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Population profile and glycemic control following initiation or switch of injectable therapies in Tianjin, China: A real-world retrospective cohort study of adults with type 2 diabetes

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ABSTRACT

Aims: To evaluate characteristics and glycemic outcomes in individuals with type 2 diabetes using injectable therapies in real-world clinical practice in Tianjin, China.

Materials and methods: Data from inpatients and outpatients receiving injectable therapies between January 2015 and December 2019 were collected from the Tianjin regional electronic medical records and retrospectively analyzed. Seven cohorts were identified, including individuals initiating injectable therapies (premixed insulin [*n* = 4,687], basal insulin [4,177], or glucagon-like peptide-1 receptor agonists [541]) or switching injectable therapies (premixed insulin to basal insulin [1,298], basal insulin to premixed insulin [1,457], basal insulin to basal + bolus insulin [1,772], or glucagon-like peptide-1 receptor agonists to basal insulin ± glucagon-like peptide-1 receptor agonists [82]).

Results: In participants initiating therapy, glycated hemoglobin and fasting plasma glucose were highest in the basal insulin cohort, while among participants switching therapy, the highest values were in the basal insulin ± glucagon-like peptide-1 receptor agonists cohort. Initiating therapy with premixed or basal insulin and switching from basal insulin to basal + bolus insulin improved glycemic control over 12 months. A mean delay in initiating therapy of up to 13 months after oral glucose-lowering drug failure was observed, with 60% having a delay of >6 months. This delay was associated with a lower proportion achieving glycemic control 3 months after initiation.

Conclusions: Effectiveness was not observed at all time points in all cohorts, suggesting some treatments were not used in the appropriate population. Delays in initiating injectable therapies were observed and were associated with poor glycemic control.

INTRODUCTION

China has the highest number of individuals with diabetes of any country globally, in part due to its large population[1]. In 2021, 140.9 million adults (aged 20–79 years) had diabetes in China, with an increase to 174.4 million expected by 2045[1].

The goals of diabetes treatment are to prevent or delay disease-related complications and maintain quality of life, which is achieved by adequate glycemic control[2]. Treatment intensification with injectable therapies is recommended in individuals with sub-optimal glycemic control on oral glucose-lowering drugs (GLDs) alone, whereas in individuals with sub-optimal glycemic control on injectable therapy, treatment adjustment or intensification is recommended[2,3]. Available injectable therapies

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include insulin (rapid- and short-acting [bolus insulin], intermediate and long-acting [basal insulin (BI)], premixed) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) administered alone or in combination. Guidelines recommend not delaying treatment intensification or adjustment[3], given that delays in treatment modifications, and thus glycemic control, can increase the risks of adverse microvascular and cardiovascular outcomes[4–6] and mortality[7], and can make subsequent achievement of adequate glycemic control more difficult[8].

A substantial proportion of individuals with diabetes in China do not achieve adequate glycemic control. Surveys of Chinese individuals with type 2 diabetes (T2D) indicate that only 20–50% had glycated hemoglobin (HbA1c) <7% (<53 mmol/mol)[9–12], suggesting that treatment adjustment and intensification are not being appropriately managed.

We conducted a study to evaluate the characteristics, the time from oral GLD failure to injection initiation and glycemic outcomes of individuals with T2D using injectable therapies in real-world clinical practice in a large urban center in China, with the aim of assisting in understanding treatment gaps and developing approaches to improve outcomes in these individuals.

MATERIALS AND METHODS

Study design and participants

This was a retrospective longitudinal cohort study of individuals with T2D initiating or switching injectable therapies in Tianjin, a metropolis in Northern China. Data for adult inpatients and outpatients (≥18 years old) who had ≥2 clinical visits pertaining to their diabetes and prescriptions for anti-diabetic therapy between January 2015 and December 2019 were collected from the Tianjin Healthcare and Medical Big Data Platform, which includes electronic medical records from 75 hospitals (39 tertiary and 36 secondary hospitals). Seven treatment cohorts were identified, including participants who initiated injectable therapies after oral GLD treatment (Cohort 1: premixed insulin; Cohort 2: BI; Cohort 3: GLP-1 RA) or those who switched from one injectable therapy regimen to another (Cohort 4: premixed insulin to BI; Cohort 5: BI to premixed insulin; Cohort 6: BI to BI + bolus insulin; Cohort 7: GLP-1 RA to BI ± GLP-1 RA). All treatment regimens could be given with or without oral GLD. Further definitions for each treatment cohort are provided in Table S1.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The study protocol was approved by the ethics committee of the Chu Hsien-I Memorial Hospital (approval number: ZXYJNYYhMEC2022-1). As this was a retrospective study, informed consent was not required; the waiver of informed consent was approved by both Chu Hsien-I Memorial Hospital and the Human Genetic Resource Administration of China.

Baseline variables and outcomes

Participant demographics, physical examination (weight and height), laboratory tests (HbA1c, fasting plasma glucose [FPG], postprandial glucose [PPG]), and oral GLD treatment patterns were collected in the baseline period, defined as the 3 months prior to the index date (the date when the participant initiated or switched injectable therapy), with the exception of diabetes complications and comorbidities, for which baseline was defined as any time before the index date.

Outcomes were (i) HbA1c and FPG at 3, 6, 9, and 12 months (±1.5 months) after initiating/switching injectable therapy and the change in HbA1c and FPG from baseline; (ii) glycemic control rates, defined as the proportion of participants achieving an HbA1c <7% (<53 mmol/mol) or an FPG <7 mmol/L at 3, 6, 9, and 12 months after initiating/switching injectable therapy; (iii) the time from oral GLD failure (defined as an HbA1c ≥7% [≥53 mmol/mol] on oral GLD therapy, or FPG ≥7 mmol/L if no HbA1c records were available) to initiation of injectable therapy; (iv) factors associated with poor glycemic control (defined as an HbA1c ≥7% [≥53 mmol/mol]) 3 months after initiating/switching injectable therapy; and (v) factors associated with delayed initiation of injectable therapy.

Statistical analysis

Descriptive statistics were used, with continuous variables summarized as means and standard deviations (SD) and categorical variables summarized as number and proportion of participants. The mean ± standard error (SE) changes in HbA1c and FPG from baseline to different time points were analyzed within each treatment cohort using paired *t*-test based on non-missing values. For the time from oral GLD failure to initiation of injectable therapy, the mean ± SD was determined for Cohorts 1–3 (with a one-way analysis of variance [ANOVA] used to test the differences between cohorts) as well as the proportion of participants who initiated injections in ≤3, 3–6, and >6 months (with the chi-squared test used to test the differences between cohorts). Subsequent characteristics at the time of initiation by different durations of delay (≤6 and >6 months) were compared using either one-way ANOVA or chi-squared test.

Univariable analyses were conducted to explore if any baseline characteristics were factors for participants not achieving glycemic control (HbA1c ≥7% [≥53 mmol/mol]) at 3 months after initiating/switching injectable therapy, with odds ratios (OR) and 95% confidence intervals (CIs) calculated using logistic regression. Factors with *P*-values <0.05 in the univariable analysis were further included in the multivariable model to confirm significance.

All statistical analysis were undertaken using R and SAS version 9.4.

RESULTS

Participants

Data from participants who initiated injectable therapy (premixed insulin [*n* = 4,687], BI [4,177], and GLP-1 RA [541]) and who switched injectable therapies (from premixed insulin to BI [*n* = 1,298], from BI to premixed insulin [1,457], from BI to BI + bolus insulin [1,772], and from GLP-1 RA to BI ±

GLP-1 RA [82]) were collected. The participants' mean age and BMI ranged from 52.8 to 61.4 years and 25.6–28.8 kg/m^2, respectively, with participants who initiated GLP-1 RA or switched from GLP-1 RA to BI ± GLP-1 RA being numerically younger (52.8 and 53.7 years, respectively) and with a higher BMI (28.8 and 28.2 kg/m^2, respectively; Table 1).

Table 1 | Baseline characteristics and demographics

Characteristic	Oral GLD to premixed insulin (*n* = 4,687)	Oral GLD to BI (*n* = 4,177)	Oral GLD to GLP-1 RA (*n* = 541)	Premixed insulin to BI (*n* = 1,298)	BI to premixed insulin (*n* = 1,457)	BI to BI + bolus insulin (*n* = 1,772)	GLP-1 RA to BI ± GLP-1 RA (*n* = 82)
Age, years	61.0 ± 10.1	60.4 ± 10.6	52.8 ± 11.8	59.8 ± 10.4	60.0 ± 9.8	61.4 ± 10.8	53.7 ± 11.8
Age, *n* (%)							
18–54 years	1,012 (21.6)	1,048 (25.1)	272 (50.3)	349 (26.9)	368 (25.3)	353 (19.9)	38 (46.3)
55–64 years	2,019 (43.1)	1,697 (40.6)	181 (33.5)	540 (41.6)	637 (43.7)	794 (44.8)	31 (37.8)
≥65 years	1,656 (35.3)	1,432 (34.3)	88 (16.3)	409 (31.5)	452 (31.0)	625 (35.3)	13 (15.9)
Male, *n* (%)	2,404 (51.3)	2,156 (51.6)	304 (56.2)	681 (52.5)	678 (46.5)	893 (50.4)	45 (54.9)
BMI, kg/m^2	25.8 ± 3.4	25.9 ± 3.5	28.8 ± 4.6	26.1 ± 3.5	26.2 ± 3.4	25.6 ± 3.5	28.2 ± 4.4
BMI, *n* (%)	*n* = 1,970	*n* = 1,732	*n* = 191	*n* = 538	*n* = 636	*n* = 762	*n* = 38
<24 kg/m^2	637 (32.3)	581 (33.6)	32 (16.8)	169 (31.4)	185 (29.09)	286 (37.5)	7 (18.4)
24–<28 kg/m^2	887 (45.0)	720 (41.6)	61 (31.9)	229 (42.6)	268 (42.1)	303 (39.8)	12 (31.6)
≥28 kg/m^2	446 (22.6)	431 (24.9)	98 (51.3)	140 (26.0)	183 (28.8)	173 (22.7)	19 (50.0)
HbA1c, %	8.2 ± 1.7	8.7 ± 1.7	7.7 ± 1.4	8.7 ± 1.8	9.2 ± 1.7	9.1 ± 2.0	9.4 ± 1.8
HbA1c, mmol/mol	66 ± 19	71 ± 18	60 ± 16	72 ± 20	77 ± 19	76 ± 22	79 ± 20
FPG, mmol/L	9.6 ± 3.0	10.4 ± 2.9	8.9 ± 2.5	10.7 ± 3.4	10.3 ± 3.3	10.5 ± 3.8	12.3 ± 3.7
PPG, mmol/L	13.8 ± 5.4	15.3 ± 4.9	10.9 ± 3.2	17.4 ± 4.8	15.1 ± 5.9	17.2 ± 6.2	16.8 ± 0.0
Diabetic complications, *n* (%)	1,688 (36.0)	1,284 (30.7)	148 (27.4)	423 (32.6)	511 (35.1)	878 (49.4)	23 (28.1)
Nephropathy	613 (13.1)	360 (8.6)	54 (10.0)	140 (10.8)	185 (12.7)	227 (12.8)	13 (15.9)
Retinopathy	242 (5.2)	194 (4.6)	22 (4.1)	95 (7.3)	118 (8.1)	169 (9.5)	2 (2.4)
Neuropathy	1,082 (23.1)	876 (21.0)	99 (18.3)	284 (21.9)	373 (25.6)	503 (28.4)	13 (15.9)
Cardiovascular disease	179 (3.8)	142 (3.4)	43 (8.0)	34 (2.6)	41 (2.8)	334 (18.9)	2 (2.4)
Stroke	58 (1.2)	51 (1.2)	10 (1.9)	13 (1.0)	15 (1.0)	144 (8.1)	0
Diabetic foot	63 (1.3)	31 (0.7)	3 (0.6)	10 (0.8)	9 (0.6)	27 (1.5)	0
Comorbidities, *n* (%)	693 (14.8)	772 (18.5)	230 (42.5)	229 (17.6)	319 (21.9)	526 (29.7)	30 (36.6)
Hypertension	260 (5.6)	338 (8.1)	87 (16.1)	80 (6.2)	138 (9.5)	363 (20.5)	6 (7.3)
Hyperlipidemia	85 (1.8)	90 (2.2)	46 (8.5)	23 (1.8)	32 (2.2)	115 (6.5)	2 (2.4)
Obesity	458 (9.8)	436 (10.4)	180 (33.3)	140 (10.8)	184 (12.6)	181 (10.2)	27 (32.9)
Number of oral GLDs	2.3 ± 0.9	2.7 ± 1.0	2.7 ± 1.1	2.4 ± 1.1	2.6 ± 1.1	2.1 ± 1.1	2.1 ± 1.1
Number of oral GLDs, *n* (%)							
1	882 (18.8)	501 (12.0)	82 (15.2)	174 (13.4)	143 (9.8)	306 (17.2)	18 (22.0)
2	1,801 (38.4)	1,313 (31.4)	156 (28.8)	412 (31.7)	404 (27.7)	672 (37.8)	30 (36.6)
≥3	2,004 (42.8)	2,363 (56.6)	303 (56.0)	649 (50.0)	840 (57.7)	627 (35.3)	29 (35.4)
Oral GLD category, *n* (%)							
DPP-4 inhibitors	384 (8.2)	695 (16.6)	184 (34.0)	198 (15.3)	263 (18.1)	209 (11.8)	10 (12.2)
Metformin	2,924 (62.4)	2,585 (61.9)	430 (79.5)	789 (60.8)	871 (59.8)	891 (50.3)	56 (68.3)
Sulfonylureas	1,681 (35.9)	2,446 (58.6)	275 (50.8)	619 (47.7)	685 (47.0)	546 (30.8)	35 (42.7)
Thiazolidinediones	669 (14.3)	939 (22.5)	168 (31.1)	283 (21.8)	281 (19.3)	175 (9.9)	14 (17.1)
AGI	3,874 (82.7)	3,419 (81.9)	307 (56.8)	1,035 (79.7)	1,188 (81.5)	1,343 (75.8)	51 (62.2)
Glinides	1,446 (30.9)	1,009 (24.2)	73 (13.5)	229 (17.6)	514 (35.3)	539 (30.4)	7 (8.5)
SGLT-2 inhibitors	2 (<0.1)	2 (<0.1)	2 (0.4)	0	0	0	1 (1.2)

Data are presented as mean ± SD or *n* (%). AGI, alpha glucosidase inhibitor; BI, basal insulin; BMI, body mass index; DPP-4, dipeptidyl peptidase-4; FPG, fasting plasma glucose; GLD, glucose-lowering drug; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; PPG, postprandial glucose; SGLT-2, sodium-glucose cotransporter-2.

At initiation of injectable therapy, 42.8–56.6% of participants were receiving ≥3 oral GLDs, with an average number of oral GLDs ranging from 2.3 to 2.7. The most common oral GLDs received at baseline were alpha glucosidase inhibitors (in 56.8–82.7% of participants), metformin (61.9–79.5%), and sulfonylureas (35.9–58.6%).

In participants initiating injectable therapy (Cohorts 1–3), HbA1c and FPG values were highest in the BI cohort, followed by the premixed insulin and GLP-1 RA cohorts. In participants switching injectable therapy (Cohorts 4–7), the lowest HbA1c and highest PPG values were observed in the premixed insulin to BI treatment cohort, while those in the GLP-1 RA to BI ± GLP-1 RA cohort had the highest HbA1c and FPG values. Baseline glycemic measurements were comparable between the BI to BI + bolus insulin and BI to premixed insulin cohorts.

Glycemic outcomes

In participants initiating injectable therapy (Cohorts 1–3), switching from an oral GLD to premixed insulin, BI, or GLP-1 RA was associated with a significant reduction (all $P < 0.001$) in HbA1c after 3 months (Figures 1A and S1A). This significant improvement was maintained in the oral GLD to premixed insulin and oral GLD to BI cohorts at 12 months, but not in the oral GLD to GLP-1 RA cohort. At 12 months, mean ± SD HbA1c was 7.7 ± 1.4% (61 ± 15 mmol/mol), 7.9 ± 1.4% (63 ± 15 mmol/mol), and 7.1 ± 1.2% (54 ± 13 mmol/mol) in participants initiating premixed insulin, BI, and GLP-1 RA, respectively. This was associated with a mean ± SE change in HbA1c from baseline of −0.2 ± 0.1% (−2.2 ± 1.1 mmol/mol; $P = 0.030$), −0.4 ± 0.1% (−4.4 ± 1.1 mmol/mol; $P < 0.001$), and −0.4 ± 0.2 (−4.4 ± 2.2 mmol/mol; $P = 0.058$) in the respective cohorts.

In participants switching injectable therapy (Cohorts 4–7), significant reductions in HbA1c were observed at 3 months in the BI to premixed insulin and BI to BI + bolus insulin cohorts (both $P < 0.001$; Figures 1B and S1B). These significant improvements were maintained in these two cohorts at 12 months, and the mean ± SE changes from baseline in HbA1c at 12 months were −0.7 ± 0.2% (−7.7 ± 2.2 mmol/mol; $P = 0.001$) and −0.6 ± 0.2% (−6.6 ± 2.2 mmol/mol; $P = 0.01$), respectively. Non-significant reductions in HbA1c at 12 months were observed in the premixed insulin to BI and GLP-1 RA to BI ± GLP-1 RA cohorts.

In participants initiating injectable therapy (Cohorts 1–3), significant improvements in FPG at 12 months were observed in participants initiating premixed insulin (−1.1 ± 0.3 mmol/L, $P < 0.001$ vs. baseline) and BI (−0.9 ± 0.2 mmol/L, $P < 0.001$), but not in those initiating GLP-1 RA (Figures 1C and S1C).

In participants switching injectable therapy (Cohorts 4–7), significant FPG reductions were observed at 3 months in the premixed insulin to BI ($P = 0.006$), BI to premixed insulin ($P = 0.039$), and BI to BI + bolus insulin ($P = 0.014$) cohorts (Figures 1D and S1D). This improvement was only maintained at 12 months in the BI to BI + bolus insulin cohort, with a change from baseline of −1.5 ± 0.6 mmol/L ($P = 0.02$).

At 12 months, the proportion of participants who achieved an HbA1c <7% (<53 mmol/mol) ranged from 31.5% to 47.1% in those initiating injectable therapy, with the GLP-1 RA cohort experiencing the highest glycemic response rate (Figure S2A). In participants switching injectable therapy, 15.3–27.6% achieved an HbA1c <7% (<53 mmol/mol) at 12 months, with the highest glycemic response rate in the premixed insulin to BI cohort (Figure S2B). The proportions of participants with FPG <7 mmol/L are shown in Figure S2C,D.

Time from oral GLD failure to initiation of injectable therapies

In participants who initiated injectable therapy, the mean ± SD time between failure of oral GLDs and initiating injectable therapy was 13.1 ± 13.0 months ($n = 2,214$). Participants in the GLP-1 RA cohort had a significantly longer time to initiating injectable therapy compared with those in the premixed insulin and BI cohorts (16.9 ± 16.4 months vs. 13.5 ± 12.8 and 12.5 ± 12.9 months, respectively; $P = 0.004$). Individuals who had a longer time to initiating injectable therapy (>6 months after oral GLD failure) were older and had higher baseline HbA1c at the time of initiation of injectable therapies than those with a shorter time to initiating injectable therapy (≤6 months; Table S2).

The majority of participants (60.9%) initiated treatment with an injectable therapy >6 months after failure of oral GLDs (Figure 2; $P = 0.015$ for comparison of time categories).

Factors associated with glycemic control

In participants initiating injectable therapies (Cohorts 1–3), multivariable analysis showed that the odds of not achieving glycemic control at 3 months were significantly higher in those with a delay in initiation of injectable therapy of ≥6 months after oral GLD failure (75.7% vs. 67.3%; OR 1.92; 95% CI 1.06–3.56; $P = 0.034$) and a higher baseline HbA1c ≥8.5% (≥64 mmol/mol; OR 3.40; 95% CI 1.81–6.70; $P < 0.001$; Table 2).

In participants switching injectable therapies (Cohorts 4–7), 36.1% of participants with a baseline HbA1c <8.5% (<64 mmol/mol) achieved target HbA1c at month 3 compared with 8.5% of participants with a higher baseline HbA1c. In the multivariable analysis, participants with a baseline HbA1c ≥8.5% (≥64 mmol/mol) had a significantly higher probability of not achieving HbA1c <7% (<53 mmol/mol) at month 3 than those with a baseline HbA1c <8.5% (<64 mmol/mol; OR 5.59, 95% CI 2.93–11.24; $P < 0.001$; Table S3).

DISCUSSION

This real-world study of individuals with T2D treated in Tianjin, China, found that initiating injectable therapy with premixed insulin or BI was associated with statistically significant improvements in glycemic control over 12 months and

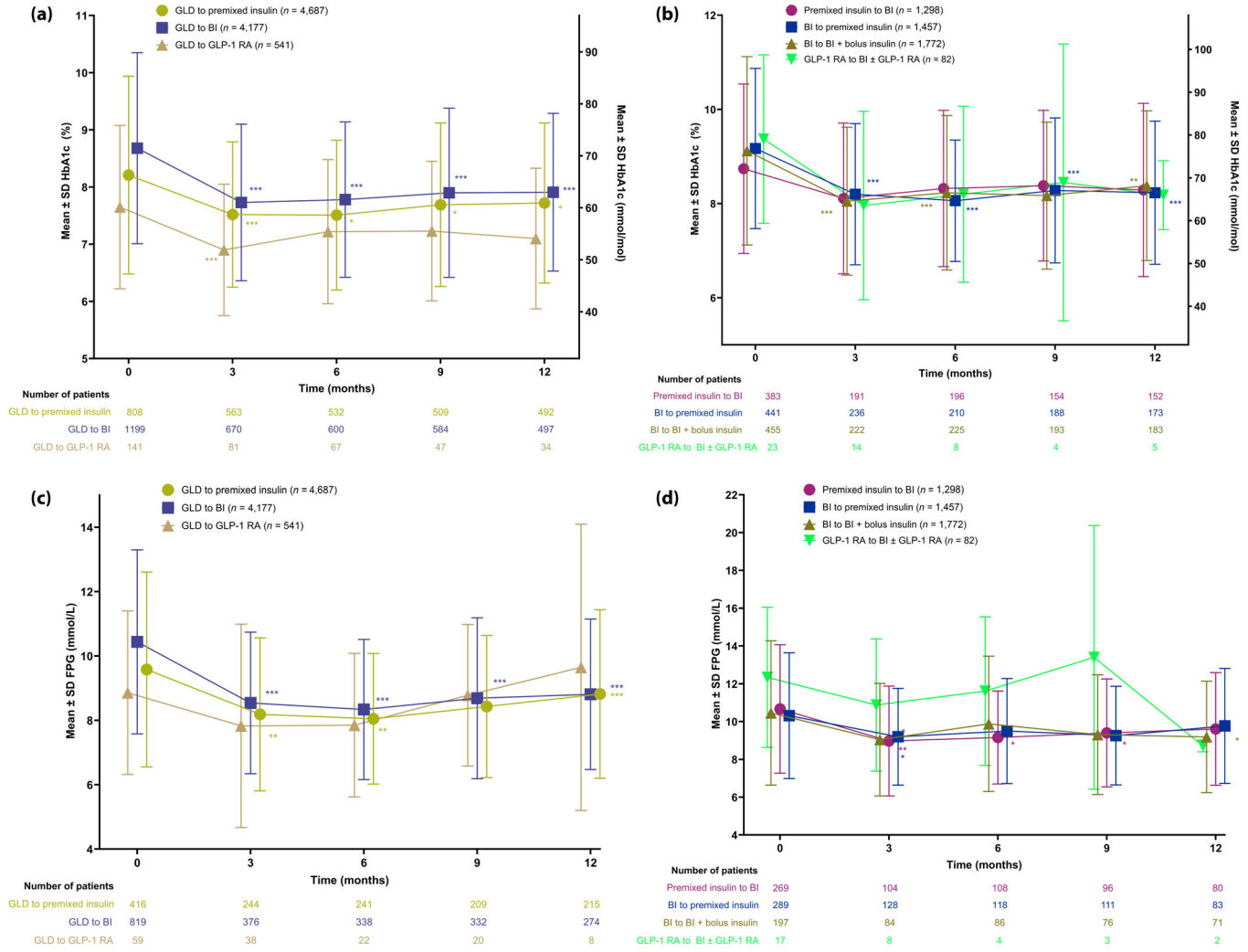

Figure 1 | Mean ± SD glycated hemoglobin at baseline and 3, 6, 9, and 12 months after (a) initiating injectable therapy (premixed insulin, basal insulin, or glucagon-like peptide-1 receptor agonists) and (b) switching between injectable therapy regimens;[†] and mean ± SD fasting plasma glucose at baseline and 3, 6, 9, and 12 months after (c) initiating injectable therapy (premixed insulin, basal insulin, or glucagon-like peptide-1 receptor agonists) and (d) switching between injectable therapy regimens.[†] *$P < 0.05$ vs. baseline; **$P < 0.01$ vs. baseline; ***$P < 0.001$ vs. baseline. [†]Sample size was limited for the switching from GLP-1 RA to BI ± GLP-1 RA cohort. BI, basal insulin; FPG, fasting plasma glucose; GLD, glucose-lowering drug; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; SD, standard deviation.

highlighted the prevalence and impact of delays in treatment intensification.

A clinically meaningful improvement in glycemic control (i.e., >0.3% reduction in HbA1c) was seen in participants initiating GLP-1 RAs, although this was not statistically significant. This may be partly due to the small number of participants initiating GLP-1 RAs, making the impact of this treatment intensification difficult to determine. Participants initiating injectable therapy were more likely to receive insulin than a GLP-1 RA because, although GLP-1 RA therapy has been approved in China since 2009, access to reimbursement was only initiated in late 2020 (i.e., after the study data collection period of 2015–2019)[13]. Premixed insulin and BI were prescribed at similar rates in our study. Previous studies from China have indicated that premixed insulin has been the preferred insulin treatment, with higher prescription rates than BI for individuals initiating treatment intensification during 2009–2010 (77.3% vs. 11.8%, respectively)[14] and for previously insulin-naïve individuals during 2010–2015 (75.5% vs 24.5%)[15], but a more recent study reported that the prescription rates for BI were higher relative to premixed insulin among individuals previously treated with non-insulin medications during 2017–2021 (57.3% vs. 42.7%, respectively)[16]. Moreover, a separate cross-sectional analysis of data from the current study found a decreasing trend in the overall use of premixed insulin and an upwards trend over time in the use of BI-based regimens between 2015 and 2019[17].

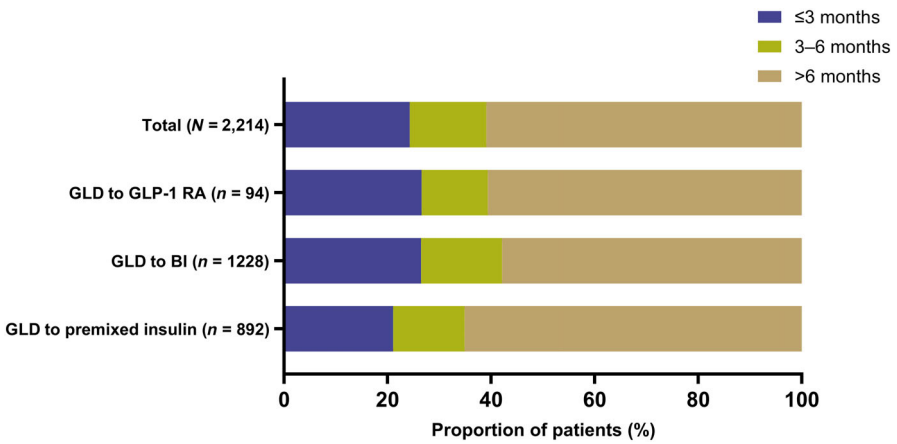

Figure 2 | Time to initiation of injectable therapy (premixed insulin, basal insulin, or glucagon-like peptide-1 receptor agonists) after failure of oral antidiabetic drugs. BI, basal insulin; GLD, glucose-lowering drug; GLP-1 RA, glucagon-like peptide-1 receptor agonist.

Some differences in characteristics were noted between the cohorts initiating injectable therapy. For example, participants initiating premixed insulin had slightly lower baseline HbA1c and FPG than those initiating BI and had been treated with fewer oral GLDs, but were similar in age. This suggests that premixed insulin is being initiated somewhat earlier in the institutions that contributed data to this analysis, as the Chinese Diabetes Society recommends BI as the preferred formulation for initiation of insulin therapy[18]. In contrast to the current study, a prospective, real-world study of 10 Chinese diabetes centers reported lower HbA1c and FPG in participants initiating BI than in those initiating premixed insulin, suggesting that the Chinese Diabetes Society guidelines were being followed more closely in those institutions at the time of the study[16]. Furthermore, in the current study, participants initiating insulin therapy were older, had a lower BMI, were less likely to be obese (BMI ≥28 kg/m^2) or have comorbidities, and had higher baseline FPG and HbA1c than those initiating GLP-1 RA therapy, which is consistent with the findings of an observational retrospective database study of oral GLD-treated participants from 15 cities across China who were initiating GLP-1 RA or insulin therapy[13].

Despite the positive impact of injectable therapy, this study showed considerable delay in initiating all types of injectable therapy after the failure of oral GLDs, with 60% of participants having a delay of >6 months. Similar delays in treatment intensification were previously reported among individuals initiating insulin after failure of oral GLDs in Fuzhou, Southeast China (27.8% had a delay of >6 months)[19] and in a Korean study of people with diabetes inadequately controlled (44.5% had a delay of ~72 months)[20]. Our study showed that longer delays in initiating injectable therapy led to poorer glycemic outcomes. Likewise, in the Chinese study mentioned above, HbA1c targets at 3 months were achieved by only 16% of participants with >6-month delay in insulin initiation after oral GLD failure compared with 38% of participants with more timely initiation[19]. Our study findings may explain this phenomenon, as a longer initiation delay (>6 vs. ≤6 months) was associated with higher baseline HbA1c at the time of initiation, which was then a factor for poor glycemic control at month 3. Indeed, the Chinese Diabetes Society 2020 guidelines recommend timely initiation or switching of injectable therapy in individuals who fail to achieve glycemic control within 3 months of starting oral GLDs or their prior line of insulin treatment[18].

In addition to higher baseline HbA1c[19] and older age[20], which have been previously identified as factors associated with delayed treatment intensification in Asia, other possible risk factors were the presence of comorbidities[19] and a shorter duration of diabetes[20]. Patient-reported reasons for delayed insulin initiation include inconvenience, fear of injections, concern about pain associated with injections, and the therapy being an indication of the "end of life."[20] Physician-reported reasons include patient refusal, concerns about compliance, concerns about hypoglycemia, and considering that symptoms could be controlled with oral GLDs[20]. Future studies evaluating effect of modifying these factors on timely initiation of insulin therapy are warranted.

In our study, switching injectable therapy was associated with significant improvements in glycemic control over 12 months. Switching from BI to BI + bolus insulin or premixed insulin was associated with significant HbA1c reductions at 12 months; however, only participants who switched from BI to BI + bolus insulin had significantly reduced FPG. This suggests that further treatment intensification is an appropriate choice if BI alone fails to provide adequate glycemic control.

Interestingly, we found that switching from premixed insulin to BI had limited impact on glycemic control. A significant FPG reduction was seen after 9 months, but no effect was seen at 12 months, and no effect was seen on HbA1c across the study period. These effects are in contrast to those found in

Table 2 | Factors associated with a glycated hemoglobin ≥7% (≥53 mmol/mol) at 3 months after switching from oral antidiabetic drugs to injectable therapy (premixed insulin, basal insulin, or glucagon-like peptide-1 receptor agonists)

	N	HbA1c ≥7% (≥53 mmol/mol) at 3 months, *n* (%)	Univariable analysis[†]		Multivariable analysis[‡]	
			OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age						
18–54 years	345	213 (61.7)	Ref		–	–
55–64 years	560	363 (64.8)	1.14 (0.86–1.51)	0.349	–	–
≥65 years	409	257 (62.8)	1.05 (0.78–1.41)	0.757	–	–
Sex						
Female	665	425 (63.9)	Ref		–	–
Male	649	408 (62.9)	0.96 (0.76–1.20)	0.695	–	–
BMI						
<24 kg/m^2	175	116 (66.3)	Ref		–	–
24 to <28 kg/m^2	227	137 (60.4)	0.77 (0.51–1.17)	0.222	–	–
≥28 kg/m^2	124	88 (71.0)	1.24 (0.76–2.06)	0.392	–	–
Number of oral GLDs						
1	135	75 (55.6)	Ref		Ref	
2	407	228 (56.0)	1.02 (0.69–1.51)	0.925	0.40 (0.05–1.87)	0.285
≥3	772	530 (68.7)	**1.75 (1.21–2.54)**	**0.003**	0.62 (0.09–2.70)	0.561
Microvascular complications[§]						
Without	875	557 (63.7)	Ref		–	–
With	439	276 (62.9)	1.51 (0.82–2.92)	0.201	–	–
Macrovascular complications[¶]						
Without	1,264	797 (63.1)	Ref		–	–
With	50	36 (72.0)	0.97 (0.76–1.23)	0.780	–	–
Comorbidity[††]						
Without	1,047	643 (61.4)	Ref		Ref	
With	267	190 (71.2)	**1.55 (1.16–2.09)**	**0.003**	1.01 (0.51–2.06)	0.978
Baseline HbA1c						
<8.5% (<64 mmol/mol)	297	150 (50.5)	Ref		Ref	
≥8.5% (≥64 mmol/mol)	196	170 (86.7)	**6.41 (4.06–10.45)**	**<0.001**	**3.40 (1.81–6.70)**	**<0.001**
Delayed duration of initiation of injectable therapies						
≤6 months	193	130 (67.3)	Ref		Ref	
>6 months	272	206 (75.7)	**1.51 (1.00–2.28)**	**0.047**	**1.92 (1.06–3.56)**	**0.034**

[†]Univariable analysis only included participants with available data for that single factor and the 3-month HbA1c outcome. [‡]Multivariable analysis only included participants with available data for all factors and the 3-month HbA1c outcome. [§]Nephropathy, retinopathy, neuropathy, or diabetic foot. [¶]Cardiovascular disease or stroke. [††]Hypertension, hyperlipidemia, or obesity. 95% CI, 95% confidence interval; BMI, body mass index; GLD, glucose-lowering drug; HbA1c, glycated hemoglobin; OR, odds ratio.

other studies[21–24]. These divergent findings may be associated with the different baseline characteristics of the participants in this cohort in our study. Our study participants had higher HbA1c (mean: 8.74%) and FPG (mean: 10.7 mmol/L) than those in other studies (mean HbA1c range: 7.8–8.6%; mean FPG range: 8.1–9.5 mmol/L)[21,23,24], suggesting they were less appropriate candidates for BI therapy. Indeed, a subgroup analysis from a previously described 16-week Chinese study determined that lower baseline HbA1c and FPG (in addition to younger age and shorter diabetes duration) were characteristics associated with a greater likelihood of glycemic control following a switch to BI[22]. Second, higher PPG (mean: 17.4 mmol/L) observed in our study suggested residual hyperglycemia in some participants (i.e., high PPG contributing more to failure of HbA1c target); therefore, other therapies, such as adding bolus or switching to BI + short-acting GLP-1 RA[25,26], may have been more appropriate to improve PPG levels. In addition, we speculate that clinicians do not follow standard-of-care advice on the implementation of appropriate goals and titration methods for BI dosing when switching from premixed insulin to BI[3,27,28]. The lack of data on treatment adherence and persistence from our study also limits further investigation of this issue.

Switching from GLP-1 RA to BI ± GLP-1 RA was not associated with improved glycemic control, possibly due to the limited sample size with insufficient statistical power and incorrect insulin titration. Nevertheless, participants in this cohort had the highest baseline HbA1c and FPG among the seven cohorts, suggesting the need for early simultaneous initiation instead of sequential initiation of BI and GLP-1 RA, as well as an

appropriate titration algorithm and goal-setting facilitation. A retrospective real-world study demonstrated greater achievement of glycemic targets when BI and GLP-1 RAs were initiated simultaneously (≤30 days apart), with significantly fewer participants achieving targets when initiating treatments sequentially (>90 days apart)[29]. The lack of effect of switching to BI ± GLP-1 RA could also have been related to the timing of BI therapy initiation. Furthermore, when combining BI plus a GLP-1 RA, correct titration based on individualized FPG is crucial for optimal glycemic control[28]. Moreover, the participants in this cohort also appeared to be under-treated with oral GLDs, being more likely to be on only one oral GLD at baseline than the other cohorts that switched injectable therapies (22% vs. 10–17%).

The current study has a number of strengths, including a large sample size and participant data from a regional database that allowed continuous clinical records to be captured. The study also evaluated the real-world effectiveness of treatment intensification in a broad population of participants with T2D; thus, providing evidence complementary to randomized controlled trials that used rigorous inclusion criteria and procedures that limit the generalizability of their populations.

However, the study does have several limitations. Its retrospective observational design may have introduced selection bias, as there was marked attrition in data availability in glycemic control measurements, and between baseline and the 12-month time point. The analyses were only conducted for participants with available laboratory data. As laboratory tests were not regularly scheduled, these could have been predominantly conducted among participants with worsening glycemic control, which may have led to underestimation of treatment effectiveness based on the available data. In addition, some cohorts had a small size, particularly the GLP-1 RA to BI ± GLP-1 RA cohort (n = 82 enrolled, n = 141 at baseline, n = 34 at 12 months). Furthermore, this study did not evaluate long-term endpoints, such as the incidence of cardiovascular events and other diabetes complications; assessment of these endpoints is warranted in future studies. Finally, the data were limited to individuals living in the Tianjin area and are likely representative of clinical practice and patient experience in Northern China, but may not be generalizable to the broader population of Chinese individuals with T2D.

In conclusion, this retrospective longitudinal cohort study demonstrated that initiating or switching between injectable therapy regimens was not always effective in people with T2D. This suggests that some GLDs are not being used in the appropriate populations in Tianjin, China. Despite the obvious therapeutic benefit of treatment intensification, initiation of injectable therapy was often delayed, with adverse consequences for participants.

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DISCLOSURE

Liming Chen, Qiumei Zhang, Yaqing Fan, Xixi Liu, and Ming Li declared no conflict of interest. Minlu Zhang, Jiewen Zhang, and Lei Kang are employees of Sanofi China.
Approval of the research protocol: The study protocol was approved by the ethics committee of the Chu Hsien-I Memorial Hospital (approval number: ZXYJNYYhMEC2022-1).
Informed consent: N/A.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.

DATA AVAILABILITY STATEMENT

Data for this longitudinal analysis were sourced from the Tianjin Healthcare and Medical Big Data Platform, which is not available online. On-site access is available, upon reasonable request from Tianjin Healthcare and Medical Big Data Co., Ltd.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Definitions of the seven treatment cohorts.

Table S2. Patient characteristics at the time of initiation of injectable therapy (premixed insulin, basal insulin or glucagon-like peptide-1 receptor agonists) in patients who had ≤6 or >6 months between oral antidiabetic drug failure and initiating injectable therapy.

Table S3. Factors associated with a glycated hemoglobin ≥7% (≥53 mmol/mol) at 3 months after switching from premixed insulin to basal insulin, from basal insulin to premixed insulin, from basal insulin to basal + bolus insulin or from glucagon-like peptide-1 receptor agonists to basal insulin ± glucagon-like peptide-1 receptor agonists.

Figure S1. Mean ± SE changes from baseline to 12 months in glycated hemoglobin after (A) initiating injectable therapy (premixed insulin, basal insulin or glucagon-like peptide-1 receptor agonists) and (B) switching between injectable therapy regimens;[†] and mean ± standard error changes from baseline to 12 months in fasting plasma glucose after (C) initiating injectable therapy (premixed insulin, basal insulin or glucagon-like peptide-1 receptor agonists) and (D) switching between injectable therapy regimens.[†] *$P < 0.05$ vs. baseline; **$P < 0.01$ vs. baseline; ***$P<0.001$ vs. baseline. [†]Sample size was limited for the switching from GLP-1 RA to BI ± GLP-1 RA cohort. BI, basal insulin; FPG, fasting plasma glucose; GLD, glucose-lowering drug; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; SE, standard error.

Figure S2. Proportion of participants achieving a glycated hemoglobin <7% (<53 mmol/mol) at 3, 6, 9, and 12 months after (A) initiating injectable therapy (premixed insulin, basal insulin or and glucagon-like peptide-1 receptor agonists) and (B) switching between injectable therapy regimens;[†] and proportion of participants achieving a fasting plasma glucose <7 mmol/L at 3, 6, 9 and 12 months after (C) initiating injectable therapy (premixed insulin, basal insulin or glucagon-like peptide-1 receptor agonists) and (D) switching between injectable therapy regimens.[†] [†]Sample size was limited for the switching from GLP-1 RA to BI ± GLP-1 RA cohort with the 0% of patients achieving the glycemic target at some timepoints. BI, basal insulin; FPG, fasting plasma glucose; GLD, glucose-lowering drug; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin.