

# Cost Change After Initiating Basal Insulin for 6 Months in Patients with Type 2 Diabetes: A Registry Study in China

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**Abstract:** This study aims to examine short-term treatment cost changes after initiating basal insulin in insulin naïve patients with type 2 diabetes for 6 months in routine clinical practice. Observational Registry of Basal Insulin Treatment (ORBIT) program is a 6-month, prospective study in China. Patients with type 2 diabetes inadequately controlled ( $HbA1C \geq 7\%$ ) by oral antidiabetic drugs (OADs) and willing to initiate basal insulin treatment were enrolled from 209 hospitals of eight geographic regions of China. Type and dose of BI were at the physician's discretion and patients' willingness. Interviews were conducted at baseline, month 3 and month 6. Daily treatment cost (including cost of OAD medication, insulin therapy, self-monitoring of blood glucose and dealing with minor hypoglycemia) of per person before and after adding BIs was evaluated. After adding on Basal insulin, the weighted mean  $\pm$  standard deviation (SD) daily treatment cost for insulin-naïve patients with type 2 diabetes increased from  $\$1.25 \pm \$0.74$  (baseline) to  $\$2.57 \pm \$0.68$  at month 6, a median (Q1, Q3) increase of 1.51 (0.38, 4.11) times over 6 months. The daily treatment cost increased with growing baseline HbA1c level and prolonged diabetes duration. The reduction in HbA1c was 2.2%, with minor hypoglycemia increased by 0.68 times/person/year. Insulin cost accounted for the highest proportion (47.9%) of costs. Our findings suggest adding-on BI therapy may increase the daily treatment cost by 1.5 times at 6 months. Early initiation of BI therapy may provide an opportunity to achieve treatment goals with low cost and low risk of hypoglycemia.

**Keywords:** Basal Insulin, Cost, Type 2 Diabetes

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## 1. Introduction

Type 2 diabetes mellitus (T2DM) is a major public health challenge in China. With the largest population with T2DM in the world—estimated at 98.4 million people in 2013 [1]—the prevalence of T2DM in China has risen dramatically over the decades [2]. Nationally representative samples reported a prevalence rate of 9.7% in 2007 [3] and 2010 [4], based on 1999 World Health Organization diagnostic criteria [5].

Moreover, only approximately 25% of patients with T2DM in China have access to treatment, with only 39.7% of those achieving adequate glycemic control [4]. Poor glycemic control and the consequential development of complications associated with T2DM increase treatment costs.

As T2DM progresses, introduction of insulin becomes imperative to maintain adequate glucose control [6, 7]. Guidelines on diabetes management recommend the addition of basal insulin (BI) in combination with second- or third-line

of antihyperglycemic therapy and use of BI as an initial treatment in patients with inadequate glucose control with oral antidiabetic drugs (OADs) [8-12].

The therapeutic choices for BI include neutral protamine hagedorn (NPH) insulin and the long-acting analogs, insulin glargine and insulin detemir. Clinical trials [13-17] and observational [18-22] studies have evaluated the efficacy and effectiveness of BI therapies in T2DM patients, and shown that when added to existing OADs, all these forms of BIs can effectively control glucose, although BI analogs have demonstrated lower risk of hypoglycemia compared with NPH insulin.

Besides effectiveness and safety, the acceptability of a certain therapy also depends on the influence of that therapy on costs following initiation of it, which relates to affordability. Previous studies on the costs of BIs, either in clinical trials or observational studies (prospective or retrospective cohort) [23-27], emphasized on evaluating the long-term cost-effectiveness (through the index of cost/quality-adjusted life-years [QALYs]) by using diabetes models, such as the Center for Outcomes Research (CORE) model [28, 29]. Few studies have evaluated short-term change in treatment cost caused by regimen conversion from insulin-naïve therapy to add-on insulin therapy. Thus, the treatment cost changes during this conversion is unknown. In the real world, types and dose of BIs were initiated based on physicians' judgment and patients' preference. This large-scale observational study aimed to evaluate the short-term cost changes for patients undergoing a conversion from OAD-only regimen (insulin-naïve patients) to add-on insulin therapy in routine clinical practice.

## 2. Materials and Methods

### 2.1. Study Design

ORBIT was a 6-month, multicenter, prospective registry study conducted in China. A nationally representative sample of patients with established T2DM was enrolled at hospitals representative of eight geographic regions and two hospital tiers at secondary (county or district) and tertiary (provincial or national) levels. Insulin-naïve patients with T2DM aged 18–80 years inadequately controlled with OADs (glycated hemoglobin [HbA1c]  $\geq 7\%$ , 53 mmol/mol) and willing to accept BI treatment were consecutively enrolled by their physicians from the end of 2011 to June 2013, in same number of secondary and tertiary hospitals all over China. The type and dose of BI were prescribed based on the physicians' judgment and patients' preferences.

For each participant, the costs were investigated before the initiation of BI (visit 0), immediately after the initiation of BI (visit 1), at mid-term (3 months, visit 2), and at the end of the study (6 months, visit 3). Patients were asked to bring their routine medications for taking for interviewers to check during investigation. Types and doses of daily consumed OADs and insulin, number of needles used for injection per day, self-reported frequency of SMBG (self-monitoring of

blood glucose) and minor hypoglycemia in the previous one month were documented for each patient. According to the American Diabetes Association (ADA) recommendations [11], minor hypoglycemia episodes included documented symptomatic, asymptomatic, probable symptomatic, or pseudo-hypoglycemia. The frequency of severe hypoglycemia was extremely low, with 0.05 episodes/person-year in visit 1 and 0.03 episodes/person-year at visit 3. Given the short observation period, it was not included in this cost analyses [11].

The protocol was approved by the Institutional Review Board (IRB) of Peking University, and when necessary, by local IRBs. Further details on the study design and baseline characteristics are available in a previous article [30].

### 2.2. Cost Definition and Calculations

Diabetes treatment costs in this study consisted of cost of OAD medication, insulin therapy (including needles used for injection), SMBG (including blood glucose testing strips and lancets), and cost to deal with minor hypoglycemia.

#### 2.2.1. Definition of Unit Cost

- Unit cost of insulin: Based on the sale price of a certain insulin in the hospital, the unit cost of insulin = the sale price of insulin (\$)/the total dose of a single commodity (International unit, IU).
- Unit cost of OADs: Based on the sale price of a certain OAD in the hospital, the unit cost of an OAD = the sale price of an OAD (\$)/the total dose of a single commodity (mg).
- Unit cost of needles used for injection, blood glucose testing strips and lancets were based on the sale price for a single unit in each hospital.

The average cost for dealing with each minor hypoglycemia episode was 2.4 Chinese yuan (CNY) [31].

#### 2.2.2. Cost Calculations

Daily treatment cost was evaluated in this study. For each patient, the daily cost was calculated as follows:

- Daily cost of OADs medication =  $\sum_{i=1}^k \text{Unit cost of OAD}_i \times \text{OAD}_i \text{ dose used per day}$ , where k is the number of types of OAD;
- Daily cost of insulin therapy =  $\sum_{i=1}^k \text{Unit cost of insulin}_i \times \text{insulin}_i \text{ dose used per day}$ , where k is the number of types of insulin;
- Daily cost of needles = (Number of needles used in past 7 days  $\times$  unit cost of needle)/7.
- Daily cost of SMBG = Frequency of SMBG in past 30 days  $\times$  (unit cost of strips + unit cost of lancets)/30;
- Daily cost of hypoglycemia event = (Frequency of hypoglycemia in past 30 days  $\times$  average cost of hypoglycemia treatment)/30;
- Total daily treatment cost for each patient = Daily cost of OADs medication + Daily cost of insulin therapy + Daily cost of needles + Daily cost of SMBG + Daily cost of hypoglycemia event;
- Daily treatment cost change from visit 0 to visit 3 for each patient = Total daily treatment cost at visit 3 - Total

daily treatment cost at visit 0;

- h) Times of cost increase for each patient= Daily treatment cost change from visit 0 to visit 3/ Total daily treatment cost at visit 0.

### 2.3. Statistical Methods

Descriptive statistics were used in analyses. Characteristics of overall patients and patients in individual region were described. Daily treatment cost change from visit 0 to visit 3 and times of cost increase were described in each region. The weighted mean of overall cost increase from visit 0 to visit 3, and weighted overall times of cost increase were calculated from the value of each region. The weight for each region was calculated by using following process. Firstly, according to the prevalence [32] of T2DM and population of each province [33], the number of patients with T2DM in each province was calculated. Then, the total number of patients with T2DM in each region was calculated by gathering the patients' number in each province included in that region. Third, the weight of each region was calculated by using the number of patients in that region divided by the total number of patients in eight regions. After calculation, the weights of eight regions were: Southwest (0.10), Northwest (0.04), Mid-Yangtze River (0.16), Mid-Yellow River (0.15), South Coast (0.13), East Coast (0.12), North Coast (0.20), Northeast (0.10). Detailed calculation process was showed in Table 5.

Weighted mean of cost increase and weighted times of cost increases were also described in subgroups such as region, hospital tier, source of patients, baseline HbA1c level and diabetes duration etc. Changes in the factors related to costs, including OAD number, insulin dose, SMBG and hypoglycemia frequency were described from visit 0 to visit 3. Cost proportion of each item at each visit were also described.

For continuous variables, a normality test was performed. Continuous variables with normal distribution were presented

as mean  $\pm$  SD values. Continuous variables for skewed distribution, commonly treated as normal data in most studies, were also reported as mean  $\pm$  SD, while other variables were reported as median (Q1, Q3). Discrete variables were presented as n (%). All costs were presented in US dollar (\$).

## 3. Results

### 3.1. Baseline Characteristics

18,995 patients qualified for recruitment. Detailed baseline characteristics at baseline have been described in a different publication [30]. Of the 18,995 participants, 16,341 completed the 6-month follow-up. The mean age was  $55.4 \pm 10.3$  (mean  $\pm$  SD) years, and 52.8% of the participants were men; the mean body weight was  $67.4 \pm 11.8$  kg; the mean HbA1c and fasting plasma glucose (FPG) were  $81$  (9.6%)  $\pm 21.9$  mmol/mol and  $11.6 \pm 4.0$  mmol/L at baseline, respectively; and the mean duration of diabetes was  $6.5 \pm 5.3$  years. Percentage of patients in different subgroups in overall and eight geographical regions were demonstrated in Table 6.

### 3.2. Daily Treatment Cost in Eight Regions

Overall, before initiation of BIs, the weighted mean of daily treatment cost for insulin-naïve T2DM patients was \$1.25  $\pm$  \$0.74, which increased to \$2.29  $\pm$  \$0.51 following prescription of Bis and \$2.57  $\pm$  \$0.68 after 6 months, a median (Q1, Q3) increase of 1.51 (0.38, 4.11) times over 6 months. The daily treatment cost change and times of cost increase varied in regions (Table 1). Clinical outcomes at month 6 in overall and eight regions were listed in Table 7. The overall reduction in HbA1c was 2.2%. The frequency of minor hypoglycemia increased by 0.68 times/person/year, with a slight increase in body weight.

**Table 1.** Daily treatment cost at each visit, daily treatment cost change and times of cost increase at month 6 in total and 8 regions.

Regions	Treatment cost at v0		Treatment cost at v1		Treatment cost at v3		Treatment cost change (v3-v0)	Times of cost increase at 6 months <sup>‡</sup>
	N	Mean $\pm$ SD (\$)	N	Mean $\pm$ SD (\$)	N	Mean $\pm$ SD (\$)	Mean $\pm$ SD (\$)	Median (Q1, Q3)
North coast	3273	1.41 $\pm$ 1.96	3273	2.46 $\pm$ 1.56	2917	2.82 $\pm$ 1.70	1.45 $\pm$ 2.21	1.47 (0.38, 4.18)
Yangtze River	3018	1.18 $\pm$ 2.00	3018	2.41 $\pm$ 1.31	2605	2.56 $\pm$ 2.49	1.40 $\pm$ 2.02	1.51 (0.44, 4.29)
Southwest	2913	1.33 $\pm$ 2.25	2913	2.01 $\pm$ 1.31	2175	2.46 $\pm$ 1.78	1.11 $\pm$ 2.66	1.45 (0.26, 4.02)
Yellow River	2830	0.89 $\pm$ 1.25	2830	1.67 $\pm$ 1.16	2628	1.88 $\pm$ 1.16	1.02 $\pm$ 1.39	1.59 (0.32, 4.46)
East coast	2267	1.38 $\pm$ 2.16	2267	2.43 $\pm$ 1.36	1978	2.86 $\pm$ 1.77	1.49 $\pm$ 2.49	1.46 (0.45, 3.35)
South coast	1987	1.42 $\pm$ 2.21	1987	2.53 $\pm$ 1.27	1620	2.77 $\pm$ 1.86	1.32 $\pm$ 2.47	1.07 (0.22, 3.22)
Northeast	1670	1.09 $\pm$ 2.51	1670	2.68 $\pm$ 1.37	1435	2.82 $\pm$ 1.62	1.82 $\pm$ 1.96	2.41 (0.81, 5.67)
Northwest	1037	1.24 $\pm$ 1.98	1037	2.45 $\pm$ 1.05	977	2.60 $\pm$ 1.11	1.37 $\pm$ 2.19	1.38 (0.48, 3.39)
Total <sup>†</sup>	18995	1.25 $\pm$ 0.74	18995	2.29 $\pm$ 0.51	16335	2.57 $\pm$ 0.68	1.35 $\pm$ 0.80	1.51 (0.38, 4.11)

<sup>†</sup>For the total values, weighted means of daily treatment cost for each visit and weighted medians for times of cost increase at month 6 were calculated. The weights for each region were: Southwest (0.10), Northwest (0.04), Mid-Yangtze River (0.16), Mid-Yellow River (0.15), South Coast (0.13), East Coast (0.12), North Coast (0.20), Northeast (0.10). v0, visit 0- Before initiation of BI; v1, visit 1- Immediately after the initiation of BI; v3, visit 3- End of the study at month 6; SD, standard deviation; Q1, 25th percentile; Q3, 75th percentile.

<sup>‡</sup>Times of cost increase= (Treatment cost change)/ Treatment cost at v0.

### 3.3. Daily Treatment Cost in Subgroups

Patients in tertiary hospital, in-patients had higher daily treatment cost increase than patients in secondary (\$1.42 vs. \$1.27,  $p < 0.05$ ) and out-patients (\$1.38 vs. \$1.32,  $P < 0.05$ )

respectively. Treatment cost change increased with the growing of baseline HbA1c level (Figure 1A) and prolonged diabetes duration (Figure 1B). Patients with insulin glargine ( $1.49 \pm 2.09$ ) or detemir ( $1.66 \pm 2.54$ ) had higher treatment

cost change than those with NPH insulin ( $0.56 \pm 2.14$ ). Patients using only one OAD had the highest cost increase than those who had used two or more OADs (Table 2).

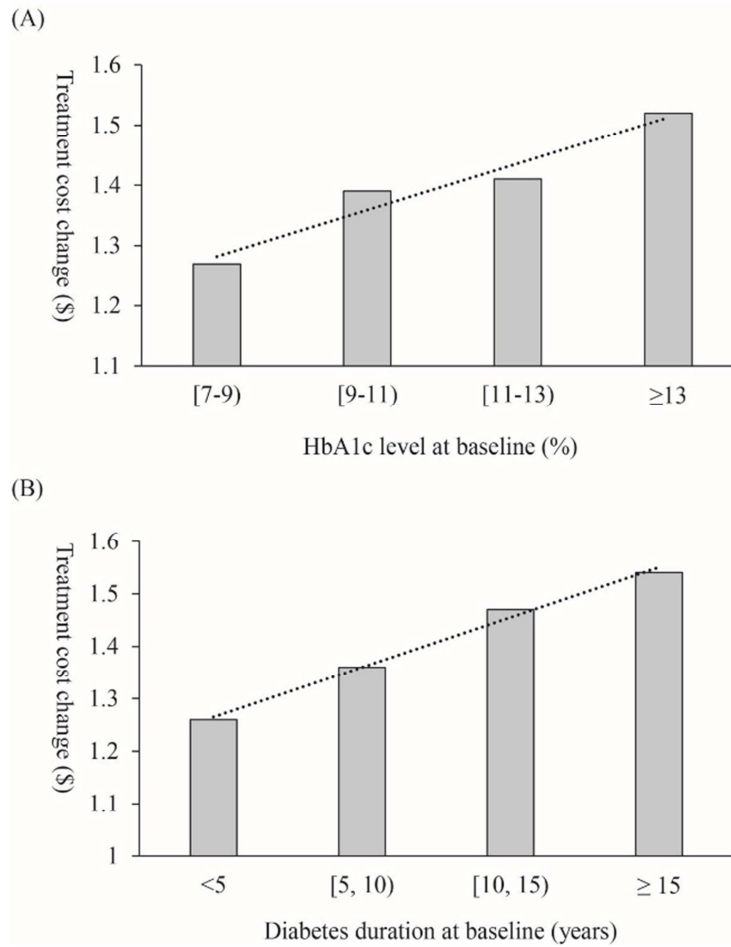


Figure 1. Association between treatment cost change at month 6 and (A) baseline HbA1c (%) level, (B) baseline diabetes duration (years).

Table 2. Daily treatment cost at each visit, daily treatment cost change and times of cost increase in various subgroups<sup>†</sup>.

Group variable	Treatment cost at v0		Treatment cost at v1		Treatment cost at v3		Treatment cost change (v3-v0) (\$)	Times of cost increase at 6 months‡, Median (Q1, Q3)
	N	Mean ± SD (\$)	Mean ± SD (\$)	N	Mean ± SD (\$)			
Total	18,995	1.25 ± 0.74	2.29 ± 0.51	16335	2.57 ± 0.68	1.35 ± 0.80	1.51 (0.38, 4.11)	
Hospital level								
Secondary	9443	1.12 ± 2.10	2.10 ± 1.41	8421	2.39 ± 1.87	1.27 ± 2.10	1.55 (0.4, 4.35)	
Tertiary	9552	1.36 ± 1.98	2.48 ± 1.29	7914	2.75 ± 1.73	1.42 ± 2.28	1.45 (0.36, 3.85)	
Age (years)								
<40	1277	1.13 ± 2.32	2.35 ± 1.54	1097	2.50 ± 1.98	1.45 ± 2.08	1.86 (0.41, 5.13)	
[40, 50)	4253	1.24 ± 2.57	2.27 ± 1.25	3647	2.52 ± 2.22	1.27 ± 2.73	1.57 (0.37, 4.21)	
[50, 60)	6541	1.22 ± 1.88	2.30 ± 1.42	5675	2.58 ± 1.62	1.38 ± 2.00	1.51 (0.40, 4.13)	
≥60	6924	1.28 ± 1.75	2.28 ± 1.35	5916	2.60 ± 1.67	1.34 ± 2.01	1.42 (0.36, 3.81)	
Gender								
Male	9968	1.24 ± 2.01	2.35 ± 1.35	8623	2.62 ± 1.90	1.38 ± 2.24	1.55 (0.38, 4.16)	
Female	9027	1.24 ± 2.08	2.21 ± 1.38	7712	2.51 ± 1.71	1.31 ± 2.14	1.46 (0.38, 4.07)	
Baseline HbA1c (%)								
[7, 8)	8532	1.04 ± 2.08	2.29 ± 1.33	7500	2.40 ± 1.69	1.27 ± 1.85	1.31 (0.33, 3.41)	
[9, 11)	6087	1.11 ± 2.05	2.40 ± 1.37	5199	2.52 ± 1.79	1.39 ± 1.87	1.60 (0.43, 4.30)	
[11, 13)	3048	1.18 ± 1.60	2.19 ± 1.34	2535	2.58 ± 1.52	1.41 ± 2.52	1.93 (0.49, 5.41)	
≥13	1328	1.29 ± 2.53	2.37 ± 1.41	1101	2.68 ± 2.19	1.52 ± 2.50	2.04 (0.37, 5.72)	
Diabetes duration (years)								
<5	8805	1.11 ± 2.13	2.18 ± 1.29	7545	2.35 ± 1.84	1.26 ± 2.20	1.37 (0.38, 3.66)	
[5, 10)	5495	1.29 ± 1.84	2.33 ± 1.46	4722	2.64 ± 1.79	1.36 ± 2.23	1.46 (0.39, 3.79)	
[10, 15)	3309	1.38 ± 1.65	2.41 ± 1.37	2877	2.83 ± 1.68	1.47 ± 2.06	1.35 (0.39, 3.54)	
≥15	1385	1.56 ± 2.86	2.54 ± 1.40	1190	2.99 ± 1.85	1.54 ± 2.26	1.24 (0.32, 3.71)	
Education degree								

Group variable	Treatment cost at v0		Treatment cost at v1		Treatment cost at v3		Treatment cost change (v3-v0) (\$)	Times of cost increase at 6 months‡, Median (Q1, Q3)
	N	Mean ± SD (\$)	Mean ± SD (\$)	N	Mean ± SD (\$)			
Primary school or illiterate	5154	1.16 ± 2.35	2.06 ± 1.27	4334	2.27 ± 1.97	1.13 ± 2.27	1.54 (0.33, 4.52)	
Junior high school	5859	1.23 ± 2.03	2.24 ± 1.42	5011	2.51 ± 1.77	1.30 ± 2.32	1.49 (0.37, 4.18)	
Senior high school	4724	1.29 ± 1.97	2.45 ± 1.43	4160	2.74 ± 1.77	1.49 ± 2.10	1.44 (0.38, 3.73)	
Junior college	1965	1.29 ± 1.71	2.46 ± 1.32	1715	2.83 ± 1.64	1.53 ± 2.08	1.58 (0.47, 4.19)	
Bachelor degree or higher	1293	1.36 ± 1.39	2.54 ± 1.19	1115	2.91 ± 1.56	1.59 ± 1.63	1.53 (0.47, 3.48)	
Current residence								
Urban	13019	1.34 ± 2.09	2.44 ± 1.39	11170	2.75 ± 1.88	1.44 ± 2.13	1.42 (0.37, 3.66)	
Rural	5976	1.02 ± 1.92	1.96 ± 1.27	5165	2.16 ± 1.59	1.15 ± 2.30	1.77 (0.40, 5.2)	
Patient resource								
Outpatient clinic	8361	1.32 ± 2.15	2.19 ± 1.30	7326	2.62 ± 1.90	1.32 ± 2.13	1.36 (0.36, 3.49)	
Inpatient ward	10634	1.18 ± 1.95	2.36 ± 1.42	9009	2.52 ± 1.73	1.38 ± 2.24	1.68 (0.39, 4.69)	
Out of pocket costs (%)								
<20	2940	1.51 ± 2.28	2.68 ± 1.38	2513	2.95 ± 1.68	1.47 ± 2.11	1.07 (0.30, 2.95)	
[20, 40)	7202	1.26 ± 1.62	2.39 ± 1.44	6253	2.71 ± 1.63	1.47 ± 1.95	1.55 (0.44, 3.94)	
[40, 60)	4276	1.10 ± 1.77	2.10 ± 1.30	3682	2.35 ± 1.75	1.27 ± 2.30	1.75 (0.41, 5.11)	
[60, 80)	2045	1.06 ± 2.13	1.96 ± 1.19	1737	2.22 ± 1.69	1.16 ± 2.58	1.73 (0.32, 4.82)	
≥80	2528	1.26 ± 2.95	2.11 ± 1.24	2150	2.35 ± 2.43	1.14 ± 2.36	1.42 (0.34, 4.04)	
BMI (kg/m2) at v1								
<24	8149	1.25 ± 2.10	2.19 ± 1.32	6946	2.48 ± 1.61	1.26 ± 2.26	1.42 (0.36, 3.94)	
[24, 28)	7927	1.24 ± 2.15	2.30 ± 1.39	6864	2.61 ± 2.02	1.39 ± 2.16	1.58 (0.4, 4.2)	
≥28	2918	1.23 ± 1.54	2.52 ± 1.41	2525	2.69 ± 1.71	1.47 ± 2.07	1.55 (0.38, 4.38)	
Macro complications								
No	16137	1.23 ± 2.15	2.28 ± 1.36	13830	2.56 ± 1.86	1.35 ± 2.27	1.54 (0.39, 4.2)	
Yes	2858	1.30 ± 1.33	2.35 ± 1.39	2505	2.63 ± 1.51	1.33 ± 1.73	1.29 (0.30, 3.61)	
Micro complications								
No	13587	1.22 ± 2.10	2.25 ± 1.37	11679	2.53 ± 1.89	1.33 ± 2.29	1.55 (0.39, 4.16)	
Yes	5408	1.29 ± 1.90	2.38 ± 1.35	4656	2.66 ± 1.59	1.40 ± 1.93	1.41 (0.34, 3.98)	
Number of OADs before v1								
1	8675	0.72 ± 0.89	2.20 ± 1.24	7462	2.44 ± 1.59	1.73 ± 1.68	3.02 (1.12, 7.65)	
2	8351	1.47 ± 2.46	2.30 ± 1.46	7185	2.61 ± 2.00	1.19 ± 2.31	1.08 (0.27, 2.6)	
≥3	1969	2.61 ± 2.78	2.61 ± 1.47	1688	2.94 ± 1.83	0.35 ± 3.09	0.29 (-0.13, 0.8)	
BI type at v1								
Glargine	13294	1.26 ± 2.05	2.47 ± 1.29	11287	2.72 ± 1.87	1.49 ± 2.09	1.58 (0.47, 4.16)	
Detemir	2385	1.27 ± 1.94	2.76 ± 1.32	2135	2.94 ± 1.82	1.66 ± 2.54	1.80 (0.57, 4.84)	
NPH	3316	1.14 ± 2.07	1.23 ± 1.17	2913	1.68 ± 1.22	0.56 ± 2.14	0.99 (0.10, 3.37)	

†Weighted means or medians were calculated for each subgroup. HbA1c, glycated hemoglobin; BMI, body mass index; OADs, oral antidiabetic drugs; BI, basal insulin; NPH, neutral protamine Hagedorn; v0, visit 0- Before initiation of BI; v1, visit 1- Immediately after the initiation of BI; v3, visit 3- End of the study at month 6; SD, standard deviation; Q1, 25th percentile; Q3, 75th percentile.

‡Times of cost increase= (Absolute cost increase)/ Self-report cost at v0.

### 3.4. Cost Proportion

The number of OADs used at visit 0 decreased substantially at visit 1 and remained stable at the following visits. BI dose and total insulin dose decreased at visit 3, while the frequency

of SMBG and minor hypoglycemia increased at visits 2 and 3 (Table 3). The cost of Insulin accounted for the highest proportion (approximately 50%) of costs, with costs of OAD medications ranking second (37.3%) (Table 4).

Table 3. Changes in factors related to cost of treatment†.

Variables	Before initiation of BI: v0 (n=18995)	Immediately after the initiation of BI: v1 (n=18995)	Mid-term at month 3: v2 (n=17253)	End of the study at month 6: v3 (n=16336)
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
OAD number	1.67 ± 0.25	1.24 ± 0.32	1.31 ± 0.31	1.31 ± 0.31
BI dose (IU/day)	-	11.50 ± 1.68	10.91 ± 2.58	10.53 ± 2.90
Insulin dose (IU/day)	-	17.67 ± 4.63	16.57 ± 4.98	15.94 ± 5.06
SMBG frequency per month	5.07 ± 3.73	-	6.94 ± 3.58	6.09 ± 2.85
Needle number per week	-	-	3.04 ± 3.50	2.73 ± 3.21
Hypoglycemia frequency per month	0.15 ± 0.33	-	0.22 ± 0.30	0.20 ± 0.42

†Weighted means were calculated for each variable according to their values in each region and the weights for each region. BI, basal insulin; OADs, oral antidiabetic drugs; SMBG, self-monitoring of blood glucose; v0, visit 0; v1, visit 1; v2, visit 2; v3, visit 3; SD, standard deviation.

**Table 4.** Cost (\$) of each item and cost proportion (%) at each visit<sup>†</sup>.

Variable	Before initiation of BI: v0 (N=18995)		Immediately after the initiation of BI: v1 (N=18995)		Mid-term at month 3: v2 (N=17253)		End of the study at month 6: v3 (N=16335)	
	Mean ± SD	Proportion (%)	Mean ± SD	Proportion (%)	Mean ± SD	Proportion (%)	Mean ± SD	Proportion (%)
OAD cost (\$)	1.10 ± 0.73	88.6	0.93 ± 0.43	40.9	0.97 ± 0.52	36.4	0.96 ± 0.54	37.3
Insulin cost (\$)	-	-	1.35 ± 0.30	59.1	1.28 ± 0.34	47.8	1.23 ± 0.36	47.9
Needle cost (\$)	-	-	-	-	0.23 ± 0.14	8.5	0.21 ± 0.12	8.1
SMBG cost (\$)	0.14 ± 0.11	11.2	-	-	0.19 ± 0.10	7.1	0.17 ± 0.09	6.6
Hypoglycemia cost (\$)	0.00 ± 0.00	0.2	-	-	0.00 ± 0.00	0.1	0.00 ± 0.01	0.1
Total cost (\$)	1.25 ± 0.74	100.0	2.29 ± 0.51	100.0	2.68 ± 0.66	100.0	2.57 ± 0.68	100.0

<sup>†</sup>Weighted means of cost for each variable were calculated. OADs, oral antidiabetic drugs; SMBG, self-monitoring of blood glucose; v0, visit 0; v1, visit 1; v2, visit 2; v3, visit 3; SD, standard deviation.

## 4. Discussion

This large registry study showed that the introduction of BI therapy may increase the daily treatment cost (including OADs, insulin, SMBG, and dealing with hypoglycemia) by 1.5 times at 6 months, with a 2.2% reduction in HbA1c levels and a slight increase in frequency of hypoglycemia. Higher HbA1c level and longer diabetes duration at baseline were related to the higher treatment cost increase after initiation of BI.

Daily treatment cost and change of daily treatment cost at month-6 increased with the growing of baseline HbA1c level and prolonged diabetes duration. Also, the ones with longer diabetes duration ( $\geq 15$  years) had lower HbA1c reduction at month 6 (1.75% vs. 2.47%), compared to the ones with shorter diabetes duration ( $< 5$  years). This is consistent with a sub-analysis from the MOTIV study which found that patients with shorter duration of diabetes needed lower dose of insulin (which means lower cost of insulin) compared with those having longer duration of diabetes to achieve the same reduction in their HbA1c levels [34]. Furthermore, the ones with higher baseline HbA1c level or longer diabetes duration had higher frequency of minor hypoglycemia (Table 7). All of these suggest that to the insulin-naïve patients with T2DM uncontrolled by OADs, early initiation of BI therapy might provide an opportunity to achieve treatment goals with low cost and low risk of hypoglycemia.

After adding BI to an OAD-only treatment, cost of insulin therapy accounted for 48% of the total treatment costs. This percentage was similar to that observed in Canada (48.6%) [35], but is lower than that in the United States (75.5%) [36]. OADs medication costs accounted for 36.0% of the total treatment cost, higher than that among insulin users in western countries (range: 19.5%-27.0%) [35, 36]. This is not a surprising finding when considering the differences between Asian and Western cultures. Chinese patients prefer to use OADs rather than insulin injection, because they believe being treated with insulin causes family and friends to be more concerned about them, and that they will also be more dependent on their doctors [37]. Most Chinese patients view the insulin treatment as the last choice.

For patients using insulin injections, SMBG is recognized as a core component of effective diabetes self-management. However, little is known about the real-world frequency and true costs associated with SMBG. This study showed that

following addition of BI for 3 and 6 months, the frequency of SMBG doubled (from 2 times/month to 4 times/month) and SMBG-related costs accounted for around 7% of the total treatment cost for insulin users; the average cost of SMBG (including blood testing strips and lancets) per patient per day was around \$0.20. The percentage and daily cost of SMBG in ORBIT were much lower than those observed in western countries [35, 36] wherein SMBG accounted for approximately 23.1% to 41.6% of the total diabetes-related pharmacy costs, and the average cost per testing strip was \$0.79 to \$0.98. The difference between China and western countries might be due to the different methods of data collection. Previous studies on SMBG in western countries were all retrospective studies, with the number of blood testing strips calculated according to pharmacy-based SMBG testing. Moreover, in the aforementioned studies, at least one pharmacy claim for blood glucose testing strips was required. However, in ORBIT study, SMBG behavior was home-based instead of as prescribed by a physician, and patients decided whether to perform SMBG or not. Hence, not all patients in the ORBIT study had SMBG. Compared with previous studies that calculated SMBG cost according to pharmacy claim records (record of blood testing strips), the results of ORBIT may better reflect home-based SMBG frequency and cost, which is more pertinent to the practical self-management behavior of patients in China. Owing to the lack of awareness and skill of performing SMBG, home-based SMBG costs accounted for a lower percentage of costs in diabetes treatment.

This study also collected data on the frequency of hypoglycemia. Most hypoglycemic events were minor, and no requirement for medication or formal health care. Patients always dealt with hypoglycemia by food intake or more rest. Thus, costs of dealing with hypoglycemia were relatively low, accounting for only 0.1% of the total costs.

Strengths of this study included the large sample size (almost 20,000 participants) drawn from all major regions of China among a clinically relevant heterogeneous population. This enables economically valid assessment of the influences of introducing BI therapy on cost changes at the regional and hospital level under real-life clinical practice conditions. However, as shown in Table 1 and 2, differences exist in daily treatment cost change and times of cost increase among regions and hospitals, and attention needs to be paid when applying the

results of this study to specific regions or hospitals.

In ORBIT, the three most commonly used BIs (insulin glargine, insulin detemir, and NPH insulin) were considered as a whole group to assess the overall daily costs following addition of these BIs to insulin-naïve T2DM patients. Results on the costs of BI types in the subgroups were crude results without adjusting for the confounding factors. Therefore, further research have been planned to focus on cost comparison among the three most commonly used BIs in the real world, with adjustment for covariate variables such as baseline variables.

## 5. Conclusions

Adding-on BI therapy may increase the daily treatment cost by 1.5 times at 6 months. Early initiation of BI therapy may provide an opportunity to achieve treatment goals with low cost and low risk of hypoglycemia. For patients who are insulin naïve and uncontrolled by oral antidiabetic drugs, physicians and patients can predict the cost change once initiated basal insulin and make decision accordingly. Further studies are needed to compare the cost changes caused by specific basal insulin initiation, such as insulin glargine,

insulin detemir, and NPH insulin.

## Author Contributions

conceptualization, D. Z. and P. Z.; methodology, D. Z.; formal analysis, X. L. and J. J.; investigation, J. L. and W. J.; data curation, D. Z.; writing—original draft preparation, D. Z.; writing—review and editing, P. Z.; supervision, L. J.; funding acquisition, L. J.

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## Conflicts of Interest

Linong Ji reports 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. All other authors declare no conflict of interest.

## List of Supporting Information

*Table 5. Calculation of the weights for each region.*

Regions and provinces	Population in each province (Unit: 10000)	Prevalence of type 2 diabetes in each province (%)	Number of patients with type 2 diabetes in each province	Weight for each region <sup>†</sup>
Southwest				
Yunnan	4333	7.3	3163090	
Guizhou	3837	7.3	2801010	
Sichuan	8673	1.4	1214220	
Chongqing	3107	12.4	3852680	
Guangxi	4822	10.4	5014880	
All			16045880	0.10
Northwest				
Gansu	2593	10.4	2696720	
Qinghai	529	7.3	386170	
Ningxia	572	7.3	417560	
Tibet	267	7.3	194910	
Xinjiang	1905	14.3	2724150	
All			6419510	0.04
Mid-Yangtze River				
Hubei	5988	10.4	6227520	
Hunan	6629	7.3	4839170	
Jiangxi	4222	10.4	4390880	
Anhui	6338	14.3	9063340	
All			24520910	0.16
Mid-Yellow River				
Shaanxi	3674	7.3	2682020	
Shanxi	3294	12.4	4084560	
Henan	9613	14.3	13746590	
Inner Mongolia	2379	14.3	3401970	
All			23915140	0.15
South Coast				
Fujian	3466	12.4	4297840	
Guangdong	7859	18.75	14735625	
Hainan	803	10.4	835120	
All			19868585	0.13
East Coast				
Shanghai	1625	18.75	3046875	
Jiangsu	7381	12.4	9152440	





Characteristics	Region								
	Total	North Coast	Yangtze River	Southwest	Yellow River	East coast	South Coast	Northeast	Northwest
<24	8149 (42.9)	1105 (33.8)	1466 (48.6)	1352 (46.4)	1099 (38.8)	1074 (47.4)	1137 (57.3)	493 (29.5)	423 (40.8)
[24-28)	7927 (41.7)	1493 (45.6)	1171 (38.8)	1154 (39.6)	1302 (46.0)	896 (39.5)	662 (33.3)	788 (47.2)	461 (44.5)
≥28	2918 (15.4)	675 (20.6)	381 (12.6)	407 (14.0)	429 (15.2)	297 (13.1)	187 (9.4)	389 (23.3)	153 (14.8)
Regular OAD treatment duration group									
[0-3)	6998 (36.9)	1147 (35.1)	1131 (37.5)	1179 (40.5)	1104 (39.0)	521 (23.0)	730 (36.8)	722 (43.2)	464 (44.7)
[3-6)	4373 (23.0)	733 (22.4)	674 (22.3)	710 (24.4)	657 (23.2)	538 (23.7)	431 (21.7)	372 (22.3)	258 (24.9)
[6-9)	2974 (15.7)	520 (15.9)	506 (16.8)	410 (14.1)	429 (15.2)	423 (18.7)	303 (15.3)	232 (13.9)	151 (14.6)
≥9	4645 (24.5)	871 (26.6)	706 (23.4)	614 (21.1)	640 (22.6)	785 (34.6)	521 (26.2)	344 (20.6)	164 (15.8)
Macro complication									
No	16137 (85.0)	2630 (80.4)	2581 (85.5)	2572 (88.3)	2305 (81.4)	2023 (89.2)	1793 (90.2)	1307 (78.3)	926 (89.3)
Yes	2858 (15.0)	643 (19.6)	437 (14.5)	341 (11.7)	525 (18.6)	244 (10.8)	194 (9.8)	363 (21.7)	111 (10.7)
Micro complication									
No	13587 (71.5)	2260 (69.0)	2250 (74.6)	2120 (72.8)	2024 (71.5)	1926 (85.0)	1468 (73.9)	858 (51.4)	681 (65.7)
Yes	5408 (28.5)	1013 (31.0)	768 (25.4)	793 (27.2)	806 (28.5)	341 (15.0)	519 (26.1)	812 (48.6)	356 (34.3)
Number of OAD at v0									
1	8675 (45.7)	1260 (38.5)	1317 (43.6)	1297 (44.5)	1339 (47.3)	840 (37.1)	700 (35.2)	1315 (78.7)	607 (58.5)
2	8351 (44.0)	1638 (50.0)	1413 (46.8)	1273 (43.7)	1268 (44.8)	1113 (49.1)	929 (46.8)	336 (20.1)	381 (36.7)
≥3	1969 (10.4)	375 (11.5)	288 (9.5)	343 (11.8)	223 (7.9)	314 (13.9)	358 (18.0)	19 (1.1)	49 (4.7)
BI type at v1									
Glargine	13294 (70.0)	2138 (65.3)	2357 (78.1)	1923 (66.0)	1515 (53.5)	1768 (78.0)	1516 (76.3)	1267 (75.9)	810 (78.1)
Detemir	2385 (12.6)	349 (10.7)	285 (9.4)	411 (14.1)	314 (11.1)	210 (9.3)	340 (17.1)	320 (19.2)	156 (15.0)
NPH	3316 (17.5)	786 (24.0)	376 (12.5)	579 (19.9)	1001 (35.4)	289 (12.7)	131 (6.6)	83 (5.0)	71 (6.8)

HbA1c, glycated hemoglobin; BMI, body mass index; OADs, oral antidiabetic drugs; BI, basal insulin; NPH, neutral protamine Hagedorn; v0, visit 0; v1, visit 1.

Table 7. Clinical outcome at month 6 in overall and different subgroups.

Group variable	N	HbA1c reduction (%)	Minor hypoglycemia increase (times/person/year)	Weight gain (kg)
		Mean ± SD	Mean ± SD	Mean ± SD
Total	18,995	2.15±2.07	0.68±15.60	0.10±2.94
Regions				
North coast	3,273	1.98±1.86	0.78±14.86	0.05±2.87
Yangtze River	3,018	2.49±2.15	1.03±25.39	-0.13±2.66
Southwest	2,913	2.15±2.19	1.88±14.55	0.45±3.15
Yellow River	2,830	2.24±2.07	0.27±14.39	0.02±3.02
East coast	2,267	1.77±1.84	0.24±8.22	0.42±2.79
South coast	1,987	2.47±2.31	0.92±14.53	0.41±2.80
Northeast	1,670	2.05±2.04	-0.28±7.87	-0.50±3.12
Northwest	1,037	1.87±1.91	-0.20±8.84	0.08±3.22
Hospital level				
Secondary	9443	2.25±2.13	0.21±12.21	0.23±2.87
Tertiary	9552	2.04±1.99	1.18±18.53	-0.03±3.01
Age (years)				
<40	1277	2.68±2.31	1.04±11.86	-0.38±3.45
[40, 50)	4253	2.21±2.04	0.89±11.00	0.04±3.14
[50, 60)	6541	2.15±2.06	0.78±20.34	0.21±2.81
≥60	6924	2.01±2.03	0.39±13.20	0.13±2.83
Gender				
Male	9968	2.20±2.09	0.94±16.66	-0.00±3.14
Female	9027	2.09±2.04	0.39±14.31	0.23±2.71
Baseline HbA1c (%)				
[7, 8)	8532	0.91±1.14	0.14±18.82	-0.14±2.80
[9, 11)	6087	2.28±1.42	0.89±12.53	0.07±2.97
[11, 13)	3048	3.83±1.74	1.47±12.01	0.53±3.08
≥13	1328	6.13±2.25	1.58±10.95	0.91±3.17
Diabetes duration (years)				
<5	8805	2.47±2.19	0.75±17.13	-0.03±3.07
[5, 10)	5495	1.88±1.89	0.43±13.52	0.15±2.87
[10, 15)	3309	1.91±1.91	0.68±14.72	0.30±2.77
≥15	1385	1.75±1.97	1.14±14.96	0.31±2.72
Education degree				
Primary school or illiterate	5154	2.31±2.18	0.61±14.75	0.35±2.87

Group variable	N	HbA1c reduction (%)	Minor hypoglycemia increase (times/person/year)	Weight gain (kg)
		Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD
Junior high school	5859	2.18 $\pm$ 2.11	0.91 $\pm$ 20.05	0.25 $\pm$ 3.02
Senior high school	4724	2.02 $\pm$ 1.95	0.53 $\pm$ 13.63	-0.08 $\pm$ 2.86
Junior college	1965	2.03 $\pm$ 1.95	0.79 $\pm$ 9.62	-0.24 $\pm$ 3.04
Bachelor degree or higher	1293	2.04 $\pm$ 2.00	0.31 $\pm$ 8.78	-0.31 $\pm$ 2.88
Current residence				
Urban	13019	2.02 $\pm$ 2.00	0.67 $\pm$ 12.26	-0.02 $\pm$ 2.93
Rural	5976	2.42 $\pm$ 2.19	0.71 $\pm$ 21.09	0.38 $\pm$ 2.96
Patient resource				
Outpatient clinic	8361	1.88 $\pm$ 1.85	0.65 $\pm$ 18.90	0.20 $\pm$ 2.72
Inpatient ward	10634	2.37 $\pm$ 2.20	0.70 $\pm$ 12.28	0.03 $\pm$ 3.11
Out of pocket costs (%)				
<20	2940	1.96 $\pm$ 2.00	0.46 $\pm$ 9.59	0.12 $\pm$ 2.89
[20, 40)	7202	2.04 $\pm$ 1.97	1.02 $\pm$ 18.06	-0.05 $\pm$ 2.96
[40, 60)	4276	2.33 $\pm$ 2.23	0.83 $\pm$ 12.98	0.19 $\pm$ 3.01
[60, 80)	2045	2.44 $\pm$ 2.19	-0.14 $\pm$ 16.12	0.17 $\pm$ 3.05
$\geq$ 80	2528	2.12 $\pm$ 1.95	0.37 $\pm$ 17.12	0.34 $\pm$ 2.70
BMI (kg/m <sup>2</sup> ) at v1				
<24	8149	2.38 $\pm$ 2.21	0.72 $\pm$ 12.83	0.93 $\pm$ 2.67
[24, 28)	7927	2.00 $\pm$ 1.97	0.72 $\pm$ 19.16	-0.21 $\pm$ 2.79
$\geq$ 28	2918	1.90 $\pm$ 1.84	0.47 $\pm$ 11.09	-1.33 $\pm$ 3.32
Regular OAD treatment duration (years)				
<3	6998	2.60 $\pm$ 2.21	1.00 $\pm$ 17.97	-0.05 $\pm$ 3.11
[3, 6)	4373	1.94 $\pm$ 1.99	0.30 $\pm$ 13.00	0.13 $\pm$ 2.92
[6, 9)	2974	1.87 $\pm$ 1.88	0.12 $\pm$ 16.57	0.18 $\pm$ 2.82
$\geq$ 9	4645	1.84 $\pm$ 1.90	0.90 $\pm$ 13.14	0.26 $\pm$ 2.76
Macro complications				
No	16137	2.19 $\pm$ 2.08	0.85 $\pm$ 15.54	0.12 $\pm$ 2.95
Yes	2858	1.92 $\pm$ 1.98	-0.25 $\pm$ 15.88	0.04 $\pm$ 2.89
Micro complications				
No	13587	2.19 $\pm$ 2.06	0.86 $\pm$ 15.83	0.12 $\pm$ 2.93
Yes	5408	2.05 $\pm$ 2.08	0.23 $\pm$ 15.00	0.07 $\pm$ 2.97
Number of OADs before v1				
1	8675	2.40 $\pm$ 2.16	0.73 $\pm$ 12.59	-0.00 $\pm$ 2.97
2	8351	1.98 $\pm$ 1.96	0.57 $\pm$ 12.49	0.14 $\pm$ 2.88
$\geq$ 3	1969	1.75 $\pm$ 1.95	0.90 $\pm$ 31.48	0.43 $\pm$ 3.06
BI type at v1				
Glargine	13294	2.09 $\pm$ 2.01	0.27 $\pm$ 11.53	0.06 $\pm$ 2.89
Detemir	2385	2.17 $\pm$ 2.01	1.77 $\pm$ 26.04	-0.20 $\pm$ 2.88
NPH	3316	2.35 $\pm$ 2.29	1.45 $\pm$ 18.72	0.49 $\pm$ 3.13

HbA1c, glycated hemoglobin; BMI, body mass index; OADs, oral antidiabetic drugs; BI, basal insulin; NPH, neutral protamine Hagedorn; v0, visit 0; v1, visit 1; v3, visit 3; SD, standard deviation.

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