ORIGINAL RESEARCH

Delays in Insulin Initiation among Patients with Type 2 Diabetes Mellitus in Southeast China: A Retrospective, Real-World Study

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Purpose: To describe the extent of delays in insulin initiation, analyze its impact on glycemic control, and explore factors influencing delayed insulin initiation among Chinese type 2 diabetes mellitus (T2DM) patients.

Methods: A real-world, retrospective cohort study with regional electronic health records from Fuzhou, southeast China was conducted among T2DM patients. Adult patients uncontrolled with oral antidiabetic drugs (OADs; $HbA_{1c} \geq 7\%$) and initiated on insulin treatment were included. Time to insulin initiation was described. After propensity-score matching, Wilcoxon rank-sum test and chi-square test were used to compare follow-up HbA_{1c} (first HbA_{1c} 3 months after insulin initiation) between timely (initiated insulin within 6 months after OAD failure) and delayed (initiated after 6 months) insulin-initiation groups. Sensitivity analysis was also performed by linear and logistic regression. Factors associated with delayed insulin initiation were explored using logistic regression.

Results: A total of 940 patients were included, with mean±SD age 66.3±11.9 years. In sum, 328 had HbA_{1c} recorded 3 months after insulin initiation. After propensity-score matching (1:1 matching), 184 patients were included for further analysis. Median follow-up HbA_{1c} was lower in the timely-initiation group than the delayed-initiation group (7.25% vs 8.25%, P=0.009). Patients in the timely initiation group also had higher odds of achieving HbA_{1c} <7% (OR=3.15, P=0.001). Results were confirmed by logistic regression. Hypertension, coronary artery disease, baseline HbA_{1c}, and hospital level at insulin initiation were associated with delays in insulin initiation.

Conclusion: Timely insulin initiation after OAD failure is associated with better glycemic control.

Keywords: type 2 diabetes mellitus, therapeutic inertia, delayed insulin initiation, glycemic control, HbA_{1c}

Introduction

The worldwide prevalence of diabetes mellitus (DM) is increasing, and the estimated burden is expected to be 693 million cases by the year 2045.[1] The prevalence of DM was estimated to be 10.9% in Chinese adults in a 2013 national survey, and about half of treated patients (50.8%) had inadequate glycemic control.[2,3] DM is associated with increased risks of retinopathy and nephropathy as well as a two- to fourfold-increased risk of cardiovascular diseases.[4]

The target of glucose control for most DM patients is glycosylated hemoglobin (HbA_{1c}) <7% (53 mmol/mol). Although oral antidiabetic drugs (OADs) are

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administered, due to disease progression and deterioration of pancreatic β-cell function, some type 2 DM (T2DM) patients who are unable to control blood glucose with OADs often require treatment intensification with insulin to maintain target HbA_{1c} levels.[5] The American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD), and China Diabetes Society (CDS) recommend treatment intensification if target HbA_{1c} has not been achieved after 3 months. However, delays in treatment intensification with insulin are common among patients with T2DM.[6,7] Therapeutic inertia, defined as the failure to initiate or intensify therapy in a timely manner, is one of the main reasons for uncontrolled hyperglycemia in T2DM according to evidence-based clinical guidelines.[8] Delays in insulin initiation after OAD failure is common in patients with T2DM, and this reluctance toward insulin initiation could be due to patient-, physician-, or health-care system–related factors.[9]

Delays in treatment intensification can occur at all stages of T2DM treatment: from initiation of oral therapy after failure of lifestyle modification with proper diet and regular exercise, use of OADs and insulin as combination therapy, or intensification of insulin. Previous studies conducted in other countries have demonstrated the negative impact of delays in treatment intensification on glycemic control,[10] but there is a paucity of data from China, even though T2DM has becoming a major public health challenge in China. As such, the purpose of this retrospective study using a regional electronic medical record database in southeast China was to provide real-world evidence of the extent of delays in insulin initiation, the impact of delays in insulin initiation on glycemic control after insulin initiation, and to explore the potential factors related to delays in insulin initiation among Chinese patients with T2DM.

Methods
Data Source
This study extracted data from a regional electronic health–record database in Fuzhou, southeast China. This regional database, a pilot of the China National Health Big Data project, contains major clinical information from multiple information systems of 37 hospitals. It includes information on >2 billion medical records belonging to 23 million patients from September 2001 to January 2018. The database contains major clinical information systems, such as hospital information systems,

laboratory information systems, electronic medical records, and picture archiving and communication systems. Data collection, processing, and management was authorized by the Fuzhou Health Commission. All data were structured, standardized, and managed in an integrated platform.[11] The database is not freely available, so review and approval were obtained from China Electronics Corporation data.

Study Design and Patient Population
In this retrospective cohort study, patients with T2DM (as defined by ICD10 or previously treated with OADs) aged ≥18 years who had been initiated on insulin treatment after failure of an OAD regimen were identified. Specifically, patients were included in the study if they had a minimum of one record of insulin prescription, OAD prescription prior to insulin initiation and a minimum of one record of preinitiation HbA_{1c} ≥7%, and a minimum of one record of postinitiation HbA_{1c}. Patients were excluded if insulin had been prescribed only transiently after OAD failure to control blood glucose during surgery or patients who had received glucagon-like peptide-1 receptor agonist (GLP-1RA). This study was approved by the China Ethics Committee of Registering Clinical Trials (ChiECRCT-20,180,224). The study was designed and conducted in accordance with the ISPE Guidelines for Good Pharmacoepidemiology Practice. This observational study used data previously collected, and did not impose any form of intervention. Therefore, informed consent was not required.

Definitions
The last OAD regimen was defined as the OADs used for treatment just before insulin initiation. The index date was defined as the date of OAD failure. If preinitiation HbA1c levels were always ≥7%, the index date (OAD failure) was the date of first HbA_{1c} reading ≥7%. If HbA_{1c} levels were not always ≥7%, the index date (OAD failure) was the date of first HbA_{1c} ≥7% following the last HbA_{1c} <7%. Preinitiation HbA1c, defined as HbA_{1c} in the 3 months after the first prescription of the last OAD regimen to insulin initiation, was used to identify the index date.

In our study, delayed insulin initiation was defined as lack of insulin initiation within 6 months after OAD failure. The period between the index date and insulin initiation was considered the time to insulin initiation. Patients were divided into two groups according to time to insulin

initiation: timely initiation (≤6 months) and delayed initiation (>6 months). HbA_{1c} measured on the index date was considered baseline HbA_{1c}. Follow-up HbA_{1c}, defined as first HbA_{1c} measured 3 months after insulin initiation, was used for comparison between the delayed-initiation and timely-initiation groups.

Study Outcomes

The study outcome was the extent of delays in insulin initiation after OAD-regimen failure in patients with uncontrolled DM. The number of patients initiated on insulin treatment within 3 months, 3–6 months, and after 6 months was estimated. Also, the impact of delays in insulin initiation on glycemic control was assessed. This was done by comparing follow-up HbA_{1c} levels, and follow-up HbA_{1c}-target attainment (<7%) between the delayed-initiation group and timely-initiation group after propensity-score matching (PSM). Furthermore, univariate and multivariate logistic/linear regression models were used for sensitivity analyses to investigate the association between therapeutic inertia and glycemic control. Factors associated with delays in insulin initiation were also assessed by multivariate logistic regression.

Statistical Analysis

Descriptive statistics (means, SD, medians, IQRs, frequency, and percentages) are used to report continuous and categorical variables. PSM was performed to balance the differences in confounding variables between the delayed-initiation and timely-initiation groups. Based on literature reviews and[6,12] clinical and research experience, variables selected from baseline characteristics for PSM were age-group, sex, last OAD regimen, baseline HbA_{1c}, hypertension, dyslipidemia, coronary artery disease, and hospital level at insulin initiation. A 1:1 greedy PSM algorithm using calipers of a specific width was deployed to compare patients between the delayed-initiation and timely-initiation groups. The best matches were defined as pairs with the highest digit match (0.0001) on PS. The matching algorithm proceeded sequentially to the next-highest digit match. No more matches were made below the lowest allowed digit of 0.1.

After PSM, Wilcoxon rank-sum and chi-square tests were performed to compare follow-up HbA_{1c} levels and target-HbA1c attainment between the delayed- and timely-initiation groups, respectively. In order to further analyze the association between delays in insulin initiation and glycemic control, linear and logistic regression were used as sensitivity analyses, with delays in insulin initiation serving as the independent variable, continuous follow-up HbA_{1c} levels or categorical follow-up HbA_{1c} (<7% or ≥7%) as the dependent variable, and the same variables used for matching in PSM as covariates. Box–Cox transformation was used to achieve approximate normality of the distribution of continuous follow-up HbA_{1c} levels to make them compatible for linear regression.[13] HbA_{1c} <7% was given the response profile "1" and HbA_{1c} ≥7% the response profile of "0".

The potential factors possibly associated with delays in insulin initiation — age-group, sex, last OAD regimen, baseline HbA_{1c}, hypertension, dyslipidemia, coronary artery disease, stroke, therapeutic department, and hospital level — at insulin initiation were explored using the univariate and multivariate logistic regression models, and ORs with 95% CIs were calculated. Two-tailed $P<0.05$ was considered statistically significant. When conducting logistic regression, delayed-initiation patients were given the response profile "1" and timely-initiation patients the response profile "0". All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).
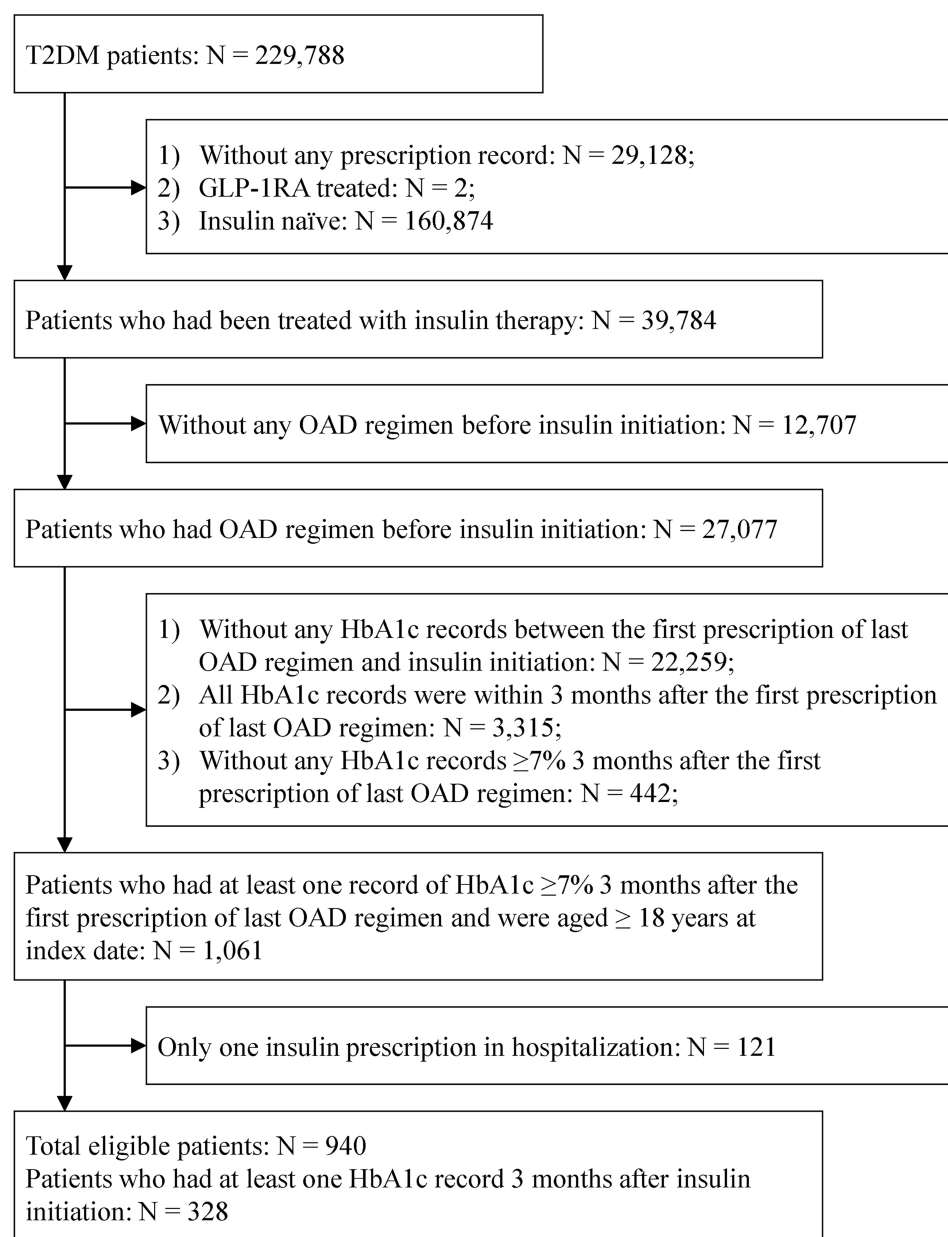
Results
Baseline Characteristics

A total of 940 patients were found eligible, of which 328 had HbA_{1c} measurement available after insulin initiation (Figure 1). The mean±SD age of the patients included in the study was 66.3±11.9 years, and 51.5% were female. The majority (82.9%) of patients had been treated with two or more OADs prior to insulin initiation. Mean±SD baseline HbA1c was 9.4%±1.9%, with 49% of patients having an HbA_{1c} ≥9% (Table 1). The 328 patients with available HbA_{1c} measurements were subjected to PSM. After PSM matching, 184 patients (92 in each group) were included for further analysis.

Delays in Insulin Initiation in Chinese Patients

Among 940 T2DM patients who had failed to have blood glucose controlled on OAD treatment, 615 (65.4%), 64 (6.8%), and 261 (27.8%) were initiated on insulin within 3 months, 3–6 months, and after 6 months, respectively, which indicated that more than a quarter of patients experienced delays in insulin initiation (>6 months) in this study.

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│ T2DM patients: N = 229,788                          │
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         │
         │      ┌──────────────────────────────────────────────────────┐
         │─────▶│ 1) Without any prescription record: N = 29,128;      │
         │      │ 2) GLP-1RA treated: N = 2;                           │
         │      │ 3) Insulin naïve: N = 160,874                        │
         │      └──────────────────────────────────────────────────────┘
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┌─────────────────────────────────────────────────────┐
│ Patients who had been treated with insulin therapy: N = 39,784 │
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         │      ┌──────────────────────────────────────────────────────┐
         │─────▶│ Without any OAD regimen before insulin initiation: N = 12,707 │
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         ▼
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│ Patients who had OAD regimen before insulin initiation: N = 27,077 │
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1) Without any HbA1c records between the first prescription of last OAD regimen and insulin initiation: N = 22,259;
2) All HbA1c records were within 3 months after the first prescription of last OAD regimen: N = 3,315;
3) Without any HbA1c records ≥7% 3 months after the first prescription of last OAD regimen: N = 442;

Patients who had at least one record of HbA1c ≥7% 3 months after the first prescription of last OAD regimen and were aged ≥ 18 years at index date: N = 1,061

Only one insulin prescription in hospitalization: N = 121

Total eligible patients: N = 940
Patients who had at least one HbA1c record 3 months after insulin initiation: N = 328

Figure 1 Screening of eligible patients.
Abbreviations: GLP1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycosylated hemoglobin; OAD, oral antidiabetic drug.

Impact of Delays in Insulin Initiation on Glycemic Control

The impact of delays in insulin initiation in both the delayed- and timely-initiation groups was assessed by considering glycemic control after insulin initiation. The 328 patients who had HbA_{1c} records available for 3 months after insulin initiation were eligible for PSM. All baseline and clinical characteristics were well balanced after PSM (Supplementary Table 1). After PSM, 184 patients were used for comparison between the delayed- and timely-initiation groups, with 92 patients in each group. Among 184 PSM patients, Wilcoxon rank-sum test revealed median HbA_{1c} levels to be significantly lower in the timely-initiation group than the delayed-initiation group (7.25% vs 8.25%, P=0.009), suggesting the beneficial impact of early initiation of insulin therapy (Table 2). In sum, 38% of patients in the timely-initiation group attained the treatment goal of HbA_{1c} <7% after 3

Table 1 Demographic and Clinical Characteristics of Enrolled Patients

	Patients (n=940)
Demographics	
Age (years)#	
Mean ± SD	66.3±11.9
Median (IQR)	66 (58–75)
Age-group (years)	
<65	401 (42.66%)
≥65	539 (57.34%)
Sex	
Male	456 (48.51%)
Female	484 (51.49%)
Last OAD regimen	
One OAD	161 (17.13%)
Two OADs	322 (34.26%)
Three or more OADs	457 (48.62%)
Medical insurance status	
With	710 (96.47%)
Without	26 (3.53%)
Missing	204
Therapeutic department at insulin initiation	
Endocrinology	472 (50.27%)
Others	467 (49.73%)
Missing	1
Hospital level at insulin initiation	
Secondary	226 (24.04%)
Tertiary	714 (75.96%)
Clinical characteristics	
Baseline HbA$_{1c}$ level (%)#	
n	940
Mean ± SD	9.37 ± 1.94
Median (IQR)	8.90 (7.80–10.55)
Baseline HbA$_{1c}$ group	
7≤ and <8	278 (29.57%)
8≤ and <9	201 (21.38%)
≥9	461 (49.04%)
Comorbidities	
Hypertension	627 (66.70%)
Dyslipidemia	627 (66.70%)
Hyperuricemia	13 (1.38%)
Coronary artery disease	205 (21.81%)

(*Continued*)

Table 1 (Continued).

	Patients (n=940)
Demographics	
Atherosclerosis	58 (6.17%)
Stroke	125 (13.30%)
Complications	
Diabetic foot	4 (0.43%)
Retinopathy	1 (0.11%)
Neuropathy	11 (1.17%)

Notes: #Age and baseline HbA$_{1c}$ levels were abnormally distributed. Data were presented as n (%) unless otherwise indicated.
Abbreviations: HbA$_{1c}$, glycosylated hemoglobin; OAD, oral antidiabetic drug.

months of insulin treatment, while the corresponding figure of patients attaining the treatment goal in the delayed-initiation group was only 16% (*P*=0.001) after PSM (Table 3). The sensitivity analyses were conducted among 328 patients using linear and logistic regression models to further depict the association between delays in insulin initiation and glycemic control and to adjust for confounders. Delays in insulin initiation served as the independent variable, and continuous (linear) or categorical follow-up HbA$_{1c}$ levels (logistic) served as the dependent variable. Since the distribution of continuous HbA$_{1c}$ levels were skewed, a Box–Cox transformation was performed before inclusion as a dependent variable in linear regression. Further, to rule out the effect of confounding factors, such as age, sex, last OAD regimen, baseline HbA$_{1c}$, hypertension, dyslipidemia, and coronary artery disease, at baseline and hospital level at insulin initiation, these factors were adjusted in the regression model. Multivariate linear regression showed that there was no statistically significant difference in Box–Cox transformed mean follow-up HbA$_{1c}$ levels between the groups (*P*=0.193, Supplementary Table 2). Multivariate logistic regression revealed the timely-initiation group had higher odds of attaining the treatment goal (OR 2.52, 95% CI 1.26–5.04; *P*=0.009) than the delayed-initiation group (Supplementary Table 3).

Factors Associated with Delays in Insulin Initiation

A logistic regression model was also used to explore potential factors associated with delays in insulin initiation. Multivariate logistic regression analysis revealed that presence of one OAD regimen (OR 1.59, 95% CI 1.04–-2.41; *P*=0.03) or a double-OADs regimen (OR 1.44, 95%

Table 2 Wilcoxon Rank-Sum Test of Median Follow-Up HbA$_{1c}$ Levels (%) Before and After PSM

Group	Before PSM				After PSM			
	n	Median (IQR)	Statistics	*P*-value	n	Median (IQR)	Statistics	*P*-value
Timely initiation	234	8.00 (7.00, 9.20)	0.68	0.495	92	7.25 (6.60, 8.75)	−2.60	0.009*
Delayed initiation	94	8.25 (7.20, 8.90)			92	8.25 (7.15, 8.85)		

Note: *P<0.05.
Abbreviations: HbA$_{1c}$, glycosylated hemoglobin; PSM, propensity-score matching.

Table 3 Chi-Square Test of Follow-Up HbA$_{1c}$-Goal Attainment (<7%) Before and After PSM

	Before PSM				After PSM			
	Timely initiation	Delayed initiation	OR (95% CI)	*P*-value	Timely initiation	Delayed initiation	OR (95% CI)	*P*-value
<7%	58 (24.79%)	15 (15.96%)	1.74 (0.93–3.25)	0.082	35 (38.04%)	15 (16.30%)	3.15 (1.57–6.32)	0.001*
≥7%	176 (75.21%)	79 (84.04%)			57 (61.96%)	77 (83.70%)		

Note: *P<0.05.
Abbreviations: HbA$_{1c}$, glycosylated hemoglobin; PSM, propensity-score matching.

CI 1.03–2.03; *P*=0.034) prior to insulin initiation, HbA$_{1c}$ level 7%–8% (OR 3.09, 95% CI 2.16–4.41; *P*<0.001) or 8%–9% (OR 2.47, 95% CI 1.66–3.67; *P*<0.001), tertiary-class hospital (OR 1.95, 95% CI 1.29–2.94; *P*=0.001), presence of hypertension (OR 1.69, 95% CI 1.17–2.45; *P*=0.005), and coronary artery disease (OR1.60, 95% CI 1.10–2.34; *P*= 0.015) were associated with a higher possibility of experiencing delays in insulin initiation (Supplementary Table 4).

Discussion

In this study, delays in insulin initiation (defined as lack of insulin initiation within 6 months after OAD failure) were observed in 27.8% of patients with T2DM. Since there is no standard threshold duration for defining delays in treatment intensification among patients with OAD-treatment failure, different studies have reported different thresholds. In our study, insulin was the only treatment-intensification regimen analyzed. Yu et al showed 57.5% of patients with poor glycemic control receiving monotherapy with metformin were intensified by add-on therapy, including insulin.[14] Previously conducted studies have reported significant delays in insulin initiation after OAD failure.[15–17] Rubino et al showed

estimated delays in insulin initiation of 1.8 years in 25% and 4.9 years in 50% of T2DM patients after OAD failure.[16] Trends in delayed insulin initiation and intensification have been observed globally as well. In the Western Pacific region, around 66% of T2DM patients had HbA$_{1c}$ >9% at initiation of insulin, despite 74% having been treated with two or more OADs,[18] whereas in Middle East and north African regions, 67.6% had HbA$_{1c}$ >9% at insulin initiation, despite 68.3% of them having been treated with two or more OADs.[19] The disparity in the published literature might be due to different definitions used for delays in intensification and also the intensification regimens used. Our study findings substantiate the proportion of delays in insulin treatment in real-world health-care settings in current clinical practice in China.

In our study, an HbA$_{1c}$ level of 7% (53 mmol/mol) or higher was considered the baseline for patient selection. However, other studies have considered HbA$_{1c}$ levels of ≥6.5 or 8%.[20,21] Moreover, our study considered treatment intensification as addition of insulin alone after OAD failure. In contrast, other studies have considered addition of another OAD after metformin to intensify the treatment regimen[20] or addition of a third OAD or injectable drug to the previous OAD regimen.[21] Also, in our study there were many insulin-

experienced patients without HbA$_{1c}$ ≥7% prior to insulin initiation (excluded), which indicated that Chinese health-care providers might intensify treatment by referring to fasting or postprandial blood–glucose levels other than HbA$_{1c}$. Therefore, future research may consider these as supplementary indicators to HbA$_{1c}$ when judging OAD-regimen failure to control blood glucose.

The main analyses revealed that after PSM, median follow-up HbA$_{1c}$ was lower and the percentage of patients achieving the HbA$_{1c}$ target of <7% was higher in the timely-initiation group than the delayed-initiation group. The result of HbA$_{1c}$-goal attainment was confirmed by sensitivity multivariate logistic regression, but the result of average follow-up HbA$_{1c}$ was different between the Wilcoxon rank-sum test and sensitivity linear regression (Box–Cox transformation). The reason is that the Wilcoxon rank-sum test tests the difference in median follow-up HbA$_{1c}$ level, while linear regression tests the difference in mean Box–Cox transformed follow-up HbA$_{1c}$ level. Also, because of the skewed distribution of follow-up HbA$_{1c}$ levels, medians would be a more robust indicator of central tendency and a better choice to describe average follow-up HbA$_{1c}$. Our findings are in line with other studies.[6,12] Fu and Sheehan used 6 months as the threshold to define delays in insulin initiation, and reported that HbA$_{1c}$ dropped from 9.4% to 7.9% in patients who had had insulin initiation within 6 months of OAD-treatment failure, while, the corresponding change in HbA$_{1c}$ was from 9.0% to 8.2%. The mean change in HbA$_{1c}$ was also significantly greater in the timely-initiation group (−0.33%, 95% CI −0.41% to −0.25%) within 1 year of follow-up, which is in line with our current study. Other studies have also shown large delays in treatment intensification to be associated with poor glycemic levels and increased incidence of vascular complications.[16,22,23]

Early initiation of insulin is beneficial in recovery and preservation of β-cell function, achieving tight glycemic control, altering disease progression, and preventing cardiovascular risk.[24,25] This was highlighted by Goodall et al, who compared the clinical consequences of delayed insulin initiation versus timely initiation. This study reported increased life expectancy (approximately 0.61 years), quality-adjusted life expectation (0.34 years), and also significant reductions in DM-related complications among timely insulin–initiated T2DM patients.[15] Another study demonstrating real-world clinical and economic outcomes among early versus delayed insulin initiation

reported that 32% of patients that had insulin initiated early showed significant reductions in HbA$_{1c}$, concluding that early insulin initiation may be cost-effective in controlling hyperglycemia compared to delayed initiation.[25]

This study also explored potential factors influencing delays in insulin initiation. A low HbA$_{1c}$ level at the index date was one of the factors associated with higher odds of experiencing delays in insulin initiation. Further, HbA$_{1c}$ >9% was the strongest influencing factor for insulin initiation. Our findings are comparable with other similar studies.[10,21,26] Additionally, patients receiving one or more OAD regimens in our study were associated with higher odds of experiencing delayed initiation of insulin. This might be because physicians are more likely to increase the dose or add another OAD to intensify treatment in Chinese patients treated with one or two OADs with poor glycemic control. However, patients receiving three or more OADs with poor glycemic control were more likely to be intensified with insulin. Similar findings have been observed in other studies with patients receiving two or more OADs at the time of insulin initiation with HbA$_{1c}$ ≥9%.[18,19]

In our study, the presence of comorbidities, such as coronary artery diseases and hypertension, was associated with higher odds of delays in insulin initiation. This could be because patient visits are time-constrained, and the physician and patient may have prioritized to treat a comorbidity, which might have led to delays in treatment intensification.[28] All these comorbidities have been reported in previous studies to be linked to a likelihood of delays in intensification of therapy.[27,29-31] Furthermore, in our study health-care providers in tertiary-care hospitals were less likely to ensure timely initiation of insulin than in secondary hospitals. This could be because patients visit tertiary hospitals mostly when their glucose level is high or they have been unable to be controlled in lower-tier hospitals. This suggests that the clinical situation of patients in tertiary-care hospitals may be different. However, previous studies have shown that health-care providers in tertiary-are hospitals tend to intensify treatment with insulin after OAD failure, because of better knowledge of DM management, updated recommendation guidelines, and less concern about hypoglycemic events.[30,31] Furthermore, studies suggest that specialists are more likely to use insulin therapies[32] and that they tend to initiate insulin treatment sooner than primary-care physicians.[33] This probably reflects a referral bias, with specialists managing the most advanced and complex patients and hence those

with the worst glycemic control. However, in this study we had no relevant data to assess differences in delays in insulin initiation between specialists and primary-care physicians.

The cause of delays in insulin initiation is complex. It is challenging for both health-care providers and patients to overcome. On the part of the patient, consequences of hypoglycemia, inconvenience of self-injection and monitoring blood glucose, concerns of weight gain, or the unacceptability of insulin injection could lead to rejection and nonadherence to treatment with insulin. Bailey et al suggested that a consideration of clinical and organizational context is necessary to reinforce timely administration of insulin, especially with respect to time constraints for diagnosis and management of comorbidities, health-care costs, and appreciation of patient concerns.

One of the strengths of this study is that the database considered covers multiple and different levels of hospitals within the city, which allowed for better capturing of medical information and patient visits. In this study, PSM was used and was well balanced to correlate with the timing of insulin initiation and HbA_{1c} outcomes. Univariate and multivariate logistic/linear regression models were additionally used to test the robustness of the PSM results.

Limitations

Our study has limitations that should be taken into consideration. As it was an observational study, we cannot conclude that the association between delayed insulin initiation and poor outcomes is causal, although we included a number of covariates in PSM and regression, which should reduce but not necessarily eliminate residual confounding of unmeasured variables. For instance, such factors as poor economic conditions, poor adherence to treatment, and low health literacy could delay insulin initiation and also make the patients' ability to control their blood glucose worse, which means that delayed insulin could be a mediated index variable between these factors and follow-up HbA_{1c}. Additionally, the data obtained were confined primarily to Fuzhou, capital of Fujian Province in southeast China, and hence the study findings might not be an ideal representation of clinical practice in other parts of China.

Conclusion

This retrospective cohort analysis showed that more than a quarter (27.8%) of patients with T2DM had delayed initiation of insulin. Delays in timely insulin initiation were associated with poor glycemic control. More insightful studies are required to investigate the long-term benefits of timely insulin initiation and to establish reasons for delays in insulin initiation. This in turn will help health-care providers raise awareness of timely initiation of insulin therapy among patients unresponsive to OADs.

Ethical Approval and Informed Consent

This study was approved by the China Ethics Committee of Registering Clinical Trials (ChiECRCT-20,180,224). Ethical approval was obtained from the Chinese Clinical Trial Registry (ChiCTR), and the ChiECRCT was responsible for the review process. The approval statement reads as follows. This is a retrospective research based on electronic medical records of secondary and tertiary hospitals in Fuzhou. As there is no direct risk toward the objectives, informed consent is not required. The research conforms with medical research ethics and is approved to be conducted in accordance with the research protocol.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, took part in drafting the article or revising it critically for important intellectual content, gave final approval to the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

Li Zhou, Xiao Ma, and Hong Chen are employees of Lilly. Ke Wang was an employee of Lilly at the time of manuscript preparation. Pin Chen has nothing to disclose. Li Zhou reports personal fees from Eli Lilly and Company

during the conduct of the study. The authors report no other potential conflicts of interest for this work.

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