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ORIGINAL RESEARCH

Where to Initiate Basal Insulin Therapy: Inpatient or Outpatient Department? Real-World Observation in China

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Background: This study aims to compare the effectiveness of initiating insulin therapy in inpatient and outpatient settings during a 6-month follow-up period among patients with type 2 diabetes mellitus (T2DM) in real-world settings.

Materials and Methods: The study was based on the ORBIT study, a real-world observational study which recruited patients with inadequate glycemic control by oral antidiabetic drugs (OAD) and initiated basal insulin (BI). We compare difference in initiation and evolution of insulin therapy and glycemic control after six months were compared between patients initiating basal insulin in the inpatient department (inpatient initiators) and those starting in outpatient (outpatient initiators) among participants without rehospitalization during the six months follow-up.

Results: Among all 18,995 participants in the ORBIT study, 56.0% were inpatient initiators and 44.0% outpatient. We conducted in-depth analysis among 14,860 patients without rehospitalization, 8129 inpatient initiators and 6731 outpatient initiators. (1) Inpatient initiators had lower insulin therapy persistence during six months (64.2%) than outpatient ones (78.6%) ($p<0.001$), which was mainly explained by more therapy switches from basal-bolus regimen to other therapies among inpatient initiators (50.1%) than that among outpatient initiators (37.5%) ($p<0.001$). (2) Inpatient initiation had a higher proportion of people achieving glucose targets (HbA1c <7%) than outpatient initiation. However, the benefit of inpatient initiation versus outpatient initiation was mainly observed among patients persisting with the initial insulin therapies (46.3% vs 39.5% $p<0.001$), rather than those nonpersistent (37.3% vs 36.2%, $p=0.723$). (3) Among patients with HbA1c <9%, taking only one OAD and without complications at baseline, inpatient insulin initiation did not show a higher proportion of people achieving glucose target than outpatient initiation (adjusted odds ratio=0.96, 95% CI: 0.76–1.21).

Conclusion: For patients with HbA1c ≥9%, who were taking more than one OAD and had complications at baseline, initiating insulin treatment during hospitalization has a higher proportion of people achieving glucose target than that in the outpatient department, but the premise is that the initial therapy is acceptable and can be maintained after discharge. Patient-centered approach with co-agreed decision-making to select a suitable insulin regimen should be strengthened.

Keywords: type 2 diabetes mellitus, T2DM, basal insulin, BI, hospitalization, outpatient, glycemic control

Introduction

The prevalence of type 2 diabetes mellitus (T2DM) in Chinese adults was estimated to be 10.9%. However, only 36.5% were aware of their condition, and only 49.2% of treated patients had optimal glycemic control.[1] It is significant to treat T2DM patients with effective therapy at the early stage.

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The current guidelines recommend stepwise treatment intensification for maintaining optimal glucose control in T2DM.[2,3] When oral antidiabetic drugs (OADs) and lifestyle management fail to maintain adequate glycemic control, the intensification therapy of exogenous insulin is required. Basal insulin (BI) alone is typically added to OAD(s) as initial insulin therapy unless the patient is still markedly hyperglycemic or symptomatic and will require the addition of bolus insulin to achieve appropriate glycemic targets eventually.[2,3]

Several large randomized control trials indicated that timely insulin therapy reduced the long-term risk of microvascular and macrovascular diseases.[4–6] Various insulin regimens including basal, prandial and premix had been developed. However, no clinical guideline had recommended the most effective starting insulin regimen for patients with suboptimal glycemic control by OADs. The appropriate choice of starting insulin regimen according to baseline A1C, FPG, lifestyle and eating habit influence the effect, cost and quality of life for T2DM patients.[7]

Hospitalization is a significant opportunity to intensify therapy for previously diagnosed but poorly controlled T2DM.[8,9] Evidence showed that physicians and patients might concern with the complexity of insulin therapy and algorithms during initiation and adjustment, the fears of hypoglycemia, and the limited patient education in outpatient settings. Therefore, hospitalization to initiate insulin therapy is preferred.[10,11] Also, medical reimbursements for inpatients are usually higher than outpatients. As a result, initiating insulin in inpatient settings is a usual practice in China.

Observational Registry of Basal Insulin Treatment (ORBIT) study has reported a significant positive effect of add-on BI on glycemic control for both inpatient and outpatient initiation.[12] Uncertainty remains on whether the improvements on glycemic control differ between that initiated insulin therapy in inpatient or outpatient settings among patients with T2DM in real-world settings. Therefore, this study will provide insights into the optimal use of starting insulin in clinical practices.

Materials and Methods

Study Design and Participants

Data analyzed in this study were from the Observational Registry for Basal Insulin therapy study (ORBIT).[12] This was a 6-month, prospective, real-world study, conducted in China from 2011 to 2013. Participants included were insulin-naive patients with T2DM aged 18–80 years who initiated BI therapy due to uncontrolled hyperglycemia (HbA1c ≥7%) by OADs, with both the type and dose of BI at physicians' discretion and patients' willingness. Each participant was interviewed at baseline when initiated BI and at six months to collect study information.

Exclusion criteria were as follows: patients prescribed any type of insulin in the last two years (except for the situation of discontinued use within less than one month before each visit), clinically significant acute major organ or systemic disease or other condition that would create difficulty for the six-month follow-up as judged by the investigator, current or planned pregnancy or lactating women, lost to follow-up, or subjects involved in another clinical trial at least one month before the study enrolment. Patients with rehospitalization during 6-month study period were also excluded in the in-depth comparison analysis to avoid significant influence on results since rehospitalization would broadly adjust previous insulin therapy.

The ORBIT study protocol complied with the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of Peking University (No. IRB00001052-11070) and, when necessary, by local IRBs. Written informed consents were obtained from all patients.

Data Collection and Definition

Data from each participant were collected through study-specific records and traditional medical forms, consisting of baseline information on socio-demographic characteristics (gender, age, education level, location, hospital levels and medical insurance), patient resources (non-intensive care inpatient or outpatient), diabetes complications (coronary heart disease, stroke, peripheral vascular disease, diabetic kidney disease, diabetic retinopathy, peripheral neuropathy, and others), hypoglycemia events, and current treatment regimen (types of OADs, types of insulin regimen and insulin dose). Hypoglycemic events in the past one month (%) were defined as the percentage of participants who reported at least one of any kind of hypoglycemia in the past one month at baseline. Hypoglycemia was

categorized as severe hypoglycemia, documented symptomatic, asymptomatic, probable symptomatic or pseudo-hypoglycemia according to the American Diabetes Association recommendations.[13] Physical examination (body height and weight) and laboratory test (HbA1c and fasting plasma glucose (FPG)) were conducted according to a standard protocol and recorded at baseline and 6-month. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. A basal-bolus regimen was defined as being prescribed with prandial insulin in addition to BI.

All eligible participants were divided into two groups based on the scenes where they initiate the insulin therapy at baseline: inpatients and outpatients. The "inpatients" group are those initiating insulin therapy during hospitalization, while the "outpatients" first prescribe the treatment at the clinic.

The basal alone regimen is defined as using basal insulin only, including glargine, detemir or Neutral Protamine Hagedorn (NPH) insulin, and basal-bolus regimen is defined as taking bolus insulin in addition to basal insulin (glargine, detemir or NPH).

The titration of insulin dose without changing the insulin regimen was considered as persistence. Patients who persisted in initiating insulin regimen at baseline were defined as "persistence with original insulin regimen group". While patients who switched initial insulin therapy after six months, including changing to another insulin regimen or stopped insulin therapy were defined as "non-persistence with original insulin regimen".

HbA1c, oral antidiabetic drugs and complication (HOC) reflected patients' disease condition at baseline was calculated based on HbA1c level (HbA1c ≥9% scored as one and HbA1c <9% as zero) plus number of OADs (OAD numbers ≥2 scored as one and OAD number = 1 as zero) and complications before insulin initiation (having complications in the past scored as one and without complication in the past as zero). Therefore, if a patient had HbA1c level ≥9%, OAD numbers ≥2 with complications before insulin initiation, the HOC level was calculated as three, being the most severe situation in this study, whilst being the least severe scored as zero for patients with HbA1c <9%, OAD number =1 and having no complication before insulin therapy. Proportions of patients who reached HbA1c target (HbA1c <7%) at six months were calculated by insulin persistence groups, stratified by baseline HbA1c (≥9% or <9%), complications (yes or no) and OAD numbers (≥2 or 1) used before insulin initiation.

Statistical Analysis

Descriptive statistics were calculated as frequencies (n) and percentages (%) for categorical variables; means and SD for continuous variables. t-tests or Chi-square tests were used to assess differences in baseline characteristics between inpatient and outpatient, as appropriate. Proportions of patients who persisted with the initial insulin regimen, switched to another insulin regimen different from the initial regimen or stopped insulin therapy after 6 months were calculated.

Multivariate logistic regression was performed to compare the difference in glycemic control between "inpatients" and "outpatients", insulin persistent and nonpersistent groups, and among different HOC groups. In multivariate logistic regression, regions of patients recruited, gender, age, education, location, hospital levels, medical insurance, disease duration, OAD treatment duration, BMI, baseline HbA1c levels and basal insulin alone or basal-bolus insulin initiation were adjusted.

All statistical analyses were performed using STATA 13, with two-sided $P<0.05$ considered statistically significant.

Results

Among all 18,995 participants in the ORBIT study, 56.0% were inpatient initiators, and 44.0% were outpatient. 14,860 participants without rehospitalization during the six months follow-up were included for in-depth analysis, of which 8129 (54.7%) and 6731 (45.3%) were from inpatient and outpatient settings, respectively. Figure 1 shows the patient selection procedure.

Participants' Characteristics

Table 1 presents the baseline demographics and clinical characteristics of patients included in the analysis. Overall, the participants had a mean age of 55.3 years, with an average diabetes duration of 6.4 years, OAD treatment duration of 5.6

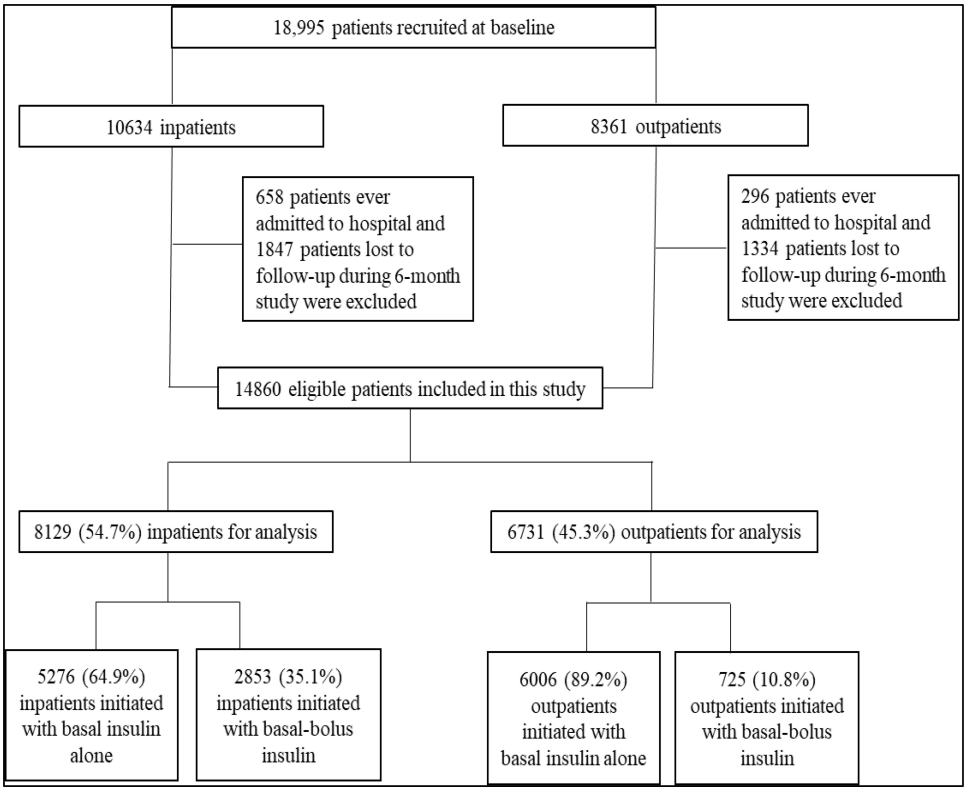

Figure 1 Flow of patients included in the analysis. Patients ever admitted to hospital or lost to follow-up after insulin therapy initiation during 6-month study period were excluded.

years. 35.9% participants had complications and the mean HbA1c level was 9.6% before insulin initiation. The baseline characteristics of inpatient initiators and outpatient initiators with or without persisting to initial insulin therapy at six months are shown at Supplementary Table 1.

Table 1 Baseline Characteristics of Inpatients and Outpatients Initiated with Basal Insulin

Characteristics	Overall N=14860	Inpatients N=8129	Outpatients N=6731	p value
Demographics				
Male, n (%)	7873 (53.0)	4408 (54.2)	3465 (51.5)	0.001
Age (years), mean ± SD	55.3 ± 10.3	55.7 ± 10.3	54.8 ± 10.3	<0.001
Education (senior high school or higher), n (%)	6406 (43.1)	3631 (44.7)	2775 (41.2)	<0.001
Urban residence, n (%)	10,119 (68.1)	5689 (70.0)	4430 (65.8)	<0.001
Hospital levels, n (%)				
Secondary hospitals	7774 (52.3)	4437 (54.6)	3337 (49.6)	<0.001
Tertiary hospitals	7086 (47.7)	3692 (45.4)	3394 (50.4)	
Out-of-pocket ratio (%), mean ± SD	41.5 ± 27.1	35.9 ± 22.4	48.3 ± 30.5	<0.001
BMI (kg/m^2), mean± SD	24.8 ± 3.4	24.8 (3.4)	24.8 (3.3)	0.962
Diabetes duration (years), mean ± SD	6.4 ± 5.2	6.4 ± 5.4	6.4 ± 5.1	0.391
HbA1c (%), mean ± SD	9.6 ± 2.0	9.8 ± 2.1	9.3 ± 1.8	<0.001
HbA1c ≥ 9%, n (%)	8015 (53.9)	4692 (57.7)	3323 (49.4)	<0.001
FPG level (mmol/L), mean ± SD	11.6 ± 4.0	11.7 ± 4.3	11.5 ± 3.5	<0.001

(*Continued*)

Table 1 (Continued).

Characteristics	Overall N=14860	Inpatients N=8129	Outpatients N=6731	p value
Complication in the past (Yes), n (%)	5327 (35.9)	3480 (42.8)	1847 (27.4)	<0.001
Numbers of OADs ≥2, n (%)	8003 (53.9)	3902 (48.0)	4101 (60.9)	<0.001
OAD treatment duration (years), mean ± SD	5.6 ± 5.0	5.5 ± 5.1	5.8 ± 4.9	0.006
Participants experienced hypoglycaemia in the past 1-month (Yes), n (%)	801 (5.4)	437 (5.4)	364 (5.4)	0.931
Insulin initiation at baseline				
Basal-only insulin, n (%)	11,282 (75.9)	5276 (64.9)	6006 (89.2)	<0.001
Basal-bolus insulin, n (%)	3578 (24.1)	2853 (35.1)	725 (10.8)	<0.001
Total dose of insulin (IU), mean ± SD	17.4 (12.5)	19.9 (14.2)	14.3 (9.3)	<0.001

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; OAD, oral antidiabetic drugs.

Patterns of Insulin Therapy at Initiation

75.9% of patients initiated with basal insulin alone and 24.1% initiated with a basal-bolus regimen, and the mean insulin dose at initiation was 17.4 IU/day. Compared with the outpatients, inpatients showed a much higher proportion of initiating with basal-bolus insulin (35.1% vs 10.8%) and higher insulin dose (19.9 IU/day vs 14.3 IU/day) at BI initiation (Table 1).

Evolution of Insulin Therapy After Six Months

Figure 2 shows the evolution of insulin therapy after 6-month follow-up for inpatient and outpatient initiation. Overall, 64.2% of inpatients persisted with the initial insulin therapy after six months, while the number for outpatients was 78.6%. Among the 3578 patients initiated with a basal-bolus regimen, the six months persistent rate was 37.5% (1071/2853) for inpatients and 50.1% (363/725) for outpatients. Of the 11,282 patients who initiated basal insulin alone, the persistent rate was 78.6% (4146/7276) and 82.0% (4927/6006), respectively (Figure 2). Figure 2 shows the rates of switching to other insulin regimen or stopping insulin treatment.

Glycemic Control Between Persistent and Nonpersistent Groups

After adjustment for potential confounders, the overall proportion achieving HbA1c <7% for patients persisted with initial insulin therapy was 42.9% after 6 months, significantly higher than patients who changed the initial regimen (37.0%, p<0.001). A similar difference in glycemic control also supported the persistent sub-group among participants stratified by the baseline HbA1c levels, complications in the past and OAD numbers at baseline (Figure 3).

Glycemic Control Among Persistent Inpatient and Outpatient Initiators

In the subgroup analysis, inpatient initiators showed a higher proportion of achieving HbA1c <7% compared to outpatient initiators (46.3% vs 39.5%, p<0.001; Table 2) for patients who persisted with the initial insulin therapy after six months. After stratified by the baseline HbA1c levels, complications in the past and OAD numbers at baseline, inpatient initiators showed a higher proportion of people achieving glucose target than outpatient initiators in the persistent group (Table 2).

Table 3 shows the comparison of proportion achieving HbA1c <7% between inpatient and outpatient insulin initiation among those persisting with initial insulin therapy after 6 months according to HOC level that reflected the severity of T2DM at baseline. Compared with outpatient initiators, inpatient initiators showed a higher proportion of people achieving glucose target in patient with HOC level from 1 to 3, especially among participants with the condition of HbA1c ≥9%, with complications and OAD numbers ≥2 at baseline after adjusted for regions of patients recruited, gender, age, education, location, hospital levels, medical insurance, disease duration, OAD treatment duration, BMI, baseline HbA1c levels and basal insulin alone or basal-bolus insulin (adjusted OR (95% CI): 2.06 (1.49–2.86), p<0.001). Whereas for patients with the condition of HbA1c <9%, without complications and OAD number=1 at baseline, inpatient initiation

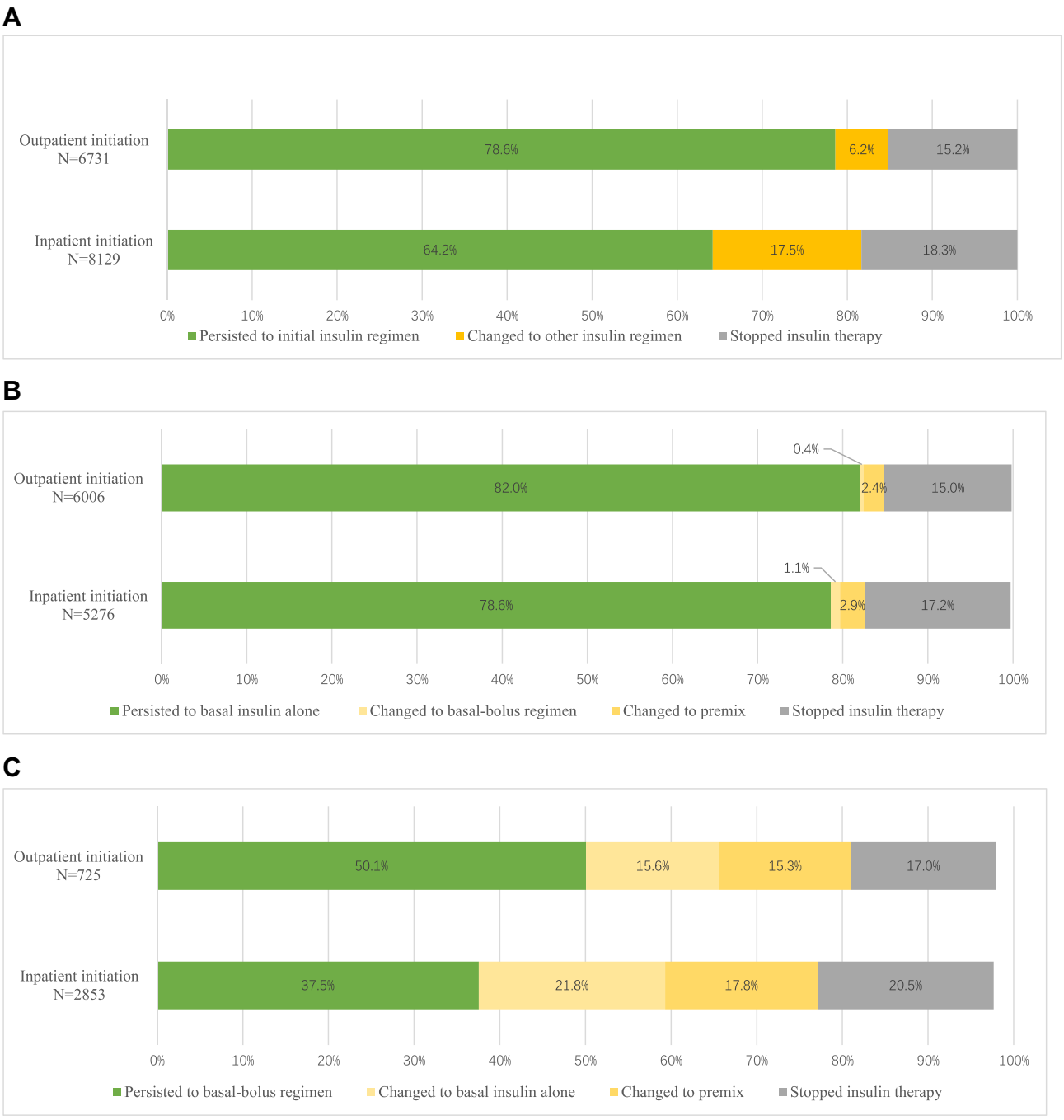

Figure 2 Evolution of insulin therapy after 6-month follow-up for inpatient and outpatient initiation. (**A**) Treatment transition after 6 months among all patients. (**B**) Treatment transition after 6 months among patients initiated with basal insulin alone. (**C**) Treatment transition after 6 months among patients initiated with basal-bolus insulin.

did not show a difference in glycemic control compared to outpatient initiation (adjusted OR (95% CI): 0.96 (0.76–1.21), p=0.726) (Table 3).

Glycemic Control Among Nonpersistent Inpatients and Outpatients

No significant difference was observed between inpatient and outpatient initiation for the proportion achieving HbA1c <7% among nonpersistent patients (37.3% vs 36.2%, p=0.723, Table 2). Among patients who did not persist in initiating

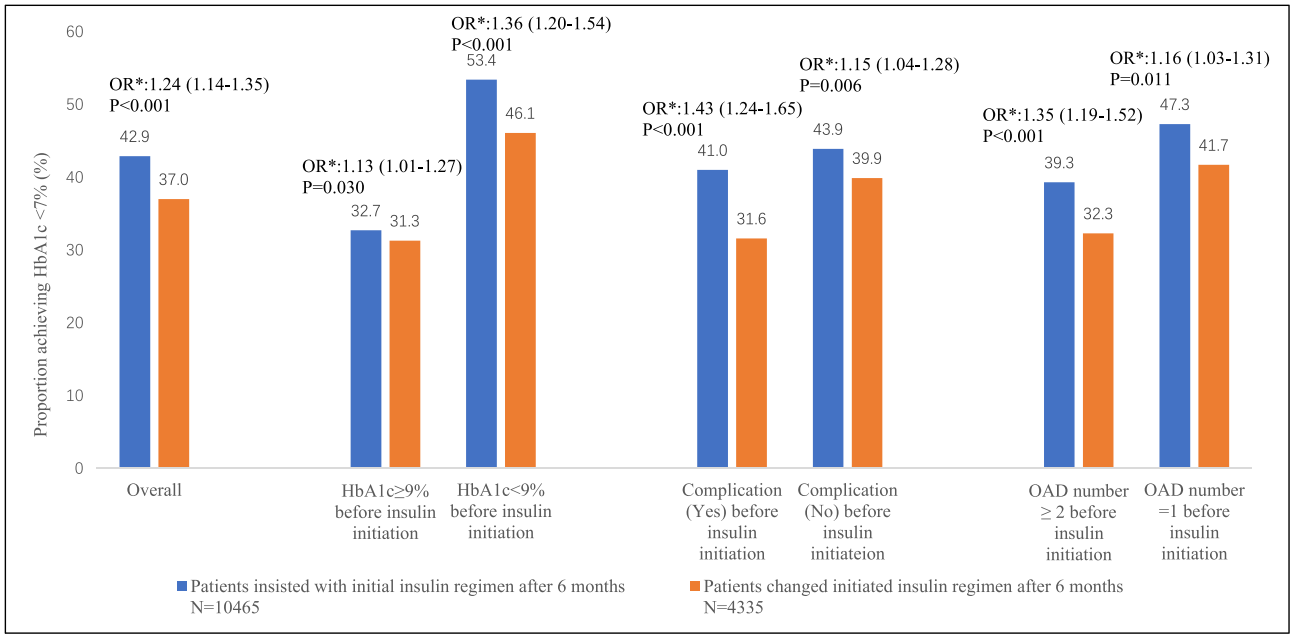

Figure 3 Proportion achieving HbA1c <7% between patients persistent or nonpersistent to initial insulin therapy after 6 months.
Note: 60 patients were not included in the analysis due to no results after 6 months. *Odds ratios were adjusted for region, patient resource (inpatient or outpatient initiation), age, gender, education, residence, hospital levels, disease duration, BMI, initiation with basal only or basal-bolus insulin and baseline HbA1c levels.

insulin therapy, patients with inpatient initiation only showed a higher proportion of people achieving glucose targets (33.0% vs 27.2%, p=0.038) in baseline HbA1c ≥9% stratification (Table 2).

Discussion

In this multi-center, observational study conducted in a nationwide representative sample of T2DM patients with suboptimal glycemic control by OADs in China, basal-bolus regimen was initiated approximately one-third in the inpatient setting and 10% in the outpatient setting. For participants initiated with basal-bolus regimen, only around one-third of inpatient initiators and half of outpatient initiators persisted with the initial insulin therapy after six months. Overall, patients persisted with the initial insulin therapy had a higher proportion of people achieving glucose targets after six months compared to patients who switched. Inpatient initiators showed higher glycemic control compared to

Table 2 Subgroup Analysis of Proportion Achieving HbA1c <7% Among Persistent and Nonpersistent Groups Between Inpatient Initiators and Outpatient Initiators After 6 Months

Baseline Characteristics Before Insulin Initiation	Patients Persistent to Initial Insulin Therapy		Adjusted Odds Ratio*	p value	Patients Nonpersistent to Initial Insulin Therapy		Adjusted Odds Ratio*	p value
	Inpatient Initiators N=5196†	Outpatient Initiators N=5269†			Inpatient Initiators N=2898‡	Outpatient Initiators N=1437†		
Overall	46.3 (44.9–47.6)	39.5 (38.2–40.9)	1.34 (1.23–1.47)	<0.001	37.3 (35.6–39.1)	36.2 (33.7–38.7)	1.03 (0.88–1.20)	0.723
HbA1c≥9%	36.8 (35.0–38.6)	28.2 (26.4–29.9)	1.37 (1.20–1.56)	<0.001	33.0 (30.9–35.1)	27.2 (24.2–30.4)	1.25 (1.01–1.55)	0.038
HbA1c<9%	57.2 (55.2–59.2)	50.0 (48.1–51.9)	1.26 (1.12–1.43)	<0.001	45.5 (42.4–48.6)	47.0 (43.2–50.9)	0.85 (0.68–1.06)	0.146
Complication (Yes)	43.6 (41.6–45.7)	37.0 (34.6–39.6)	1.41 (1.21–1.64)	<0.001	31.4 (28.8–34.1)	32.5 (27.9–37.5)	0.87 (0.66–1.16)	0.353
Complication (No)	48.3 (46.5–50.1)	40.5 (38.9–42.1)	1.31 (1.18–1.47)	<0.001	41.5 (39.2–43.9)	37.5 (34.6–40.4)	1.18 (0.99–1.42)	0.071
OAD number ≥ 2	43.8 (46.5–50.1)	35.9 (34.3–37.6)	1.45 (1.29–1.64)	<0.001	33.6 (31.1–36.1)	30.2 (27.1–33.5)	1.10 (0.88–1.37)	0.402
OAD number =1	48.6 (46.7–50.5)	45.5 (43.3–47.7)	1.16 (1.01–1.32)	0.033	40.8 (38.3–43.3)	43.8 (40.0–47.7)	0.94 (0.76–1.16)	0.551

Notes: †60 patients in total were not included in the analysis due to no HbA1c data at 6-month follow-up. *Odds ratios were adjusted for region, age, gender, education, residence, hospital levels, disease duration, BMI, initiation with basal only or basal-bolus insulin and baseline HbA1c levels.
Abbreviation: OAD, oral antidiabetic drugs.

Table 3 Comparison of Proportion Achieving HbA1c <7% After 6 Months Between Inpatient and Outpatient Insulin Initiation by HOC Level Among Patients Persisting with Initial Insulin Therapy

HOC Level	Inpatient (N=5196)		Outpatient (N=5269)		Adjusted Odds Ratio*	p value
	n	HbA1c<7% rate, % (95% CI)	n	HbA1c<7% rate, % (95% CI)		
3	600	32.7 (29.0–36.5)	457	19.0 (15.7–22.9)	2.06 (1.49–2.86)	<0.001
2	1856	39.9 (37.7–42.2)	1849	33.6 (31.5–35.8)	1.31 (1.12–1.52)	0.001
1	2043	50.9 (48.7–53.0)	2208	42.1 (40.0–44.1)	1.47 (1.28–1.68)	<0.001
0	697	61.4 (57.7–65.0)	755	58.9 (55.4–62.4)	0.96 (0.76–1.21)	0.726

Notes: HOC: The HbA1c, oral antidiabetic drugs and complication (HOC) level reflected patients' condition at baseline and was calculated based on HbA1c level (HbA1c≥9% scored as one and HbA1c <9% as zero) plus OADs numbers (OAD numbers ≥2 scored as one and OAD number = 1 as zero) and complications before insulin initiation (having complications in the past scored as one and without complication in the past as zero). *Odds ratios were adjusted for region, age, gender, education, residence, hospital levels, disease duration, BMI, initiation with basal only or basal-bolus insulin and baseline HbA1c levels.

outpatient initiators after six months among participants with good persistence, while no difference between inpatient and outpatient initiation was observed among those nonpersistent with the initial insulin therapy. However, inpatient initiators did not show a higher proportion of people achieving glucose targets compared to outpatient initiators for participants with HbA1c <9%, taking only one OAD and without complications at baseline.

The overall proportion (24.1%) of initiating BI with basal-bolus regimen in this study was higher than studies in western and other Asian countries. One study by Kim et al reported basal-bolus insulin only accounted for 1.6% when initiating BI,[14] Whilst Patrick et al reported 13% of patients using basal-bolus as the BI initiation regimen.[15] In comparison, patients in our study had a higher average HbA1c level (9.6%) than Kim et al's study (9.2%),[14] a shorter diabetes duration (6.4 years) compared to previous studies ranging from 8.9 to 11.7 years.[14,16–19] This might be due to a low proportion of early diabetes diagnoses since only 36.5% of Chinese diabetes patients were aware of their diagnosis,[1] contributing to severe hyperglycemia with a shorter duration of diagnosed T2DM. Chinese guidelines recommend initiating BI when HbA1c ≥7% after three months of OAD treatment.[2] Therefore, this finding may further reflect a delay of insulin initiation, which led to a high proportion of initiation with basal-bolus regimen.

In our study, one-third of inpatients initiated with basal-bolus regimen compared to only 10.8% of outpatients. Guidelines recommend the addition of prandial insulin to basal insulin as antihyperglycemic therapy in patients with uncontrolled blood glucose after triple therapy consisting of three oral agents or drugs with well-titrated basal insulin.[2,3] However, our study observed around 55% (1976/3578) patients initiated with basal-bolus regimen prescribed only one oral agent before insulin therapy and the majority were inpatient initiators (80%, 1575/1976). One reason might be patients with only one OAD before insulin initiation might have more complications and worse renal function than those with two or more OADs, so they tended to initiate a basal-bolus regimen at hospitalization. Further study is needed to investigate the reason behind this.

As observed in our results, inpatient initiation had overall a higher proportion of people achieving glucose target compared to outpatient initiation if they had good persistence, especially for those with comparatively higher HbA1C, more complications and more oral agents at baseline. However, the advantages of inpatient initiation did not exist in those with poor persistence. The 6-month persistent rate of basal insulin therapy after BI initiation in our study was similar to the 1-year rates reported by some studies from large commercial insurance databases with approximately 55–80% of T2DM patients prescribed basal insulin being persistent within the year after initiation.[20,21] However, with regard to basal-bolus regimen, the persistent rate in our study was lower compared to previous studies, particularly for inpatient initiation, only 38% of inpatient initiators persisted in basal-bolus therapy after six months. The difference in the persistent rates may also be attributed to the different definitions and data resources. The survey reported a 51% persistent rate among insulin-naïve patients after six months using questionnaire-based phone interview,[22] and another defined nonpersistent as the absence of reimbursement for insulin over six months or one year after the initiation date with insurance claims.[23] By comparison, we defined persistence by treatment status reported by physicians at 6-month

visits, which would be more strict. In addition, as patients were followed up for six months, we could not know whether they resumed initial insulin therapy after the study period, and it was only a temporary interruption.

For patients initiated with basal-bolus in our study, more than half switched to other regimens or even stopped insulin after 6 months, especially among inpatient initiators. 22% inpatient initiators switched to basal insulin alone, 18% switched to premix and 21% stopped insulin after 6 months. The majority (98% for inpatient initiation and 99% for outpatient initiation) of patients initiating a full basal-bolus regimen injecting three more times for bolus insulin per day in addition to BI. The guideline recommended basal-bolus should be offered individualized with patient-centered stepwise approach through titration of bolus doses whatever during hospitalization or initiated from outpatient settings.[3,24,25] Because it would be burdensome for patients to comply with the basal-bolus regimen, the high switching rate in patients initiating with basal-bolus observed in our study might because some physicians used a short-term intensive insulin therapy during hospitalization and would switch to other regimens or stopped insulin after discharging from hospital. For patients taking basal-bolus insulin as short-term intensification, a Chinese clinical recommendation of insulin therapy after insulin initiation published in 2018 suggested basal-bolus insulin can convert to premix or basal insulin only when HbA1c is well controlled during intensification.[26] Since we did not record if the patients were for short-term intensification, we could not know how many patients switched basal-bolus regimen because their glycemia was well controlled during intensification therefore change to a simplified regimen. However, the overall glycemic control was worse among those switched initial insulin observed in our study. Thus, this may still indicate the well-discussion between patients and physicians when initiating insulin therapy to determine discreet insulin regimen that patients could persist in the long run. Moreover, education of patients about the long-term benefits of lowering their blood glucose and training on how to achieve the glycemic control with a low risk of hypoglycemia and weight gain[27] with a patient-driven insulin titration regimens[28] may help to increase the persistence.

We found no significant difference was observed for glycemic control among patients with comparatively low baseline HbA1c level (<9%), no complication and took only one OAD before insulin initiation. This finding may suggest that hospitalization to initiate insulin therapy for patients with HbA1c <9%, taking only one OAD and without complications at baseline may not be a better choice than outpatient settings. Our nationally representative data indicated around 13% (1940/14,860) patients had baseline HbA1c level <9%, with no complication and took only one OAD before insulin initiation, among whom 49% initiated insulin at outpatient and 51% at hospitalization. Since insulin will be eventually required in most T2DM patients due to the progressive nature of the disease,[2] outpatient initiation instead of hospitalization for patients with less severe disease condition may reduce large amounts of medical resources and cost. Outpatient initiators still showed worse glycemic control generally observed in our study compared to inpatient initiators, the improvement for the quality of outpatient insulin initiation would be critical.

Strengths and Limitations

This study examined the patterns of insulin therapy when initiated from inpatient or outpatient settings, and the following 6-month persistence and effectiveness based on a large nationally representative sample of Chinese adults with T2DM, which provides robust estimates of insulin initiation, evolution and effectiveness in real-world settings. A major strength of this study is the observational study design that reflects the actual use and change of insulin therapy. Secondly, the large sample size with the recruitment of patients with different socio-economic backgrounds, diverse regions, and from different hospital levels to ensure the heterogeneous of the study results. With the increased prevalence of T2DM, more patients will initiate insulin treatment at outpatient or primary healthcare settings whatever from developing or developed countries in the future. Therefore, this study may provide insight to other settings especially developing countries.

There are several limitations to our study. First, we only included T2DM patients willing to use BI at their insulin initiation, while patients willing to initiate other types of insulin such as premix insulin were excluded. Secondly, the inclusion criteria of HbA1c level were 7% or higher, which missed those who initiated BI with a HbA1c level lower than 7%, therefore the mean level of HbA1c at insulin initiation might be overestimated. Given that premix insulin is also an option for insulin initiation with effective and safety being proved, and more than 15% patients initiated with basal-bolus regimen switched to premix after 6 months indicated in this study, further study involving premix insulin would help us picture a more representative insulin initiation status in China. Second, this study did not collect information on marital

status or family/social support. Given the significant role of the social/environmental support for type 2 diabetes care and control, we will consider including these information in the future research.

Conclusion

This study suggests a large proportion of patients switched insulin regimen after initiation, especially for inpatients with basal-bolus regimen initiation. Inpatient initiators showed a higher proportion of people achieving glucose target, however the necessity of hospitalization to initiate insulin among patients with less severe conditions should be further studied in the future. As more insulin initiation would be at outpatient settings with the T2DM patients increment and cost-effectiveness consideration, the improvement for the quality of outpatient initiation should be strengthened and patient-centered insulin initiation to select suitable starting insulin are needed to increase the insulin persistence in the future.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

The ORBIT study protocol complied with the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of Peking University (No. IRB00001052-11070) and, when necessary, by local IRBs. Written informed consents were obtained from all patients.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. Minyuan Chen and Puhong Zhang, are joint first authors.

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Disclosure

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