glargine is associated with greater glycemic control than insulin detemir at the same dose.

The study populations observed herein represent a subset of patients with unacceptably poor glycemic control (mean HbA_{1c} ranging from 9.4% to 10.5%). These HbA_{1c} levels would intuitively result in more substantial reductions in the glycemic endpoints observed in our study compared with randomized clinical trials; nevertheless, the HbA_{1c} reductions observed in our study (–1.27% to 2.64%) are not drastically higher than those seen in the overall FINE-Asia population, in other multinational observational studies [8], or in randomized controlled trials in patients initiating basal insulin [30, 31].

The results of this prospective, observational, registry-based study in these Asian countries suggest that initiation of insulin therapy is prolonged considerably in many Asian countries, and that glycemic control remains suboptimal in many patients. Given the importance of T2DM to the health care of the region, this is a notable concern. Duration of diabetes prior to insulinization, comorbidities, as well as baseline insulin choice and dosing (both at initiation and throughout treatment), varied significantly between countries, all of which may have impacted the level of glycemic control achieved and should be studied further.

CONCLUSION

Importantly enough, these data confirm that local conditions—as reflected by the

country-based outcomes observed herein—may play an important role in the pattern of care and outcomes. Ultimately, these country-specific findings support those from the overall FINE-Asia study, suggesting that in Asian patients with T2DM, initiation of basal insulin earlier in the course of diabetes treatment may be considered a factor for better glycemic control.

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Shih-Tzer Tsai has been a consultant for Sanofi, Takeda, and Eli Lilly, and has received honoraria for speaker services from Sanofi and Novo Nordisk.

Jay Lin is a consultant for Sanofi.

Sanjiv Bhambani has been a consultant for and received honoraria from Sanofi, Merck Sharpe & Dohme, Bristol-Myers Squibb, and Novartis.

Compliance with ethics guidelines. All procedures followed were in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in

2013. Informed consent was obtained from all patients for being included in the study.

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