Int J Clin Exp Med 2016;9(8):16252-16262
www.ijcem.com /ISSN:1940-5901/IJCEM0021647

Original Article

Safety and effectiveness of insulin therapy in Chinese patients with type 2 diabetes mellitus: findings from the real-world SEAS study

Yi-Ming Mu[1], Jian-Hua Diao[2], Feng-Mei Xu[3], Yong-Ming Zhang[4], Lin Liao[5], Min-Zhe Wang[6], Jing-Yi Zhang[7], Chun Xu[8]

[1]Department of Endocrinology, Chinese People's Liberation Army General Hospital, China; [2]Department of Endocrinology, Xuchang Central Hospital, China; [3]Department of Endocrinology, Hebi Coal Group General Hospital, China; [4]Department of Endocrinology, Anhui Provincial friendship Hospital, China; [5]Department of Endocrinology, Shandong Qianfoshan Hospital, China; [6]Department of Endocrinology, The Fifth Affiliated Hospital of Xinjiang Medical University, China; [7]Department of Endocrinology, Kailuan General Hospital, China; [8]Department of Endocrinology, General Hospital Of Chinese Armed Police, China

Received December 11, 2015; Accepted July 4, 2016; Epub August 15, 2016; Published August 30, 2016

Abstract: The study investigated clinical safety and effectiveness of insulin therapy in routine clinical practice among Chinese patients with type 2 diabetes mellitus (T2DM). In this multicenter, open-label, non-interventional 12-week study, patients were grouped by insulin regimens, basal insulin (NPH/N group), mealtime insulin (SciLin R/R group), premixed insulin 70/30 (N and R) (Premixed group) and combination group (N, R and/or premixed). Data were analyzed for safety and effectiveness. In total, 2683 patients were enrolled in 62 hospitals, with mean age of 55.9±12.2 years, diabetes duration of 6.1±5.8 years and HbA1c of 9.69±2.19% at baseline. Most patients (82.7%) used premixed insulin, 47.82% of patients received oral anti-diabetic drugs (OADs) during insulin therapy; metformin (28.69%) and α-glucosidase inhibitors (24.41%) were the most commonly used OADs. After 12 weeks of treatment, the incidence of serious adverse drug reactions (SADRs) was 0.26%, and all were severe hypoglycemia events. The mean level of HbA1c decreased significantly from 9.69±2.19% to 7.35±1.28% (P<0.001). The proportion of patients with HbA1c <7.0% was 41.4%. Fasting plasma glucose (FPG) and post-prandial glucose (PPG) levels decreased significantly in all groups (all P<0.001) with the exception of dinner PPG in the N group. In conclusion, this real-world study assessing the efficacy of late initiation of insulin therapy in China found that pre-mixed insulin is the main choice in insulin regimen. Approximately half of the patients with T2DM were also treated with OADs, including primarily metformin and/or α-glucosidase inhibitors. Insulin therapy resulted in improved blood glucose control with low incidence of severe hypoglycemia.

Keywords: Diabetes mellitus, effectiveness, glycated hemoglobin, hypoglycemia, insulin, safety

Introduction

Type 2 diabetes mellitus (T2DM) is a progressive disease with high morbidity and mortality. It has become epidemic in some countries, including China, which threatens public health and carries a heavy economic and psychosocial burden [1]. The 2013 report of the International Diabetes Federation (IDF) [2] reports that the worldwide prevalence of diabetes is about 8.3% in adults aged 20-79 years, accounting for more than 382 million patients. About 592 million patients around the world are expected to have T2DM by 2035. Between 2000 and 2010, T2DM prevalence among Chinese adults in Shanghai increased from 5.1% to 7.4% [3], and it was reported to be as high as 9.7% in 2007-2008 [4]. A recent comprehensive epidemiological survey of diabetes reported that 11.6% of Chinese adults, or 114 million people, have T2DM, representing one in three diabetes patients globally [5].

Most T2DM patients require insulin therapy. International guidelines for insulin therapy recommend initiating insulin therapy when glycated hemoglobin (HbA1c) is not normalized after high-dose oral anti-diabetic drug therapy for 3

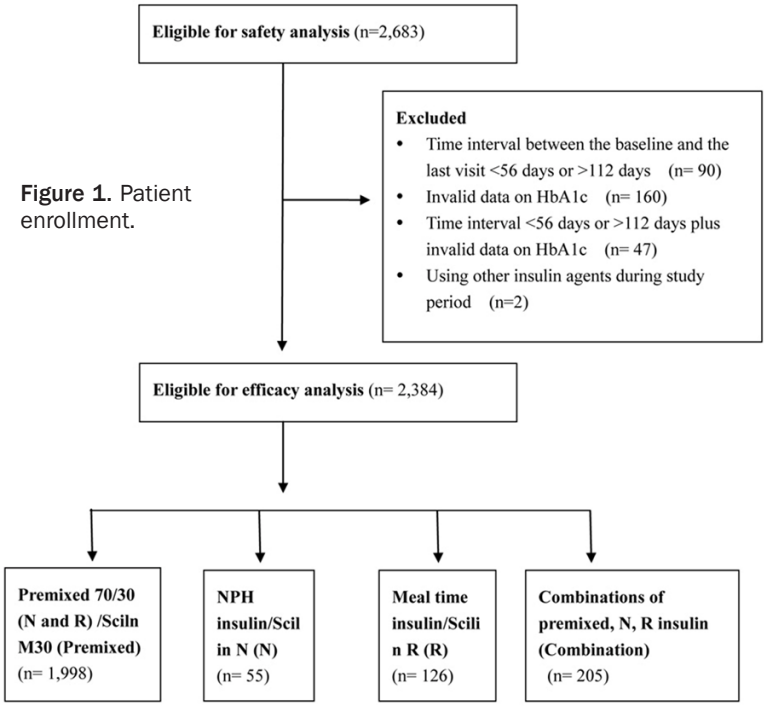

Figure 1. Patient enrollment.

months [1, 6, 7]. Recent studies have emphasized the importance of early initial therapy in view of the increased risk of disease progression when treatment is delayed [8, 9]. However, previous observational studies have shown that the initiation of insulin therapy in Chinese T2DM patients is relatively late compared to that in other populations [10]. The reasons behind late initiation of insulin therapy have not been fully explained.

Current insulin treatment using insulin analogues is considered to be more convenient and to have a low incidence of nocturnal hypoglycemia during T2DM therapy compared to human insulin [11]. However, in China, human insulin is more widely used to treat T2DM, primarily in response to pharmacoeconomic concerns [8].

Interest in patients' real-world outcomes has been growing. Accordingly, we hypothesized that understanding the true status of routine human insulin therapy in China would contribute to improving diabetes care and to reducing the related national disease burden. Theoretically, the information gained could then be used to develop corresponding management strategies focused on improving insulin therapy and glycemic control in T2DM patients in China. Therefore, the present study aimed to investigate the clinical safety and effectiveness of insulin therapy in routine clinical practice among Chinese patients with T2DM.

Methods

Study design and subject selection

This multicenter, nonrandomized, open-label, non-interventional 12-week trial, the SciLin Efficacy and Safety (SEAS) study, was conducted in 62 medical centers in China (listed in Appendix A) from August 10, 2012 to January 15, 2014.

To be included in the study, all the patients were diagnosed with T2DM according to the 1999 World Health Organization (WHO) criteria, and were treated with basal human insulin (NPH insulin/SciLin N/N group), mealtime human insulin (SciLin R/R group) or pre-mixed human insulin (premixed 70/30 [N and R]/ SciLin M30/Premixed group) (alone or in combination). Pregnant or breast-feeding women, those willing to conceive within 3 months following enrollment, patients receiving concomitant therapy with other types of insulin, and those participating in other diabetes clinical studies were excluded. The subject could choose to withdraw at any time during the study. In total, 2,683 patients were enrolled, and their data were included for analysis (**Figure 1**).

The study protocol was approved by the Institutional Review Boards and/or Ethics Committees of all participating hospitals. Procedures performed in this study were in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) principles. All subjects signed a written informed consent.

Data collection

No defined study-related procedures were performed, and all measurements were made by the treating physician team as determined by

routine clinical care. Throughout the study, patients received routine therapy as prescribed, and no interventions were administered. All SciLin insulin and oral anti-diabetic drugs (OADs) were purchased from pharmacies by the patients as usual. Patient data were collected based on their clinical records, self-monitoring diary as well as examination results (if applicable) at baseline (time of starting SciLin insulin treatment) and week 12 (after 12 weeks of treatment). The information was transferred to the case report form (CRF). Enrolled patients (n=2,683) were categorized into four groups based on the type of insulin therapy: (1) premixed insulin group (n=2,220), (2) N group (n=64), (3) R group (n=166) and (4) combination (n=233).

Demographic and basic anthropometric data were collected at baseline. Medical history in addition to the status of anti-diabetic therapy were collected at baseline and week 12, and included HbA1c measurement within four weeks of therapy initiation, most recent fasting plasma glucose (FPG) and 2-hour postprandial glucose (2-h PPG) within the one week of treatment initiation, blood pressure and serum lipids (total cholesterol [TC]), low-density lipoprotein [LDL-C], high-density lipoprotein cholesterol [HDL-C], and triglycerides [TG]) within the four weeks of therapy initiation. Hypoglycemia events, all adverse events (AEs), adverse drug reactions (ADRs) during the study were also documented.

Primary outcome measures

The primary outcome was the incidence of serious ADRs (SADRs), including severe hypoglycemia events, resulting from insulin therapy from baseline to week 12. SADRs were defined as any ADR that fit any one of the following criteria: (1) resulted in death, (2) was life-threatening, (3) required inpatient hospitalization or prolonged hospital stay, (4) resulted in persistent or significant disability or incapacity, (5) was a congenital anomaly or birth defect and (6) was an important medical event. Severe hypoglycemia events were defined as central nervous system symptoms consistent with hypoglycemia that could not be managed by patients themselves, including (1) plasma glucose <70 mg/dL (3.9 mmol/L) and (2) symptoms that were improved or resolved after intravenous injection of glucagon or glucose.

Secondary outcome measures

The secondary outcomes included change in HbA1c, FPG and 2-h PPG from baseline to week 12; the proportion of patients with HbA1c <7% (or 6.5%) at week 12; change in insulin dose, body weight, blood pressure and serum lipids from baseline to week 12 and other safety measures, including incidence rate of hypoglycemia events and ADRs during the study.

Sample size determination

Determination of sample size was based on therapeutic safety history from the time the drug became commercially available. Sample size was determined according to the Chinese Food and Drug Administration (CFDA) guideline, which advises that to find at least one case among a given number of drug users at a 95% confidence level, the sample number must be three times the reciprocal of the rate (=1/number of drug users). In this trial, around 3000 patients were required for 95% probability to detect SADRs, including severe hypoglycemia events, with an occurrence rate of at least 0.1%. The rate of 0.1% was cited from an observational study performed in 52,419 patients with T2DM using a pre-mixed insulin (BIAsp 30) regimen in routine practice, which reported an SADR rate of 0.19% [12].

Although, we planned to recruit 3000 patients for the study, the recruitment period ended earlier than scheduled due to difficulty in recruiting due to a limitation in the drug supply in the hospitals. However, the number of patients recruited was 2,683, which was sufficiently powered for the study.

Statistical analysis

The primary outcome, the incidence rate of SADRs, including severe hypoglycemia events, was assessed in a safety population. The safety population was defined as all treated subjects who finished the enrollment interview and had used any study medications at least once during a 12-week period. Additional safety outcomes, such as incidence rates of overall hypoglycemia, nocturnal hypoglycemia and ADRs, were also calculated based on the safety popu-

Table 1. Distribution of patients recruited into present study (n, %)

Items	Premixed group	N group	R group	Combination group	Total
Recruitment	2,220 (100.00%)	64 (100.00%)	166 (100.00%)	233 (100.00%)	2,683 (100.00%)
Completion	2,122 (95.59%)	58 (90.63%)	156 (93.98%)	224 (96.14%)	2,560 (95.42%)
Exclusion	98 (4.41%)	6 (9.38%)	10 (6.02%)	9 (3.86%)	123 (4.58%)
Loss to follow up	51 (2.30%)	2 (3.13%)	4 (2.41%)	3 (1.29%)	60 (2.24%)
Side events	2 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.07%)
Others	45 (2.03%)	4 (6.25%)	6 (3.61%)	6 (2.58%)	61 (2.27%)
Safety Analysis Set (SS)	2,220 (100.00%)	64 (100.00%)	166 (100.00%)	233 (100.00%)	2,683 (100.00%)
Efficacy Analysis Set (EAS)	1,998 (90.00%)	55 (85.94%)	126 (75.90%)	205 (87.98%)	2,384 (88.86%)

Premixed: premixed 70/30 (N and R)/SciLin M30; N: NPH insulin/SciLin N; R: SciLin R; Combination: Patients in the combination group used different combinations of NPH insulin, R, and/or premixed 70/30 (N and R) with/without oral anti-diabetic drugs.

lation. An efficacy analysis set (EAS) was used to evaluate secondary efficacy outcomes, including changes from baseline in HbA1c, percentage of patients with HbA1c <7% (or 6.5%), FPG, 2-h PPG, insulin dose, body weight, systolic blood pressure (SBP), diastolic blood pressure (DBP) and serum lipids. The EAS included a proportion of patients from the safety population who had not violated the study protocol and whose interval between the baseline and final visit ranged between 56 and 112 days, along with valid data on HbA1c at baseline and the final visit. No method of imputation was applied to missing data. Continuous variables are presented as mean and standard deviation (SD). Categorical variables are presented as count (%). The McNemar test was used to compare the percentage of patients with HbA1c <7% (or 6.5%) at week 12 with that at baseline. Paired t-test was performed to compare changes in efficacy parameters from baseline. All statistical analyses were performed using SAS software (V.9.2; Cary, NC., USA). A significance level of 0.05 was established for all tests.

Results

Patient enrollment

Patients were enrolled from August 10, 2012 to January 15, 2014. A total of 2,683 patients from 62 centers were deemed eligible to be included in the safety population (**Figure 1**). Of these, 2,384 patients comprised the EAS after excluding 297 patients with invalid data on HbA1c and/or time interval between baseline and final visit, and two patients who used other insulin agents during the study period (**Figure 1**).

Of the 2,683 patients enrolled, 2,220 were in the premixed group, 64 were in the N group, 166 patients were in the R group, and 233 patients were in the combination therapy group. A total of 2,560 patients completed this study. Reasons for 123 patients not completing the study included loss to follow up, side effects, self-discontinuation of the therapy or changing to other drugs (**Table 1**). The distribution of patients in this study is shown in **Table 1**. Of the 2,683 patients, 299 patients were included in the safety population, but not the EAS because their visit period between the dates of the first to last follow up was out of the 56-112 day range, or a HbA1c measurement was missing.

Patients' baseline characteristics

Patients' baseline characteristics by insulin treatment group are shown in **Table 2**. Patients' mean age was 55.9±12.2 years. Patients had a mean diabetes duration of 6.1±5.8 years, HbA1c of 9.7±2.2%, FPG of 11.6±4.1 mmol/L, weight of 67.7±11.4 kg, and body mass index (BMI) of 24.6±3.3 kg/m^2. Approximately half of the patients experienced complications/comorbidities, including diabetic neuropathy (19.5%) and diabetic retinopathy (11%). Hypertension (21.5%) was the most common comorbidity.

Drug administration

At baseline, 56.99% of patients had received OADs. The proportion of patients receiving one and two OADs was 52.71% and 36.81%, respectively. The three most commonly used OADs were metformin (63.37%), α-glucosidase inhibitors (40.42%) and sulfonylureas (26.75%).

Table 2. Characteristics of study population at time of starting SciLin treatment

	Major regimen	Other regimens			Total
	Rremixed group (n=2220)	N group (n=64)	R group (n=166)	Combination group (n=233)[1]	
Age (years)	56.4 (11.9)	51.2 (13.6)	54.1 (13.9)	54.2 (12.7)	55.9 (12.2)
Males	1,206 (54.3)	32 (50.0)	97 (58.4)	134 (57.5)	1,469 (54.8)
Weight (kg)	67.5 (11.3)	69 (12.6)	70.1 (12.4)	67.2 (11)	67.7 (11.4)
BMI (kg/m^2)	24.6 (3.3)	25.1 (3.3)	25.3 (3.9)	24.3 (3.2)	24.6 (3.3)
Diabetes history (Yes)	1,792 (80.7)	56 (87.5)	138 (83.1)	165 (71.1)	2,151 (80.2)
DM duration (years)	6.2 (5.8)	5.3 (4.5)	6.5 (5.8)	5.7 (5.3)	6.1 (5.8)
HbA1c (%)	9.6 (2.1)	9.4 (2.0)	9.5 (2.2)	10.7 (2.4)	9.7 (2.2)
Blood glucose (mmol/L)					
FPG	11.5 (4.0)	10.0 (3.3)	10.9 (3.9)	13.0 (4.6)	11.6 (4.1)
PBG_B	15.6 (4.8)	12.8 (4.2)	14.7 (4.7)	18.5 (4.9)	15.7 (4.9)
PBG_L	14.9 (4.5)	13.2 (2.8)	14.5 (4.6)	17.3 (4.7)	15.1 (4.6)
PBG_D	14.3 (4.5)	11.7 (3.2)	13.6 (4.4)	17.1 (4.8)	14.5 (4.6)
Diabetes complications and co-morbidity (Yes)	1,173 (52.8)	27 (42.2)	86 (51.8)	102 (43.8)	1,388 (51.7)
Diabetic complications					
DNeu	443 (20.0)	10 (15.6)	39 (23.5)	32 (13.7)	524 (19.5)
DR	243 (11.0)	9 (14.1)	17 (10.2)	27 (11.6)	296 (11.0)
DNep	167 (7.5)	2 (3.1)	14 (8.4)	21 (9.0)	204 (7.6)
DF	22 (1.0)	2 (3.1)	1 (0.6)	4 (1.7)	29 (1.1)
DKA	31 (1.4)	3 (4.7)	10 (6.0)	3 (1.3)	47 (1.8)
DHC	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.4)	2 (0.1)
Co-morbidity					
HTN	502 (22.6)	14 (21.9)	26 (15.7)	35 (15.0)	577 (21.5)
HL	125 (5.6)	2 (3.1)	12 (7.2)	3 (1.3)	142 (5.3)
CHD	136 (6.1)		7 (4.2)	11 (4.7)	159 (5.9)
CBD	66 (3.0)	0 (0.0)	1 (0.6)	7 (3.0)	74 (2.8)
PAD	121 (5.5)	1 (1.7)	8 (4.8)	10 (4.3)	140 (5.2)
Others	151 (6.8)	1 (1.6)	7 (4.2)	22 (9.4)	181 (6.8)
Medical Insurance					
None	182 (8.2)	8 (12.5)	15 (9.0)	21 (9.0)	226 (8.4)
LI	1,037 (46.7)	28 (43.8)	97 (58.4)	109 (46.8)	1,271 (47.4)
MIUR	472 (21.3)	19 (29.7)	28 (16.9)	63 (27.4)	582 (21.7)
NCMS	518 (23.3)	9 (14.1)	26 (15.7)	38 (16.3)	591 (22.0)
Others	11 (0.6)	0 (0.0)	0 (0.0)	2 (0.9)	13 (0.5)

Premixed: premixed 70/30 (N and R)/SciLin M30; N: NPH insulin/SciLin N; R: SciLin R; [1]Combination: Patients in combination group used different combinations of NPH insulin, R, and/or premixed 70/30 (N and R) combined with/without oral anti-diabetic drugs. DM: diabetes; FBG: fasting blood glucose; PBG_B: post-breakfast blood glucose; PBG_L: post-lunch blood glucose; PBG_D: post-dinner blood glucose; DNeu: diabetic neuropathy; DR: diabetic retinopathy; DNep: diabetic nephropathy; DF: diabetic foot; DKA: diabetic ketoacidosis; DHC: diabetic hyperosmolar coma; HTN: hypertension; HL: hyperlipidemia; CHD: coronary heart disease; CBD: cerebrovascular diseases; PAD: peripheral artery disease; LI: labor insurance; MIUR: medical insurance for urban residents; NCMS: new rural cooperative medical system.

The majority of patients in this study (82.74%) were treated with pre-mixed insulin. The top three reasons for choosing the initial insulin therapy were the expectation of improved glucose control (97.65%), the expectation of reduced glucose fluctuation (30.34%), and dissatisfaction with current therapy (29.07%). After 12 weeks of treatment, the proportion of patients maintaining initial insulin therapy was 99.8%, 91.7%, 93.7% and 69.3% in the premixed, N, R, and combination therapy groups, respectively.

During insulin therapy, 47.82% of the patients received concomitant OAD therapy (one OAD, 75.35% and two OADs, 22.81%), with metformin (28.69%) and α-glucosidase inhibitors (24.41%) being the most commonly used.

Table 3. Summary of adverse drug reactions and hypoglycemia in the four groups (safety set)

	Premixed group	N group	R group	Combination group
Number of patients	2.220	64	166	233
Total number of adverse drug reactions	42 (1.89)	0 (0)	1 (0.60)	0 (0)
Severe adverse drug reactions	0 (0)	0 (0)	0 (0)	0 (0)
Number of patients	2.154	62	160	228
Total number of hypoglycemia	384 (17.83)	9 (14.52)	24 (15)	60 (26.32)
Severe hypoglycemia	5 (0.23)	0 (0)	2 (1.25)	0 (0)
Number of patients	2.154	62	160	228
Total number of nocturnal hypoglycemia	143 (6.64)	1 (1.61)	4 (2.5)	37 (16.23)
Severe nocturnal hypoglycemia	1 (0.05)	0 (0)	0 (0)	0 (0)

Premixed: premixed 70/30 (N and R)/SciLin M30; N: NPH insulin/SciLin N; R: SciLin R; Combination: Patients in the combination group used different combinations of NPH insulin, R, and/or premixed 70/30 (N and R) combined with/without oral anti-diabetic drugs.

Among patients receiving combination therapy with one OAD, metformin (51.17%) and α-glucosidase inhibitors (42.39%) were the most commonly used OADs. Among patients receiving combination therapy with insulin and two OADs, metformin plus α-glucosidase inhibitors were mainly used (65.29%).

At baseline, lipid-lowering drugs, blood pressure-lowering drugs and aspirin were used in 259 (9.65%), 607 (22.62%) and 240 (8.95%) patients, respectively.

ADRs and hypoglycemia

The incidence of SADRs was 0.26%, all of which were, severe hypoglycemia. A total of 43 ADRs occurred, including induration or nodules (n=9), itching (n=9), rash (n=6), ophthalmological symptoms (n=5), hypersensitivity to drug (n=5), local reaction/hyperhidrosis/edema (2 each) and dizziness/hunger/pain (1 each), which improved or resolved after symptomatic therapy (**Table 3**).

A total of 477 (18.32%) hypoglycemia events were reported, including 292 (11.22%) diurnal hypoglycemia and 185 (7.10%) nocturnal hypoglycemia events. Only one severe nocturnal hypoglycemia event occurred in the premixed group (**Table 3**).

Blood glucose lowering

HbA1c levels in all groups decreased significantly at week 12 compared to baseline levels. In the premixed group, HbA1c levels were reduced from 9.61±2.14% at baseline to 7.33±1.26% at week 12 (**Table 4**). In the premixed group, the proportion of patients achieving target HbA1c levels <7.0% and 6.5% was 42.0% and 23.4% at week 12, respectively (**Figure 2**).

The differences between baseline and 12-week values of FPG and 2-h PPG are shown in **Table 4**. FPG decreased from 11.53±4.03 mmol/L at baseline to 7.17±1.69 mmol/L at week 12 in the premixed group, from 10.01±3.32 to 7.54±1.49 mmol/L in the N group, from 10.88±3.92 to 7.49±1.40 mmol/L in the R group and from 13.03±4.55 to 7.59±2.04 mmol/L in the combination group. All three measures (breakfast, lunch and dinner) of 2-h PPG also decreased significantly (all $P<0.001$) except the dinner measurement for the N group ($P=0.085$).

Body weight and insulin dose

Differences in body weight and insulin doses between baseline and week 12 are shown for each group in **Table 4**. The mean weight change during the whole study period was 0.12±2.14 Kg, and the only significant difference in weight from baseline to week 12 was observed in the premixed group (67.45±11.23 Kg vs. 67.57±10.88 Kg, $P=0.009$). The mean daily dosage of insulin increased for all groups between baseline and week 12. However, the only increase in dosage that reached statistical significance was that of the premixed group (0.44 IU/Kg/day vs. 0.43 IU/Kg/day, $P<0.001$) and the R group (0.40 IU/Kg/day vs. 0.38 IU/Kg/day, $P=0.012$; **Table 4**).

Blood pressure and serum lipids

Significant reductions in LDL-C, TC, TG, and SBP as well as an increase in HDL-C were also found

Table 4. Differences in blood glucose, body weight, insulin dose, blood pressure and lipids between baseline and week 12 (efficacy analysis set)

	Premixed group (n=1.998)		N group (n=55)		R group (n=126)		Combination group (n=205)	
	Baseline†	Week 12	Baseline†	Week 12	Baseline†	Week 12	Baseline†	Week 12
HbA1c (%)	9.61 (2.14)	7.33 (1.26)**	9.37 (2.04)	7.63 (1.24)**	9.47 (2.20)	7.42 (1.19)**	10.71 (2.41)	7.47 (1.53)**
Fasting blood glucose (mmol/L)	11.53 (4.03)	7.17 (1.69)**	10.01 (3.32)	7.54 (1.49)**	10.88 (3.92)	7.36 (1.40)**	13.03 (4.55)	7.59 (2.04)**
Post-breakfast blood glucose (mmol/L)	15.56 (4.77)	9.39 (2.26)**	12.82 (4.18)	8.92 (1.89)**	14.72 (4.71)	9.00 (1.75)**	18.50 (4.91)	9.94 (2.85)**
Post-lunch blood glucose (mmol/L)	14.90 (4.51)	9.45 (2.19)**	13.17 (2.83)	10.14 (2.61)**	14.46 (4.62)	9.10 (1.82)**	17.31 (4.72)	9.29 (2.48)**
Post-dinner blood glucose (mmol/L)	14.33 (4.46)	9.35 (2.31)**	11.70 (3.24)	10.13 (3.03)	13.61 (4.39)	8.99 (1.73)**	17.09 (4.77)	9.48 (2.88)**
Weight (Kg)	67.45 (11.23)	67.57 (10.88)*	69.74 (12.45)	69.94 (12.01)	70.41 (11.78)	70.54 (11.35)	67.15 (10.86)	67.15 (10.41)
Insulin dose (IU/Kg/day)	0.43 (0.14)	0.44 (0.14)**	0.18 (0.09)	0.19 (0.10)	0.38 (0.17)	0.4 (0.18)*	0.58 (0.22)	0.56 (0.24)
SBP (mmHg)	130.42 (14.24)	126.25 (9.31)**	125.27 (12.45)	125.00 (7.71)	130.16 (13.53)	127.80 (9.86)*	129.00 (13.40)	127.20 (10.42)
DBP (mmHg)	80.05 (9.26)	77.90 (7.64)**	82.86 (8.86)	80.63 (8.49)	80.61 (8.60)	78.97 (7.65)	79.51 (8.29)	78.29 (7.43)*
LDL-C (mmol/L)	3.06 (1.00)	2.76 (0.87)**	2.95 (0.74)	2.53 (0.96)	2.79 (1.31)	2.46 (0.92)*	2.86 (1.04)	2.71 (0.80)*
HDL-C (mmol/L)	1.27 (0.51)	1.35 (0.49)**	1.46 (0.48)	1.58 (0.40)	1.24 (0.43)	1.34 (0.50)*	1.34 (0.71)	1.46 (0.61)*
Total cholesterol (mmol/L)	5.18 (1.28)	4.69 (0.99)**	4.98 (1.31)	4.51 (1.26)	5.05 (1.38)	4.47 (1.26)**	5.00 (1.53)	4.56 (1.08)**
Triglyceride (mmol/L)	2.25 (1.96)	1.72 (0.95)**	2.38 (2.34)	2.01 (1.85)	2.48 (2.56)	2.08 (1.40)*	2.16 (2.31)	1.36 (0.61)**

Premixed: premixed 70/30 (N and R)/SciLin M30; N: NPH insulin/SciLin N; R: SciLin R; Combination: Patients in combination group used different combinations of NPH insulin, R, and/or premixed 70/30 (N and R) combined with/without oral anti-diabetic drugs. HbA1c: hemoglobin; SBP: systolic blood pressure; DBP: diastolic blood pressure; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol. Data are presented as mean (standard deviation) and tested by paired t-test. *Indicates significant difference between baseline and week 12, $P<0.05$. **Indicates significant difference between baseline and week 12, $P<0.001$. †Baseline refers to the time of starting SciLin treatment.

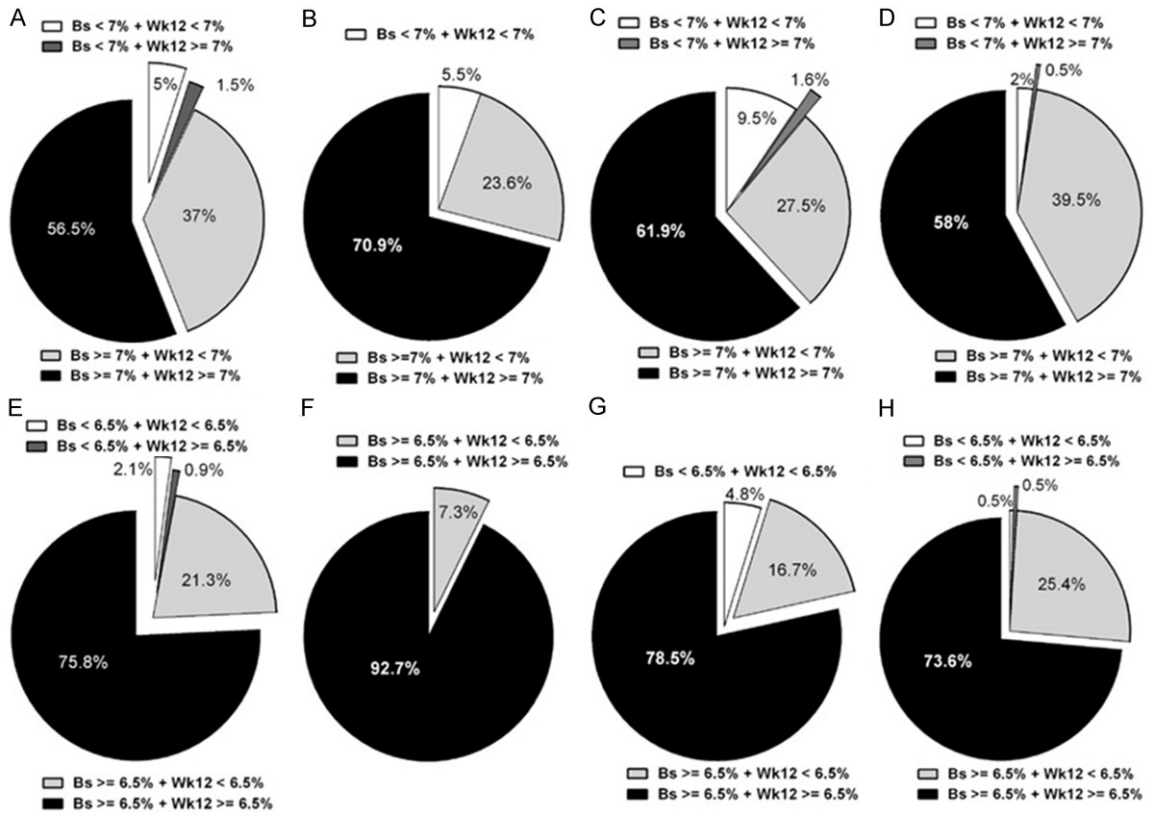

Figure 2. Differences in percentage of patients with normal HbA1c level (as defined by 7%) between baseline and week 12 (final) measurements (efficacy analysis set). (A) Premixed group (n=1998); (B) N group (n=55); (C) R group (n=126), and (D) Combination group (n=205). Normal HbA1c level, defined as 6.5%, was shown in the (E) premixed; (F) N group; (G) R group, and (H) Combination group. The McNemar test was implemented. *P*<0.001 for all groups regardless of cut-off points.

in all groups except for the N group between baseline and week 12 (all *P*<0.05; **Table 4**).

Discussion

The results of this large-scale, observational, real-world study reflect the true status of insulin therapy in Chinese T2DM patients, providing valuable evidence of the status of routine clinical therapy for T2DM in China. The study found that insulin therapy, using different treatment regimens, significantly improved blood glucose control in patients and was associated with a relatively low incidence of severe hypoglycemia. The results also revealed that blood glucose levels were relatively high at the initiation of insulin therapy in these patients, and that initial therapy is actually started rather late in China. In addition, there was a relatively high incidence of complications and concomitant diseases associated with T2DM, in particular chronic complications and cardiovascular and cerebrovascular disease. Pre-mixed insulin (premixed 70/30 [N and R]) as monotherapy was the most commonly used human insulin for treating T2DM. Overall, after the 12-week insulin therapy, an increase in patients' body weight was not obvious, and the insulin doses remained unchanged during the study.

Among T2DM patients, timely initiation of insulin therapy relieves the load of islet β cells, rapidly improves hyperglycemia, attenuates hyperglycemia-induced toxicity, improves insulin resistance and protects or even reverses residual β cell function [13]. The 2013 Chinese Guideline for T2DM [6] recommends combined therapy with OADs and insulin for T2DM patients when lifestyle modifications and use of OADs fail to control blood glucose. Insulin therapy can be initiated when HbA1c is still ≥7.0% after combined therapy with OADs at high doses. Diabetic Chinese patients have relatively low body weight and significant ß cell

deterioration, which results in reduced insulin secretion, especially in the first-phase insulin response [14]. In the present study, the mean baseline HbA1c for all enrolled patients was 9.69%, and 54.1% of patients had HbA1c of >9%, which does not adhere to the threshold of HbA1C (7%) usually recommended for initiation of insulin therapy. This also indicates that the initiation of insulin therapy in Chinese T2DM patients is relatively late. In addition to the newly diagnosed T2DM patients, 21.68% of patients were not receiving anti-diabetic therapy at baseline, which is not consistent with Chinese guidelines [6], which state that timely initiation of pharmacotherapy is preferred when lifestyle modification fails to effectively control blood glucose. Future studies must identify the reasons for gaps between real-life insulin therapy and the guideline recommendations.

In the present study, 51.73% patients had complications or concomitant diseases associated with T2DM at baseline, which consisted mainly of chronic complications and cardiovascular/cerebrovascular disease. At baseline, the proportion of patients receiving lipid-lowering, blood pressure-lowering and anti-platelet therapies was low, suggesting that physicians should emphasize the comprehensive management of T2DM risk factors in clinical practice.

The results of the present study showed that pre-mixed insulin was the most common treatment (82.74%) among Chinese T2DM patients, which was consistent with the results from a previous Chinese study (89.8%) [15]. While basal insulin (N) is often the first choice in initial insulin therapy since it is a simple regimen, [16] pre-mixed insulin is still widely used in T2DM patients in China. Asian patients have a reduced reserve capacity for insulin secretion of islet β cells as compared to Caucasian patients [17]. Additionally, the manifestations of newly diagnosed T2DM are characterized by increases in postprandial hyperglycemia, [4] and pre-mixed insulin may be better able to control both fasting and postprandial blood glucose, making it one of the most commonly used insulin in China. More recently, a premixed insulin analogue, such as biphasic insulin aspart 30, may be used and has been shown to result in better glycemic control in early T2DM [12, 18, 19].

Insulin therapy using the different SciLin protocols described in the present study was found to significantly improve blood glucose control among T2DM patients. After 12 weeks of insulin therapy, the overall HbA1c decreased from 9.69% at baseline to 7.35%, representing a -2.34% overall reduction ($P<0.0001$). The mean daily insulin dose at baseline and week 12 was 28.7 IU/d and 29.6 IU/d, respectively, and the adjustment of insulin dose was not active, as also observed in the A1chieve study [20]. In the A1chieve study, the insulin dose in the Chinese patient group increased from 31.0 IU/d at baseline to 32.0 IU/d, which may be ascribed to the concerns of physicians and patients regarding insulin-induced body weight gain and hypoglycemia [20]. In addition, no SADR was observed. The incidence of overall, nocturnal and severe hypoglycemia was 18.32%, 7.1% and 0.26%, respectively, and only one patient (0.04%) developed what was considered to be severe nocturnal hypoglycemia [20]. Another 4-month, observational study conducted in Chinese T2DM patients investigated the therapeutic safety and efficacy of human insulin 70/30 [21]. Of 644 patients, 30.4% of the patients experienced at least one hypoglycemia event during insulin therapy, and the incidence of severe hypoglycemia was 0.31%. In addition, the Chinese cohort of the IMPROVE study by Yang et al. [18] reported that 0.1% of subjects receiving BIAsp 30 experienced major hypoglycemia, and 73 SADRs (0.3%) were observed after 26 weeks of insulin therapy. Given the pre-defined blood glucose threshold of major hypoglycemia events was 3.1 mmol/L in the IMPROVE subgroup study [18] and 3.9 mmol/L in the present study, on the basis of findings from the above two observational studies, the incidence of severe hypoglycemia was still low, which might be ascribed to the emphasis on patient education about the management of blood glucose levels during insulin therapy.

Our results showed that, after 12 weeks of therapy, the mean body weight among all subjects increased by 0.12 Kg as compared to baseline levels, which may be related to the combined use of insulin and OADs. In the present study, about half of patients received insulin therapy with OADs, and metformin and/or α-glucosidase inhibitors were the most commonly used drugs, which were both consistent with guideline recommendations. Metformin in

combination with insulin may attenuate body weight gain following insulin therapy, and reduce the required dose of exogenous insulin [22, 23]. Similarly, α-glucosidase inhibitors in combination with insulin may delay the gastrointestinal absorption of carbohydrates, effectively improving blood glucose control, reducing the required dose of insulin and reducing insulin-induced weight gain [22]. The result of the recent MARCH trial demonstrated that an α-glucosidase inhibitor, acarbose, and metformin had similar efficacy for newly diagnosed patients with T2DM in China [24, 25]. In addition, we found that, besides improving HbA1c levels, patients' blood pressure and lipid levels were also improved, suggesting that patient education, comprehensive management of T2DM and active lifestyle interventions might have been enhanced with initiation of insulin therapy in this study, which, in turn, is helpful for the attenuation of body weight gain.

Certain limitations are inherent in this multicenter, real-world observational study, including the heterogeneity of local culture, economics, and patient and physician education levels, which limits the generalizability of the results to other populations. In addition, the baseline patient characteristics among the treatment groups differed (e.g., baseline blood glucose levels and the presence of diabetes complications and co-morbidities) due to the nature of the study design, which did not permit direct comparisons between the groups in terms of treatment efficacy or safety. Thus, only descriptive data were presented. Also, the study was conducted in multiple tertiary care centers in China; therefore, the results may not translate fully to daily practice in primary care settings. Additionally, there is no tightly controlled population or randomized control arm, which reduces the certainty by which outcomes can be ascribed to treatment and does not provide the same robust evidence as randomized controlled trials. The wide variance in the sizes of the four insulin therapy groups precluded performing statistical comparisons between the groups, which would not show clinical significance in this study. However, data from this observational study provide an important evidence base for routine insulin therapy among Chinese T2DM patients in conjunction with controlled clinical studies.

In conclusion, the results of the present real-world study indicate that the initiation of insulin therapy is relatively late in Chinese T2DM patients compared to international guidelines. Half of patients with T2DM receiving insulin therapy in this study were treated in combination with OADs, including primarily metformin and/or α-glucosidase inhibitors. Pre-mixed insulin is the most commonly used human insulin in the initial insulin therapy in Chinese T2DM patients. Insulin therapy with different protocols appears to significantly improve glycemic control in Chinese T2DM patients to a similar extent, has a low incidence of severe hypoglycemia and may not significantly increase body weight. The findings of the present study may provide evidence for the improvement of glucose control and insulin therapy in the diabetic population in China.

Disclosure of conflict of interest

None.

Address correspondence to: Yi-Ming Mu, Department of Endocrinology, Chinese People's Liberation Army General Hospital, 28 Fuxing Road, Handian District, Beijing 100853, China. Tel: +86 010-66887329; Fax: +86 010-66887329; E-mail: muyiming@301hospital.com.cn

References

[1] Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R and Matthews DR; American Diabetes Association (ADA); European Association for the Study of Diabetes (EASD). Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012; 35: 1364-1379.

[2] International Diabetes Foundation. IDF Diabetes Atlas. 6th Edition. International Diabetes Foundation.

[3] Li R, Lu W, Jiang QW, Li YY, Zhao GM, Shi L, Yang QD, Ruan Y, Jiang J, Zhang SN, Xu WH and Zhong WJ. Increasing prevalence of type 2 diabetes in Chinese adults in Shanghai. Diabetes Care 2012; 35: 1028-1030.

[4] Yang W, Lu J, Weng J, Jia W, Ji L, Xiao J, Shan Z, Liu J, Tian H, Ji Q, Zhu D, Ge J, Lin L, Chen L, Guo X, Zhao Z, Li Q, Zhou Z, Shan G and He J; China National Diabetes and Metabolic Disorders Study Group. Prevalence of diabetes

among men and women in China. N Engl J Med 2010; 362: 1090-1101.
[5] Xu Y, Wang L, He J, Bi Y, Li M, Wang T, Wang L, Jiang Y, Dai M, Lu J, Xu M, Li Y, Hu N, Li J, Mi S, Chen CS, Li G, Mu Y, Zhao J, Kong L, Chen J, Lai S, Wang W, Zhao W and Ning G; 2010 China Noncommunicable Disease Surveillance Group. Prevalence and control of diabetes in Chinese adults. JAMA 2013; 310: 948-959.
[6] CDS, Chinese Diabetes Society. Guideline for the Prevention and Therapy of Type 2 Diabetes Mellitus in China (2013). Chin J Diab Mellitus 2014; 6: 447-498.
[7] International Diabetes Federation Guideline Development Group. Global guideline for type 2 diabetes. Diabetes Res Clin Pract 2014; 104: 1-52.
[8] Ripsin CM, Kang H and Urban RJ. Management of blood glucose in type 2 diabetes mellitus. Am Fam Physician 2009; 79: 29-36.
[9] Wu Y, Ding Y, Tanaka Y and Zhang W. Risk factors contributing to type 2 diabetes and recent advances in the treatment and prevention. Int J Med Sci 2014; 11: 1185-1200.
[10] Ji LN, Feng B, SU Q, Lin J, Chen YL, Rong HQ, Zhuang XM, Huang W, Wang AH, Ma LZ, Pu XM, Han ZL, Jin H, Chen JM, Jiang XZ, Zhou LH, Xu Y and Lv XF. The safety and efficacy of initiating insulin therapy in Chinese patients with type 2 diabetes mellitus inadequately controlled with previous oral antidiabetic drugs. Chin J Diab 2011; 19: 746-751.
[11] Pollock RF, Erny-Albrecht KM, Kalsekar A, Bruhn D and Valentine WJ. Long-acting insulin analogs: A review of "real-world" effectiveness in patients with type 3 diabetes. Curr Diabetes Rev 2011; 7: 61-74.
[12] Wenying Y, Benroubi M, Borzi V, Gumprecht J, Kawamori R, Shaban J, Shah S, Shestakova M, Ligthelm R and Valensi P; IMPROVE Study Group Expert Panel. Improved glycaemic control with BIAsp 30 in insulin-naive type 2 diabetes patients inadequately controlled on oral antidiabetics: subgroup analysis from the IMPROVE study. Curr Med Res Opin 2009; 2: 2643-2654.
[13] Owens DR. Clinical evidence for the earlier initiation of insulin therapy in type 2 diabetes. Diabetes Technol Ther 2013; 15: 776-785.
[14] Yang WY and Weng JP. Early therapy for type 2 diabetes in China. Lancet Diabetes Endocrinol 2014; 2: 992-1002.
[15] Lu JM, Ji LN, Guo XH and Gu WJ. Glycemic and HbA1c controls of T2DM patients treated with human insulin in China. Chin J Diab 2013; 9.
[16] Brunton S. Insulin regimens for type 2 diabetes mellitus. J Fam Pract 2006; 55: 10S-7S.
[17] Chinese Society of Endocrinology. Clinical application of pre-mixed insulin. Drug Eval 2013; 10: 33-38.
[18] Yang W, Gao Y, Liu G, Chen L, Fu Z, Zou D, Feng P and Zhao Z. Biphasic insulin aspart 30 as insulin initial or replacement therapy: the China cohort of the IMPROVE study. Cur Med Res Opin 2010; 26: 101-107.
[19] Valensi P, Benroubi M, Borzi V, Gumprecht J, Kawamori R, Shaban J, Shah S, Shestakova M and Wenying Y; IMPROVE Study Group Expert Panel. Initiating insulin therapy with, or switching existing insulin therapy to, biphasic insulin aspart 30/70 (NovoMix® 30) in routine care: safety and effectiveness in patients with type 2 diabetes in the IMPROVE observational study. Int J Clin Pract 2009; 63: 522-531.
[20] Home P, Naggar NE, Khamseh M, Gonzalez-Galvez G, Shen C, Chakkarwar P and Wenying Y. An observational non-interventional study of people with diabetes beginning or changed to insulin analogue therapy in non-Western countries: the A_1chieve study. Diabetes Res Clin Pract 2011; 94: 352-363.
[21] Gu Y, Hou X, Zhang L, Pan J, Cai Q, Bao Y and Jia W. The impact of initiating biphasic human insulin 30 therapy in type 2 diabetes patients after failure of oral antidiabetes drugs. Diabetes Technol Ther 2012; 14: 244-250.
[22] Yang WY and Weng JP. Early therapy for type 2 diabetes in China. Lancet Diabetes Endocrinol 2014; 2: 992-1002.
[23] Wang H, Ni Y, Yang S, Li H, Li X and Feng B. The effects of gliclazide, metformin, and acarbose on body composition in patients with newly diagnosed type 2 diabetes mellitus. Curr Ther Res Clin Exp 2013; 75: 88-92.
[24] Yang W, Liu J, Shan Z, Tian H, Zhou Z, Ji Q, Weng J, Jia W, Lu J, Liu J, Xu Y, Yang Z and Chen W. Acarbose compared with metformin as initial therapy in patients with newly diagnosed type 2 diabetes: an open-label, non-inferiority randomized trial. Lancet Diabetes Endocrinol 2014; 2: 46-55.
[25] Wang G, Liu J, Yang N, Gao X, Fan H, Xu Y and Yang W. MARCH2: comparative assessment of therapeutic effects of acarbose and metformin in newly diagnosed type 2 diabetes patients. PLoS One 2014; 9: e105698.