TITLE

Comparative Effectiveness and Safety of Different Basal Insulins in a Real World Setting

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ABSTRACT

Aims

To compare glucose control and safety of different basal insulin (BI, including Insulin NPH, glargine and detemir) therapies in real-life clinical settings based on a large-scale registry study.

Methods

In this multi-center 6-month prospective observational study, patients with type 2 diabetes uncontrolled ($HbA1c \geq 7\%$) by oral anti-diabetic drugs (OADs) and willing to initiate BI were enrolled from 209 hospitals of eight regions of China. Type and dose of BI were at the physician's discretion and patients' willingness. Interviews were conducted at 0 month—visit 1, 3 months—visit 2, and 6 months—visit 3. Outcomes included the change of HbA1c, hypoglycemia rate and body weight from baseline at 6 months.

Results

16 341 and 9 002 subjects were used in Intention-To-Treat (ITT) and per-protocol (PP) analysis, respectively. After the PS regression adjustment, the ITT analysis showed that the reduction of HbA1c in glargine ($2.2 \pm 2.1\%$) and detemir groups ($2.2 \pm 2.1\%$) was higher than that in NPH group ($2.0 \pm 2.2\%$) ($P < 0.01$). Detemir group had the lowest weight gain ($-0.1 \pm 2.9\text{kg}$) compared with glargine ($+0.1 \pm 3.0\text{kg}$) and NPH group ($+0.3 \pm 3.1\text{kg}$) ($p < 0.05$). Glargine group had the lowest rate of minor hypoglycemia while there was no difference in severe hypoglycemia among the three groups. The results observed in PP analyses were consistent with those in ITT analysis.

Conclusion

In a real-world clinical setting in China, long-acting insulin analogues treatment were associated with better glycemic control as well as less hypoglycemia and weight gain than NPH insulin in type 2 diabetes patients. However, the clinical relevance of these observations need to be interpreted with caution.

INTRODUCTION

As type 2 diabetes mellitus (T2DM) progresses, introduction of insulin therapy is unavoidable. Guidelines on diabetes management recommend that basal insulin (BI) treatment should be considered as second- or third-line medication when individualized glucose control targets cannot be achieved by lifestyle modification and maximum dose of oral antidiabetic agents or as first-line pharmacologic therapy in patients with severe hyperglycemia.¹⁻⁴

In China, the most commonly used BIs include the intermediate-acting NPH insulin, long-acting insulin glargine U100 (hereinafter referred to as insulin glargine), and insulin detemir. Numerous randomized controlled clinical trials (RCTs) have evaluated the safety and efficacy of insulin treatment.⁵ In the experimental setting, treat-to-target studies among patients with T2DM have demonstrated that insulin glargine and detemir have equivalent glycemic efficacy (reduction of HbA1c from baseline or the ability to decrease HbA1c level to a target level) to NPH.⁶⁻⁸

Systematic reviews based on RCTs in insulin-naïve people with T2DM showed that there was no significant difference in HbA1c reduction among the three BIs, whilst NPH therapy was associated with the highest risk of hypoglycemia and the detemir therapy was associated with the least weight gain.^{6,9,10} Similar weight gain was observed between glargine therapy and NPH therapy.^{11,12}

However, the differences in safety and effectiveness among different BIs in real-world clinical settings may differ from those found in clinical trials. RCTs have been challenged for failing to predict real-world outcomes.¹³ The inherent poor external validity of RCTs limits the study results to be generalized to more complex patient populations in real-world clinical practice,¹⁴ raising concerns that more generalizable results are needed to better inform real-world clinical decisions.¹⁵ Observational studies are positioned to assess the safety and effectiveness in real-world environment.^{16,17} However, large-scale comparisons of complex insulin regimens in real-world settings, in combination with oral antidiabetic drugs (OADs), have been lacking. Only few observational studies, each with its limitations, were carried out to compare the effectiveness and safety of the three most common BIs in type 2 diabetes patients uncontrolled on OADs. One study had a large sample size yet with only detemir insulin (SOLVE study¹⁸); another study included three BIs yet with limited number of study subjects across 11 countries or regions in Asia (n=2679, FINE study¹⁹). Also, some studies about BIs were retrospective in design without a prospective follow-up.²⁰ Therefore, whether the effectiveness and safety of glargine, detemir, and NPH are similar or not in real-life clinical practice is still not clear.

Observational Registry of Basal Insulin Treatment (ORBIT) is a large-scale, prospective, observational multicenter study, which is designed to evaluate the efficacy of BI therapy among T2DM inadequately controlled on OADs in a real-world clinical setting in China.²¹ A previous paper has reported the real-life BI treatment patterns, focusing on initiation and following evolution of treatment regimens and insulin dosing as well as overall blood glucose control effect and safety issues.²² Based on ORBIT study, this analysis aims to compare the safety and effectiveness of three most commonly used BIs (glargine, detemir and NPH) in China.

METHODS

Patient Population

Inclusion and exclusion criteria have been reported previously.²¹ Briefly, from December 2011 to June 2013, patients aged 18-80 years with established T2DM were enrolled at 209 hospitals representative of eight geographic regions covering two hospital tiers at the secondary (county or district, n=105) and tertiary (provincial or national, n=104) levels in China. All patients had HbA1c level of 7.0% or more while receiving adequate doses of OADs for at least 3 months. Patients were excluded if they had been prescribed any type of insulin in the last 2 years (except for the situation of discontinued use shorter than 1 month each time); had clinically significant acute major organ or systemic disease; or were pregnant or lactating. Both inpatients and outpatients could be enrolled.

All participants provided written informed consent and confirmed their willingness to participate in the follow-up evaluations. The protocol was approved by the Institutional Review Board (IRB) of Peking University, and when necessary, local IRBs.

Study Design

ORBIT was a 6-month, multicenter, prospective, registry study conducted in China. Details on study design and baseline characteristics of the study subjects have been reported previously.²¹ For each participant, interviews were conducted at the beginning of the study (0 month—visit 1), mid-term (3 months—visit 2), and at the end of the study (6 months—visit 3) to collect study information. No intervention was given to the participants. At visit 1, BI (Insulin Glargine, Insulin Detemir, or NPH

insulin) was prescribed with or without prandial insulin at the physicians' discretion and patients' willingness. The concomitant use of OADs at the time of BI initiation could be adjusted. During follow up, there was no limitation on the therapy adjustments for insulin or OADs. Titrations of insulin dose(s) and medication regimen changes were all performed according to the provider's recommendation and the patient's willingness.

Data Collection

At visit 1, the baseline information of each patient before adding BI was collected, including the demographic information (gender, age, education level, patient's resources, current residence and medical insurance), lifestyle (diet, physical activity and smoking) in the past 7 days and clinical characteristics (diabetes duration, treatment duration with the individual OADs used, number of OADs currently used, baseline HbA1c and FPG (fasting plasma glucose) levels based on laboratory test, self-monitored blood glucose [SMBG] profiles, complication status, and hypoglycemia episodes). Standard physical examinations were conducted for each patient to collect baseline height, body weight, and blood pressure. The type and dose of BI prescribed and any adjustment on the OAD regimen were documented at visit 1.

At visit 2, in order to avoid or minimize the intervention to routine practice, a telephone interview was conducted to collect study information for all participants unless a participant spontaneously visited the investigators during the follow-up window of visit 2, in that case available data including results of physical examination and laboratory tests were collected. At the end of study (visit 3), all the participants were invited to have a face-to-face investigation and provided with free FPG and

HbA1c tests by the study hospitals for robust outcome evaluation. At visit 2 and 3, the self-reported data collected included OADs/insulins currently used, lifestyle in the past 7 days, insulin titration and serious adverse events (SAEs) from visit 1 as well as frequency of minor hypoglycemia in the previous 1 month and severe hypoglycemia in the previous 3 months. Hypoglycemia was classified as severe and minor hypoglycemia (documented symptomatic, asymptomatic, probable symptomatic, and pseudo hypoglycemia) according to ADA (American diabetes association) recommendations.²³ Different from visit 3, most FPG and HbA1c data at visit 2 were self-reported.

Primary and Secondary Outcomes

The primary outcomes were changes in HbA1c and body weight at 6 months from baseline, and proportion and rate of hypoglycemia during 6 months of follow-up in the three BI groups.

Secondary outcomes included the control rate of HbA1c (proportion of patients with an HbA1c level <7.0% (53 mmol/mol) or ≤6.5% (47.5 mmol/mol), the change in FPG level from baseline to month 3 and month 6, and control rate of FPG (proportion of patients with a FPG level of 7.0 mmol/L or less).

Statistical Analysis

In this study, both intention-to-treat (ITT) and per-protocol (PP) populations were evaluated for primary and secondary outcomes. Patients who successfully completed the 6-month visit were included in the ITT analysis, according to the three types of BI prescribed at baseline (NPH, Glargine, and Detemir), irrespective of any consequent therapy changes during follow-up. Patients who continued using the same BI regimen as at baseline during follow-up and never added any prandial insulin were included in the PP analysis.

Propensity score-adjusted multivariate linear regression models were used to evaluate change in HbA1c and body weight, while the zero-inflated Poisson regression model was used to compare the rates of hypoglycemia between the three BI groups. The propensity scores were calculated using logistic regression model to balance the baseline covariates among the three BI groups including hospital level, gender, age, body weight, diabetes duration, district (urban/area), medical insurance (actual proportion of out of pocket), HbA1c level, FPG level, diabetes complication, and number of OADs at baseline.^{24,25} Process factors which could change during follow-up, such as the BI and total insulin dose, OAD type and numbers, frequency of SMBG, physical activity, and diet consumption, were also controlled for in the propensity score-adjusted regressions.

Baseline characteristics of participants were described separately before and after propensity score adjustments, along with changes in the process factors. The basic statistics were presented by number (%), mean $\pm$ SD, or median (first quartile, third quartile), as appropriate. A closed-test procedure allowed for a pairwise comparison of groups only if the overall treatment effect was significant. A two-sided *P* value of less than 0.05 was considered to indicate statistical significance; all *P* values are based on adjusted analyses but have not been adjusted for multiple testing. Statistical analyses were performed with SAS version 9.4 statistical software (SAS Institute Inc.).

RESULTS

Characteristics of the Participants

During one and a half years of recruitment, 18995 participants were found to be eligible and included in the study after enrolling 19894 patients during the screening

period. After 6 months of follow-up, 16341 patients were found to be eligible for ITT analyses, while 9002 patients were included in the PP analyses (Figure 1). In the ITT population, 52.8% were male, had median (Q1, Q3) 5.33 (2.17, 9.92) years of diabetes duration, mean $\pm$ SD 55.4 $\pm$ 10.3 years old with BMI 24.7 $\pm$ 3.4 kg/m², HbA1c 9.6% (81 mmol/mol) $\pm$ 2.0%, and FPG 11.6 $\pm$ 3.9 mmol/L (Table 1). Before propensity score adjustments, most (15/19) of the baseline variables were statistically significantly different between the BI groups. Except for study variables associated with education level and SMBG, balance in the distributions of other study parameters by BI groups were achieved after propensity score adjustments. The baseline characteristics of the three groups in the PP population are presented in Supplementary table 1.

Process Factors during Follow-up

The changes in the process factors, including dose and regimen changes in insulin and OADs, diet, and physical exercise status are listed in Table 2 for both ITT and PP populations. The average number of OADs taken per day and the insulin dose did not change significantly over 6 months within the individual BI groups, while the trend in increasing physical exercise time was similar between the BI groups.

Primary Outcomes

In the ITT population, at the 6-month follow-up, the adjusted reduction in HbA1c from baseline was 2.2% in the insulin glargine group, 2.2% in the insulin detemir group, and 2.0% in the NPH insulin group (Table 3). Detemir group had the lowest weight gain (-0.1 $\pm$ 2.9 kg) compared with glargine group (+0.1 $\pm$ 3.0 kg) and NPH group (+0.3 $\pm$ 3.1 kg). The proportions of severe hypoglycemia were around 0.5% in the

three BI groups, without significant difference between each other, while the proportion of minor hypoglycemia was the highest in NPH insulin group (12.8%) and the lowest in glargine group (7.2%). In terms of frequency, there was no significant difference in severe hypoglycemia among three BI groups, yet for the minor hypoglycemia, the insulin glargine group had the lowest frequency (23.06 times/person/year) compared to insulin detemir group (27.41 times/person/year) and NPH insulin group (27.19 times/person/year).

Secondary Outcomes

In ITT population, there was no significant difference in the proportions of patients achieving HbA1c targets among the three BI groups, although the proportions in NPH group was the lowest (Table 3). The HbA1c control rates for the three BI groups were about 25% in criteria of HbA1c $\leq 6.5\%$ and around 40% in criteria of HbA1c $< 7\%$. The adjusted reduction in FPG from baseline was 3.8 mmol/L in insulin glargine group, 4.0 mmol/L in insulin detemir group, and 3.4 mmol/L in NPH insulin group. The NPH insulin group had the lowest FPG control rate (38.2%) compared to the insulin glargine group (43.8%) and insulin detemir group (42.2%). No statistical difference was found between glargine and detemir groups with regard to either FPG level or the proportion of patients achieving FPG target.

Overall, the extent of HbA1c and FPG reduction and the proportion of severe and minor hypoglycemia in the PP population were relatively lower than those in the ITT population, and the control rates of these parameters were higher than those in the ITT population. However, the differences among the three BI groups in PP population were consistent with those in the ITT population.

The 95% CI of HbA1c change, FPG change, and weight gain in the ITT and PP analyses are presented in Figure 2.

DISCUSSION

This study compared the effectiveness and safety among three different BIs in real world clinical setting and further enriched findings in our previous analyses where we reported that add-on BI treatment was effective and relatively safe in general.²² The present study demonstrated that after adjusting for potential bias from baseline variables and process factors, the reduction of HbA1c differed among the three groups receiving different BI therapies, with larger reduction of HbA1c in long-acting insulin analog groups than that in NPH group. This difference is of statistical significance and could be scientifically meaningful with regard to exploring the differences among BIs. However, the clinical relevance of this observation should be interpreted with prudence. No significant difference was found among the three BI groups for the proportion of patients achieving HbA1c targets.

Negligible weight gain (0.10 kg) over 6 months of insulin therapy was observed in the study population, with marginally higher weight gain in the NPH group. Rates of minor hypoglycemia were lowest in glargine group and highest in NPH group, while there were no differences in rates of severe hypoglycemia among the three BI groups.

After 6 months of follow-up, the overall reduction of HbA1c in ORBIT study was 2.1%, with 2.0% in NPH group and 2.2% in glargine and detemir groups, which were higher than those observed in many RCTs,²⁶⁻²⁹ but very similar to the reduction found in several other observational studies evaluating BIs, such as the FINE¹⁹ study and INSTIGATE³⁰ study (HbA1c reduction in both was 2.1%), as well as the

A1c achieve (reduction of HbA1c was from 1.9% to 2.4% in different age groups) study.³¹ Higher baseline HbA1c in the observational studies might be one of the explanations for larger HbA1c reduction in this study. Other possible reasons include differences in study population, combined use of oral agents and prandial insulins as well as duration of follow-up between observational and RCT studies.

Systematic reviews comparing efficacy among different BIs^{9,10} showed no difference in HbA1c reduction among the BI groups. A systematic review of RCTs comparing insulin glargine and insulin detemir reported an insignificant difference of only 0.07% in average HbA1c reduction between the two insulin analog treatment groups.¹⁰ Another systematic review of RCTs comparing long-acting insulin analogues (insulin glargine and detemir) and NPH insulin (human isophane insulin) also showed that there was no significant difference in HbA1c reduction among the three BIs.⁹ In ORBIT study, although the clinical relevance is doubtful, the HbA1c and FPG reductions achieved in glargine and detemir groups were statistically larger than that in NPH group. These disparities between RCTs and real-world observation might be due to selection bias in ORBIT study and potential imbalanced differences among the 3 BI cohorts in economic status, comorbidities, risk factors of hypoglycemia, SMBG, access to health services, insulin dose titration and ancillary hypoglycemic therapies despite of propensity score-adjusted multivariate linear regression models used. In addition, the treat-to-target design, which requires compulsory identical glucose control targets among comparative groups in RCTs, minimizes the chance of finding the glycemic control differences that may exist in real-world clinical settings. For example, the observed lower hypoglycemic risk associated with long-acting insulin analogues in this study might allow more

aggressive insulin dosing in glargine and detemir groups, thus leading to better glycemic control.

Also, while no statistically significant difference for severe hypoglycemia rates was found among the three groups, the rate of documented symptomatic and overall hypoglycemia was statistically significantly lower in patients treated with either insulin glargine or detemir than that in patients with NPH therapy. These results were consistent with previous RCTs or systematic reviews of RCTs.^{9,32} Again, although the clinical relevance is debatable, adding glargine was associated with the lowest rate of overall hypoglycemia and adding detemir was associated with lowest weight gain in ORBIT study. Similar results were observed in previous RCT studies.^{7,10,33,34}

In the ITT population, the effect of adding on one specific BI may be diluted or strengthened by regimen change or adding prandial insulin during follow-up, which might impact the comparison among different insulin treatments. In the PP population, patients who continued using the same BI solely during the observation period were analyzed, thus the relative pure effect after adding on a certain BI can be evaluated. The results of the two populations were consistent with each other, reassuring the reliability of our conclusion. We believe that our findings may be generalizable and provides complementary evidence about the effectiveness and safety of BIs from the perspective of real-world clinical settings in China.

The ORBIT study has some unique strengths. To our knowledge, it is the largest comparative effectiveness study till date evaluating the effectiveness and safety of the three most common BIs. The primary and secondary outcomes of the study were evaluated with appropriate adjustments for various potential clinical and non-clinical factors. However, in an observational study, potential confounding effects of the severity of diabetes, comorbidities, complexity of co-administrated OADs,

contraindications, and unknown factors cannot be fully accounted for, irrespective of robust design and analysis approach. Although we employed the propensity score method to adjust for potential confounding effect of baseline characteristics, the baseline homogeneity among different BI groups could not be achieved for some factors. However, the concept of real-world clinical practice-based pragmatic studies provide an expanded opportunity to observe and analyze therapeutic management strategies outside of more rigid, protocol-driven controlled clinical trials.³⁵

In conclusion, our comparative effectiveness analysis from this large observational study provides clinical evidence that in real-world clinical settings in China, after adding BI to OADs in insulin-naïve people with type 2 diabetes, the improvement in glycemic control is substantial. Long-acting insulin analogues treatment was associated with better glycemic control as well as less hypoglycemia and weight gain than NPH insulin in type 2 diabetes patients. However, the clinical relevance of these observations need to be interpreted with caution.

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Author Contributions

Professor L.Ji and P.Zhang had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: L.Ji, P.Zhang, C.Pan and S.K.Garg.

Acquisition, analysis, or interpretation of data: L.Ji, P.Zhang, D.Zhu and S.K.Paul.

Drafting of the manuscript: D.Zhu, P.Zhang.

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Statistical analysis: X.Li, J.Ji, S.K.Paul.

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Conflict of Interest

Linong Ji reported receiving consulting and lecture fees from Eli Lilly, Bristol-Myers Squibb, Novartis, Novo Nordisk, Merck, Bayer, Takeda, Sanofi, Roche, and Boehringer Ingelheim, and research grants from Roche and Sanofi.

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Table 1. Baseline Characteristics of Patients with Type 2 Diabetes in the Three BI Groups Before and After Propensity Score Adjustment (ITT Population)

	Before propensity score adjustment			After propensity score adjustment		
	Glargine (N=11,290)	Detemir (N=2,135)	NPH (N=2,916)	Glargine (N=11,290)	Detemir (N=2,135)	NPH (N=2,916)
Demographics						
Male sex (%)	53.7	57.0	46.1 [‡]	53.0	53.6	53.5
Age (years, Mean±SD)	55.5±10.4	55.2±10.6	55.4±9.9	55.4±10.5	55.4±10.4	55.4±11.0
BMI (kg/m ² , Mean±SD)	24.7±3.3	25.2±3.5	24.5±3.4 [‡]	24.7±3.3	24.8±3.3	24.8±3.5
Education (%)						
Primary school or illiterate	23.7	22.8	40.1 [‡]	25.7	27.8	26.9 [†]
Junior high school	30.4	28.5	33.3	36.7	34.8	36.2
Senior high school	26.8	28.3	18.2	28.2	28.4	27.5
Junior college	11.8	11.3	4.9	7.6	7.1	6.9
Bachelor's degree or higher	7.3	9.1	3.4	1.8	1.9	2.5
Hospital level (%)						
Secondary hospitals	46.1	57.1	68.6 [‡]	58.2	55.1	56.9
Tertiary hospitals	53.9	42.9	31.4	41.8	44.9	43.1
Recruitment site (%)						
Outpatient	45.7	40.7	44.4 [‡]	44.5	44.4	44.4
Inpatient	54.3	59.3	55.6	55.5	55.6	55.6
Current residence (%)						
Urban	73.1	72.3	47.4 [‡]	71.6	70.8	73.1
Rural	26.9	27.7	52.6	28.4	29.2	26.9
Out of pocket (%)	40.1±26.4	38.5±27.6	48.7±28.1 [‡]	41.5±25.6	41.8±25.6	41.0±27.1
Clinical						
Duration of diabetes (years, Mean±SD)	6.4±5.3	6.1±5.2	6.8±5.3 [‡]	6.5±5.3	6.5±5.3	6.4±5.6
Duration of OAD treatment (years, Mean±SD)	5.6±5.0	5.4±5.0	6.1±5.1 [‡]	5.7±5.1	5.7±5.0	5.7±5.3
SBP (mm Hg, Mean±SD)	130±16	130±16	130±16	130±16	130±16	130±17
DBP (mm Hg, Mean±SD)	80±9	80±9	80±9	80±10	79±10	80±10
HbA1c at baseline (% , Mean±SD)	9.5±1.9	9.5±1.9	9.9±2.2 [‡]	9.6±2.0	9.6±2.0	9.6±2.0

FPG at baseline (mmol/L, Mean±SD)	11.5±3.8	11.4±3.8	12.3±4.3 [‡]	11.6±3.8	11.7±3.8	11.6±4.1
SMBG (times/month, Mean±SD)	5.4±10.5	5.4±9.7	4.0±8.3 [‡]	5.2±2.3	5.2±2.3	4.6±2.4 [‡]
Minor hypoglycemia at baseline						
Percentage ^a (%)	5.4	4.3	7.1 [‡]	5.4	4.6	6.4 [‡]
Frequency (times/person/year, Mean±SD)	1.5±9.1	1.0±6.0	2.6±14.3 [‡]	1.5±1.2	1.1±1.1	2.2±1.6 [‡]
Severe hypoglycemia at baseline						
Percentage ^b (%)	0.7	0.6	0.7	0.6	0.6	0.7
Frequency (times/person/year, Mean±SD)	0.0±0.7	0.0±0.6	0.1±1.2 [‡]	0.0±0.2	0.0±0.2	0.1±0.3 [‡]
Complication at baseline (%)						
Macrovascular	14.8	14.3	18.0 [‡]	15	15.3	14.7
Microvascular	27.9	28.4	31.0 [‡]	28.3	29	27.9
Pre-insulin OAD number at baseline (%)						
1	46.0	50.9	41.7 [‡]	46.4	46.2	46.9
2	43.8	41.3	47.4	45.4	45.5	45.1
≥3	10.0	7.9	10.9	8.2	8.3	8.0

^aPercentage of patients reporting minor hypoglycemia within 1 month before initiating insulin.

^bPercentage of patients reporting severe hypoglycemia within 3 months before initiating insulin.

[‡]*P*<.05; [‡]*P*<.01

BI, basal insulin; ITT, intention-to-treat; BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; NPH, Neutral Protamine Hagedorn; OAD, oral antidiabetic drug; SBP, systolic blood pressure; SMBG, self-monitoring of blood glucose

Table 2. Process Confounding Factors During Follow-up in ITT and PP Populations

	Glargine		Detemir		NPH	
	Visit 1	Visit 3	Visit 1	Visit 3	Visit 1	Visit 3
ITT population	N=11,290		N=2,135		N=2,916	
OAD number per day (Mean±SD)	1.26±0.82	1.31±0.81	1.39±0.86	1.36±0.84	1.01±0.90	1.17±0.88
Insulin dose (IU/day/kg, Mean±SD)	0.25±0.18	0.22±0.19	0.26±0.20	0.24±0.20	0.33±0.22	0.29±0.25
SMBG (times per month, Mean±SD)	5.44±10.47	6.37±7.87	5.38±9.68	6.10±7.89	4.03±8.27	6.06±8.06
Staple food ^a (Score, Mean±SD)	3.36±1.04	3.20±0.87	3.28±1.06	3.05±0.87	3.46±1.12	3.21±0.89
Vegetables ^a (Score, Mean±SD)	3.60±1.39	3.73±1.30	3.50±1.40	3.64±1.33	3.53±1.46	3.77±1.38
Fruit ^a (Score, Mean±SD)	1.90±0.96	2.00±0.82	1.88±0.93	2.05±0.79	1.77±0.95	1.84±0.82
Meat ^a (Score, Mean±SD)	2.19±0.83	2.10±0.71	2.29±0.81	2.20±0.70	1.97±0.84	1.91±0.75
Days of participating in >30 min physical activity in past 7 days (Mean±SD)	5.38±2.48	5.86±2.06	5.15±2.59	5.60±2.24	5.54±2.50	6.08±2.01
Days of participating in specific exercise session in past 7 days (Mean±SD)	3.22±3.04	4.02±2.87	3.23±3.06	3.92±2.90	3.12±3.18	3.91±3.10
PP population	N=6,804		N=1,122		N=1,076	
OAD (number per day, Mean±SD)	1.43±0.74	1.39±0.74	1.54±0.80	1.48±0.77	1.54±0.75	1.51±0.76
BI dose (IU/day/kg, Mean±SD)	0.18±0.06	0.21±0.08	0.17±0.06	0.22±0.09	0.19±0.11	0.24±0.14
SMBG (times per month, Mean±SD)	5.79±10.45	6.59±7.80	5.35±9.28	6.27±7.99	4.52±8.22	5.12±6.64
Staple food ^a (Score, Mean±SD)	3.33±1.02	3.18±0.85	3.33±1.08	3.04±0.84	3.50±1.07	3.24±0.87
Vegetables ^a (Score, Mean±SD)	3.56±1.37	3.69±1.28	3.52±1.37	3.64±1.25	3.45±1.43	3.59±1.33
Fruit ^a (Score, Mean±SD)	1.91±0.93	2.00±0.81	1.84±0.89	2.12±0.80	1.68±0.80	1.84±0.74
Meat ^a (Score, Mean±SD)	2.17±0.82	2.08±0.70	2.29±0.82	2.18±0.69	1.87±0.80	1.85±0.76
Days of participating in >30 min physical activity in past 7 days (Mean±SD)	5.46±2.42	5.90±2.01	5.26±2.61	5.73±2.22	5.90±2.21	6.27±1.84
Days of participating in a specific exercise session in past 7 days (Mean±SD)	3.36±3.04	4.08±2.84	3.46±3.10	4.15±2.88	3.41±3.20	4.08±3.08

^aIn China, Liang is the most commonly used weight unit for food. 1 liang = 50 g; 1 Jin= 10 Liang. The consumption score is defined as: 1=0-2 Liang, 2=3-4 Liang, 3=5-6 Liang, 4=7-8 Liang, 5=9-10 Liang, 6=More than 10 Liang (1 Jin) for staple food and vegetables; and 1=0-1 Liang, 2=1-2 Liang, 3=3-4 Liang, 4=5-6 Liang, 5=7-8 Liang, 6=More than 9 Liang for fruit and meat (fish is excluded).

BI, basal insulin; ITT, intent-to-treat; NPH, Neutral Protamine Hagedorn; OAD, oral antidiabetic drug; PP, per protocol; SMBG, self-monitoring of blood glucose.

Table 3. Propensity Score Regression Results on Outcomes and Safety of Three Basal Insulins after Initiation for 6 months (Data Are Presented as Number or Mean [95% CI])

	Total	Insulin glargine	Insulin detemir	NPH insulin	P value			
					Overall	Glargine vs. detemir	Glargine vs. NPH	Detemir vs. NPH
ITT analysis, N	16,341	11,290	2,135	2,916				
HbA1c level (%)								
Mean level at 6 months	7.43 (7.41, 7.45)	7.42 (7.40, 7.45)	7.40 (7.34, 7.46)	7.50 (7.44, 7.55)	0.0379	0.5523	0.0187	0.0247
Change from baseline	-2.15 (-2.18, -2.12)	-2.17 (-2.21, -2.13)	-2.19 (-2.28, -2.10)	-2.03 (-2.10, -1.95)	0.0039	0.6923	0.0014	0.0065
Control rate of HbA1c (%)								
≤6.5%	25.06 (24.39, 25.74)	24.9 (24.1, 25.7)	26.6 (24.7, 28.5)	24.6 (23.0, 26.4)	0.2402	0.1106	0.7847	0.1428
<7.0%	40.64 (39.88, 41.40)	40.7 (39.8, 41.7)	42.0 (39.9, 44.2)	39.2 (37.3, 41.2)	0.17	0.2827	0.1791	0.0616
FPG level (mmol/L)								
Mean level at 6 months	7.85 (7.80, 7.90)	7.79 (7.73, 7.85)	7.91 (7.77, 8.05)	8.05 (7.94, 8.17)	0.0005	0.125	0.0001	0.1354
Change from baseline	-3.66 (-3.74, -3.58)	-3.82 (-3.92, -3.72)	-4.00 (-4.23, -3.76)	-3.43 (-3.62, -3.24)	0.0003	0.1725	0.0005	0.0002
Control rate of FPG (<7.0 mmol/L, %)	42.66 (41.70, 43.63)	43.8 (42.6, 44.9)	42.2 (39.5, 45.0)	38.2 (36.0, 40.4)	0.0002	0.3224	<0.0001	0.027
Weight (kg)								
Mean level at 6 months	67.47 (67.30, 67.63)	67.40 (67.20, 67.60)	67.13 (66.68, 67.59)	67.95 (67.54, 68.37)	0.0247	0.2863	0.0222	0.0101
Change from baseline	0.10 (0.06, 0.15)	0.09 (0.04, 0.14)	-0.06 (-0.19, 0.07)	0.28 (0.17, 0.40)	0.0004	0.032	0.0032	<0.0001
Severe hypoglycemia (%)	0.50 (0.40, 0.63)	0.5 (0.3, 0.6)	0.7 (0.4, 1.2)	0.5 (0.3, 0.9)	0.3195	0.1354	0.5798	0.4565
Minor hypoglycemia (%)	8.37 (7.94, 8.82)	7.2 (6.7, 7.7)	10.4 (9.2, 11.8)	12.8 (11.6, 14.2)	<0.0001	<0.0001	<0.0001	0.0131
Probable symptomatic hypo	5.70 (5.34, 6.08)	4.7 (4.3, 5.1)	8.0 (6.9, 9.2)	9.2 (8.1, 10.4)	<0.0001	<0.0001	<0.0001	0.1451
Documented symptomatic hypo	1.52 (1.34, 1.73)	1.4 (1.2, 1.6)	1.0 (0.7, 1.5)	2.8 (2.2, 3.6)	<0.0001	0.1449	<0.0001	<0.0001
pseudo hypo	1.76 (1.56, 2.00)	1.6 (1.3, 1.8)	2.1 (1.6, 2.8)	2.4 (1.9, 3.1)	0.0037	0.0639	0.0017	0.4962
Asymptomatic hypo	0.97 (0.82, 1.14)	0.9 (0.7, 1.1)	0.8 (0.5, 1.3)	1.4 (1.0, 1.9)	0.0295	0.7675	0.0117	0.0556
Severe hypoglycemia (times/person/year)	5.88 (5.34, 6.48)	6.20 (5.54, 6.94)	4.93 (3.85, 6.30)	5.45 (4.31, 6.89)	0.1977	0.0972	0.3215	0.5459
Minor hypoglycemia (times/person/year)	24.29 (24.02, 24.57)	23.06 (22.73, 23.40)	27.41 (26.69, 28.16)	27.19 (26.61, 27.77)	<0.0001	<0.0001	<0.0001	0.6325
Probable symptomatic hypo	21.25 (20.94, 21.57)	19.76 (19.38, 20.15)	27.02 (26.18, 27.88)	23.62 (22.98, 24.27)	<0.0001	<0.0001	<0.0001	<0.0001
Documented symptomatic hypo	15.80 (15.30, 16.31)	15.88 (15.27, 16.51)	13.91 (12.50, 15.49)	17.00 (16.03, 18.03)	0.0036	0.023	0.0601	0.0012
pseudo hypo	17.62 (17.12, 18.13)	17.03 (16.44, 17.64)	17.15 (15.94, 18.44)	20.05 (19.43, 21.64)	<0.0001	0.8676	<0.0001	<0.0001
Asymptomatic hypo	16.08 (15.43, 16.75)	16.65 (15.85, 17.49)	13.59 (11.94, 15.47)	15.87 (14.67, 17.17)	0.0123	0.0043	0.2904	0.0467

PP analysis, N	9,002	6,804	1,122	1,076				
HbA1c level (%)								
Mean level at 6 months	7.30 (7.27, 7.32)	7.27 (7.244, 7.305)	7.26 (7.184, 7.336)	7.48 (7.399, 7.562)	<0.0001	0.7388	<0.0001	<0.0001
Change from baseline	-1.94(-1.98, -1.91)	-1.98 (-2.02, -1.93)	-1.97 (-2.08, -1.86)	-1.71 (-1.83, -1.59)	0.0002	0.8441	<0.0001	0.0022
Control rate of HbA1c (%)								
≤6.5%	27.0 (26.1, 27.9)	27.0 (25.9, 28.1)	28.8 (26.1, 31.5)	25.0 (22.2, 27.9)	0.1806	0.2365	0.2063	0.0646
<7.0%	44.1 (43.0, 45.1)	44.3 (43.1, 45.5)	46.1 (43.1, 49.2)	40.5 (37.3, 43.8)	0.0445	0.2663	0.0378	0.0146
FPG level (mmol/L)								
Mean level at 6 months	7.57 (7.51, 7.63)	7.53 (7.46, 7.59)	7.60 (7.43, 7.77)	7.80 (7.64, 7.95)	0.007	0.0435	0.0017	0.0933
Change from baseline	-3.53 (-3.62, -3.44)	-3.67 (-3.78, -3.57)	-3.80 (-4.08, -3.52)	-3.27 (-3.52, -3.01)	0.0083	0.4221	0.0043	0.0066
Control rate of FPG (<7.0 mmol/L, %)	47.5 (46.3, 48.8)	48.7(47.2, 50.1)	46.3(42.5, 50.1)	41.6(38.2, 45.1)	0.0014	0.2666	0.0004	0.0795
Weight								
Mean level at 6 months	67.69 (67.47, 67.90)	67.72 (67.47, 67.97)	67.49 (66.87, 68.12)	67.69 (67.03, 68.36)	0.8067	0.5123	0.9456	0.6712
Change from baseline	0.02 (-0.03, 0.07)	0.056 (-0.008, 0.12)	-0.21 (-0.37, -0.045)	0.038 (-0.13, 0.21)	0.0124	0.0031	0.8461	0.045
Severe hypoglycemia (%)	0.19 (0.11, 0.32)	0.2 (0.1, 0.4)	0.2 (0.1, 0.5)	0.1 (0.0, 0.4)	0.3374	0.6195	0.1554	0.306
Minor hypoglycemia (%)	6.99 (6.47, 7.56)	6.1 (5.6, 6.7)	9.3 (7.8, 11.2)	11.8 (9.8, 14.0)	<0.0001	<0.0001	<0.0001	0.0768
Probable symptomatic hypo	4.54 (4.11, 5.01)	3.7 (3.3, 4.2)	7.5 (6.1, 9.2)	8.9 (7.3, 11.0)	<0.0001	<0.0001	<0.0001	0.2308
Documented symptomatic hypo	1.27 (1.05, 1.54)	1.3 (1.0, 1.6)	0.7 (0.4, 1.4)	2.2 (1.4, 3.4)	0.0132	0.1621	0.0172	0.0068
Pseudo hypo	1.42 (1.19, 1.69)	1.3 (1.0, 1.6)	1.9 (1.2, 2.8)	2.1 (1.4, 3.3)	0.0249	0.0737	0.0194	0.6194
Asymptomatic hypo	0.89 (0.70, 1.12)	0.9 (0.7, 1.2)	0.7 (0.3, 1.3)	1.1 (0.6, 1.8)	0.4836	0.53	0.3512	0.2538
Severe hypoglycemia (times/person/year)	4.27 (3.00, 6.07)	3.74 (2.50, 5.60)	5.63 (3.47, 9.12)	7.33 (3.46, 15.54)	0.1474	0.1459	0.0947	0.5357
Minor hypoglycemia (times/person/year)	22.20 (21.82, 22.59)	20.26 (19.83, 20.70)	36.07 (34.73, 37.45)	23.88 (22.98, 24.81)	<0.0001	<0.0001	<0.0001	<0.0001
Probable symptomatic hypo	18.69 (18.24, 19.14)	16.34 (15.85, 16.84)	36.32 (34.81, 37.90)	21.86 (20.86, 22.92)	<0.0001	<0.0001	<0.0001	<0.0001
Documented symptomatic hypo	15.14 (14.41, 15.90)	16.02 (15.17, 16.91)	12.21 (10.08, 14.80)	13.27 (11.71, 15.04)	0.0021	0.0084	0.0072	0.4635
Pseudo hypo	17.83 (17.10, 18.59)	18.40 (17.47, 19.37)	17.14 (15.22, 19.30)	15.26 (13.57, 17.15)	0.0154	0.2988	0.0049	0.1766
Asymptomatic hypo	16.38 (15.47, 17.35)	17.59 (16.48, 18.77)	12.27 (10.10, 14.90)	14.12 (12.35, 16.14)	<0.0001	0.0007	0.0024	0.2499

^aPropensity score and process factors were controlled. The process factors were used as the changes from baseline to visit 3 for BI and total insulin doses, OAD number, frequency of SMBG, physical activity, and diet consumption.
FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; ITT, intent-to-treat; NPH, Neutral Protamine Hagedorn; OAD, oral antidiabetic drug; PP, per protocol; SE, standard error; SMBG, self-monitoring of blood glucose

Figure Legends

Figure 1. Enrollment and follow-up. HbA1c, glycated hemoglobin; ITT, intent-to-treat; NPH, Neutral Protamine Hagedorn; OAD, oral antidiabetic drug; PP, per protocol; T2DM, type 2 diabetes mellitus

Figure 2. HbA1c change, FPG change, and weight gain in the ITT population (Figures A, B, and C) and PP population (Figures D, E, and F) after propensity score regression (bar: 95% CI).

CI, confidence interval; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; ITT, intent-to-treat; NPH, Neutral Protamine Hagedorn; PP, per protocol

Figure 1. Enrolment and follow-up

Figure 2. HbA1c change, FPG change and weight gain in the ITT population (Figure A, B and C) and PP population (Figure D, E and F) after the PS regression (bar: 95% CI)

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