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Association of diabetes treatment with long-term glycemic patterns in patients with type 2 diabetes mellitus: A prospective cohort study

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Abstract

Aim: This study aimed to analyze diabetes treatment and treatment changes in association with long-term glycemic patterns in an Asian population with diabetes.

Materials and methods: This was a prospective cohort study of 6218 patients with type 2 diabetes managed in public primary care clinics in Singapore. Clinical data from 2011 to 2016 were extracted from electronic medical records, including serial HbA1c measurements and dispensed antidiabetic medication records. Patterns of longitudinal HbA1c trajectories were identified using latent class growth analysis, and patients' annual treatment plans were compared between subgroups with different HbA1c patterns.

Results: We identified four distinct HbA1c patterns. Eighty-one percent of patients were classified in the low-stable group, where monotherapy and dual therapy with oral agents were the most common treatments. We also identified three groups with poorer control, with moderate-stable (14%), moderate-increase (3%), and high-decrease (2%) HbA1c patterns. Insulin treatment was most prevalent in these groups, with 61% to 72% of subjects receiving insulin treatment in 2016. More than 60% of subjects in poorer control groups had experienced treatment intensification during follow-up. Addition of multiple insulin injections was the most common intensification in moderate-increase and high-decrease groups.

Conclusions: Treatment reflected and was appropriate to the extent of dysglycemia in this population. A small group of patients had deteriorating glycemic control, in spite of being treated with multiple insulin injections, suggesting non-response or non-adherence to treatment. Further investigation is needed to identify reasons for the deteriorating control observed and design effective interventions for these patients.

KEYWORDS

antidiabetic medication, glycemic control, insulin treatment, latent class growth analysis, oral hypoglycemic agents, type 2 diabetes

1 | INTRODUCTION

Diabetes is a chronic disease which requires long-term management of glycemic levels.[1] To evaluate the level of glycemic control, glycated haemoglobin (HbA1c) is measured routinely for patients with diabetes. These serial measurements of HbA1c form a trajectory of glycemic control, reflecting the progression of diabetes for each patient. Previous analyses have suggested that these trajectories of HbA1c could be categorized into several distinct patterns in the population using latent class growth analysis (LCGA).[2] In our previous analysis, we identified four distinct trajectories in a cohort of 6079 participants, including two stable patterns with average HbA1c levels at 7.1% and 8.5%, and two unstable patterns, one with increasing trend starting from a moderately high HbA1c level and one with decreasing trend starting from a very high initial HbA1c level. We also found that these unstable patterns were associated with a two- to three-fold increase in diabetes-related complications or death although they only comprised a small proportion of the population.[3]

These distinct patterns of HbA1c may be a result of or influenced by clinical treatment as much as by disease progression. To control hyperglycemia, patients often require metformin monotherapy soon after diagnosis, followed by more advanced treatment including multiple oral hypoglycemic agents (OHAs) or insulin if the previous treatment fails.[1] While insulin is usually considered the most effective antidiabetic medication, patients may continue to have poor glycemic control despite insulin intensification. Chang et al identified a group of patients who had consistently poor glycemic control with an average HbA1c level of 11% despite the increase in proportion treated with insulin in this group from 11% 1 year before the study to 32% during the study period.[4] In our previous analysis, we also found that in the group with deteriorating glycemic control, the rate of insulin treatment increased from 32% at baseline to 80% at the end of follow-up.[3] Although medication is one of the most important aspects in maintaining glycemic control, limited studies have evaluated how long-term treatment patterns shape HbA1c trajectories.

In this study, we aimed to examine the association of diabetes medication management (hereafter referred to as treatment) with HbA1c trajectories over the same period among patients with type 2 diabetes managed by a group of public primary care clinics in Singapore. We also aimed to examine clinical inertia by analyzing the rate of treatment intensification and de-intensification among patients with different glycemic control patterns. This study may provide insights into the role of treatment in shaping HbA1c trajectories, help to identify gaps in current treatment, and provide suggestions for improving glycemic management in patients with diabetes.

2 | MATERIALS AND METHODS

2.1 | Study population

The Singapore Population Health Studies Diabetic Cohort (SPHS-DC) is a longitudinal observational cohort study of patients with type 2 diabetes mellitus in Singapore. A total of 14 033 adult patients (21 years and above) with type 2 diabetes were recruited from multiple public primary clinics and hospital specialist outpatient clinics between November 2004 and November 2010.[5] Patients with type 1 diabetes or major psychiatric illness were excluded from recruitment.

The current analysis was conducted on a subset of the SPHS-DC participants who had medical record data available between 2011 and 2016 through linkage with the electronic medical record system of National Healthcare Group Polyclinics (NHGP). The NHGP is one of the principal public primary care providers in Singapore, comprising 11 public primary care clinics and one of two clusters of primary care clinics in Singapore during the study period. Ethics approval was obtained from the National University of Singapore Institutional Review Board and National Health Group Domain Specific Review Board (NHG DSRB). Informed written consent was obtained from all participants, including for record linkage, at the time of enrollment into the SPHS-DC.

2.2 | Data source

Data used in this study included data collected at recruitment and medical data extracted from the electronic medical records in NHGP. Data at recruitment were collected through questionnaires administered by trained researchers which captured socio-demographic characteristics (ie, age, gender, ethnicity, marital status, education, occupation, and smoking status) as well as medical history of diabetes and its related comorbidities. Diabetic kidney disease was defined based on the 2012 KDIGO Clinical Practice Guidelines,[6] where patients who reported having either diabetic kidney disease history or albuminuria history (ie, albuminuria >30 mg/g) were categorized as disease positive. Anthropometric assessments were also conducted following the questionnaire survey.

The extracted medical records included visit registration, clinical measurements of HbA1c, and dispensed medication records from Jan 2011 to Dec 2016. Patients' annual treatment plan was defined using records of unique antidiabetic medications, including OHAs and insulin treatment, in the whole calendar year. OHAs in this study included the following drug classes: biguanides, sulphonylureas, alpha-glucosidase inhibitors (AGIs), dipeptidyl peptidase-4 (DPP4) inhibitors, thiazolidinediones, and meglitinides (Supplemental Table S1). Insulin treatment was categorized as basal insulin and multiple insulin injections: subjects treated with long-acting insulin only were categorized as receiving basal insulin, while those with rapid-acting or pre-mixed insulin in their treatment plans were categorized as receiving multiple insulin injections.

2.3 | Statistical analysis

LCGA was conducted using R package *lcmm* to identify distinct patterns of HbA1c trajectories.[7] We assumed a linear relationship with auto-regression correlation between time and HbA1c measurements in the model and tested models with two to six subgroups. A lower Bayesian information criterion (BIC) value and a criterion of average posterior probabilities above 0.8 for all the subgroups were used to decide the final number of subgroups.[8,9] Based on model statistics, the model with four subgroups had the lowest BIC value among

models that satisfied the average posterior probabilities criterion, thus was chosen as the final model (Supplemental Table 2).

Patient characteristics were summarized using mean (SD), median (interquartile range, IQR), or number (percentages). Patient characteristics of the four HbA1c subgroups were compared using the following tests: one-way ANOVA tests for continuous variables with normal distribution; Kruskal-Wallis' tests for continuous variables with skewed distribution; and Pearson's Chi-square tests for categorical variables.

We evaluated treatment over this period by deriving annual treatment plans from 2011 to 2016. Treatment plans were grouped into the following categories: lifestyle only, 1 OHA, 2 OHAs, 1 OHA + basal insulin, >2 OHAs, ≥2 OHAs + basal insulin, multiple insulin injections, 1 OHA + multiple insulin injections, and ≥ 2 OHAs + multiple insulin injections. To compare the change in treatment within the four HbA1c subgroups, we plotted patients' annual treatment plans by subgroup. The trend of change in proportions from 2011 to 2016 among each treatment plan category by subgroup was tested using the Cochran Armitage trend test.

Change in patients' annual treatment plan was evaluated by comparing the rate of treatment change and time to first change in treatment among the four HbA1c subgroups. Treatment change (ie, intensification/de-intensification) during the whole follow-up period was defined as change in annual treatment plan categories in any of the calendar years from 2012 to 2016 compared with the first year (2011). Subjects already receiving multiple insulin injections were grouped into the unchanged group despite addition or removal of OHA. We also compared patients' treatment plans in the first year (2011) and the last year (2016) to reflect the magnitude of final treatment change over the 6 years. Subjects were grouped into the following three categories: (1) intensified where subjects were further categorized into added OHA only, added basal insulin, and added multiple insulin injections; (2) de-intensified where subjects were further categorized into removed OHA only, removed basal insulin, and removed multiple insulin injections; (3) unchanged where their annual treatment plans were the same in the 2 years.

All analyses were conducted using R version 3.3.2.

3 | RESULTS

3.1 | Patient characteristics

From the 9574 identified subjects who ever visited NHGP after recruitment, we first excluded subjects with uncertain type 2 diabetes (n = 246) and subjects without any records of visit for diabetes (ie, HbA1c measurements, diabetic medication records) in both 2011 and 2016 (n = 2774) to ensure that included subjects were followed up routinely for diabetes management in NHGP. Next, we excluded those without at least one HbA1c measurement in each of the four or more calendar years between 2011 and 2016 (n = 336) to ensure that each subject had sufficient data for LCGA (Figure 1).

As shown in Table 1, the final sample included 6218 patients with type 2 diabetes (Mean age at recruitment 59.2 ± 9.5 years, 53.3% female). The majority of subjects were Chinese (62.4%), and the rest were Malays (19.6%) and Indians or others (18.0%). Their median duration of diabetes was 5.3 years (IQR 2.4-10.6 years), and the prevalence of diabetic retinopathy and diabetic kidney disease at recruitment were 19.4% and 44.0%, respectively.

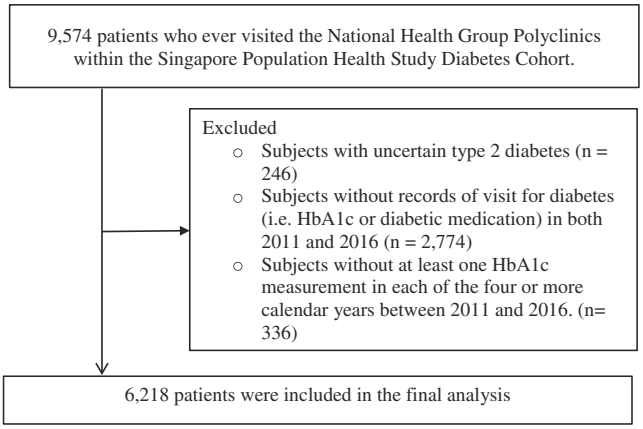

FIGURE 1 Flow of inclusion into the study

3.2 | Patterns of HbA1c trajectories

Based on the LCGA, we identified four patterns of HbA1c trajectories (Figure 2). The majority of subjects had stable HbA1c levels, with a larger group ("Group 1 low-stable," 80.5%) having average HbA1c of 7.3% and a smaller group ("Group 2 moderate-stable," 14.4%) with average HbA1c of 8.8%. A small proportion of subjects had unstable trajectories; 2.9% of subjects had deteriorating glycemic control ("Group 3 moderate-increase") which increased from 9.3% at baseline to 11.7% by the end of 6 years and 2.2% of subjects had a high average baseline HbA1c of 11.9% but were improving over time ("Group 4 high-decrease"), although the average HbA1c at the end of follow-up was still 9.0% (Supplemental Table 3). We also found that subjects in the three poorer control groups had higher proportions of Malays and Indians, higher prevalence of diabetic retinopathy, younger age of diagnosis, and longer diabetes duration than patients in the low-stable group (Table 1).

3.3 | Annual treatment plans in patients with different HbA1c patterns

Next, we compared annual treatment plans among patients with different HbA1c patterns (Figure 3) and tested the trend of these proportions from 2011 to 2016 by subgroup (Supplemental Table 4). In the low-stable group, the majority of subjects only used OHA for glycemic control, where around 27% used one OHA, 47% to 40% used two OHAs (p_{trend} < 0.001), and 7% to 12% used more than two OHAs (p_{trend} < 0.001) during the 6-year follow-up. The rate of insulin treatment in this group slightly increased from 10% to 13%.

Compared with the low-stable group, subjects in the other three groups had much higher uptake of insulin treatment. In the moderate-stable group, less than 5% of subjects were treated with lifestyle or one OHA only. Subjects treated with two OHAs decreased from 38% to 14% (p_{trend} < 0.001), and those treated with more than two OHAs increased from 17% to 23% during the follow-up

TABLE 1 Patient characteristics at recruitment to SPHS-DC

	Cohort	Low-Stable	Moderate-Stable	Moderate-Increase	High-Decrease	*P* Value
N (%)	6218 (100.0)	5005 (80.5)	898 (14.4)	179 (2.9)	136 (2.2)	
Age (mean, SD)	59.2 (9.5)	60.0 (9.3)	56.2 (9.4)	53.6 (10.0)	54.9 (9.0)	<0.001
Gender: Female (N, %)	3312 (53.3)	2664 (53.2)	484 (53.9)	86 (48.0)	78 (57.4)	0.389
Ethnicity (N, %)						<0.001
Chinese	3877 (62.4)	3288 (65.7)	461 (51.3)	71 (39.7)	57 (41.9)	
Malay	1219 (19.6)	898 (17.9)	225 (25.1)	60 (33.5)	36 (26.5)	
Indian and others	1122 (18.0)	819 (16.4)	212 (23.6)	48 (26.8)	43 (31.6)	
Marital status (N, %)						0.173
Married	4905 (78.9)	3931 (78.6)	721 (80.3)	146 (81.6)	107 (78.7)	
Never married	258 (4.2)	201 (4.0)	37 (4.1)	12 (6.7)	8 (5.9)	
Separated	1051 (16.9)	869 (17.4)	140 (15.6)	21 (11.7)	21 (15.4)	
Education (N, %)						0.134
Primary	1577 (25.4)	1296 (25.9)	211 (23.5)	46 (25.7)	24 (17.6)	
Secondary	3955 (63.6)	3160 (63.1)	584 (65.0)	110 (61.5)	101 (74.3)	
Tertiary	686 (11.0)	549 (11.0)	103 (11.5)	23 (12.8)	11 (8.1)	
Occupation: Unemployed (N, %)	2504 (40.3)	2086 (41.7)	314 (35.0)	58 (32.4)	46 (33.8)	<0.001
Smoker (N, %)	1584 (25.5)	1250 (25.0)	238 (26.5)	56 (31.3)	40 (29.4)	0.142
Age at diagnosis (mean, SD)	51.6 (10.6)	52.8 (10.4)	46.8 (9.9)	45.7 (10.3)	45.8 (8.8)	<0.001
Diabetes duration (median, IQR)	5.3 [2.4, 10.6]	4.9 [2.2, 9.7]	7.6 [3.4, 13.8]	6.0 [2.8, 12.4]	8.2 [4.8, 13.2]	<0.001
Family history of diabetes (N, %)	4065 (65.4)	3191 (63.8)	649 (72.3)	126 (70.4)	99 (72.8)	<0.001
BMI (mean, SD)	26.69 (4.48)	26.51 (4.40)	27.32 (4.70)	28.11 (4.59)	27.34 (4.97)	<0.001
WHR (mean, SD)	0.91 (0.07)	0.91 (0.07)	0.92 (0.07)	0.93 (0.07)	0.92 (0.08)	<0.001
Diabetic retinopathy (N, %)	1205 (19.4)	884 (17.7)	239 (26.6)	39 (21.8)	43 (31.6)	<0.001
Diabetic kidney disease (N, %)	2735 (44.0)	2198 (43.9)	408 (45.4)	73 (40.8)	56 (41.2)	0.582

Abbreviations: BMI, body mass index; IQR, interquartile range; SD, standard deviation; SPHS-DC, Singapore Population Health Study Diabetes Cohort; WHR, waist-to-hip ratio.

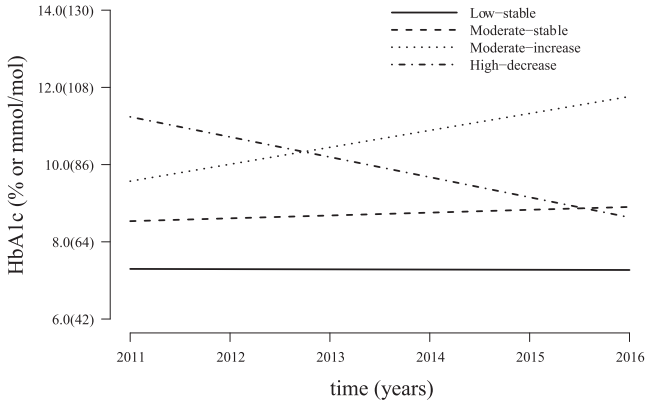

FIGURE 2 Four patterns of HbA1c trajectories identified by LCGA, including "Group 1 low-stable" (n = 5005, 80.5%), "Group 2 moderate-stable (n = 898, 14.4%)," "Group 3 moderate-increase" (n = 179, 2.9%), and "Group 3 high-decrease" (n = 136, 2.2%)

(p_{trend} < 0.001). Increase in subjects receiving insulin treatment was observed for both basal insulin (20% to 22%, p_{trend} = 0.346) and multiple insulin injections (21% to 39%, p_{trend} < 0.001). The pattern of treatment in the moderate-increase group was similar to the moderate-stable group, although a substantially larger increase in subjects receiving insulin treatment was observed. Also, the increase in subjects receiving insulin treatment resulted from the increase in use of multiple insulin injections (29% to 56%, p_{trend} < 0.001) rather than basal insulin (19% to 16%, p_{trend} = 0.305). Subjects in the high-decrease group had the highest rate of insulin usage, with 24% to 12% receiving basal insulin (p_{trend} = 0.013) and 41% to 61% receiving multiple insulin injections (p_{trend} < 0.001). The proportion of subjects receiving OHA only decreased in this group, with the larger decrease observed among subjects receiving two OHAs (21% to 11%, p_{trend} = 0.012) than those receiving more than two OHAs (13% to 10%, p_{trend} = 0.350).

3.4 | Treatment intensification and de-intensification

We then compared the change in treatment plan during the 6-year follow-up period among patients with different HbA1c patterns (Table 2). Change in treatment plan was more common in the three poorer control groups than the low-stable group. Forty percent of subjects in the low-stable group had experienced treatment intensification, while the proportions were significantly higher in other three subgroups (60% to 71%). Median time to first treatment intensification was longer in the two stable groups than the unstable groups (3 years vs 2 years). Among the four subgroups, around one-third of the subjects had experienced treatment de-intensification, and 19% to 36% of subjects had experienced both intensification and de-intensification.

To evaluate the magnitude of treatment change during the 6-year follow-up, we further compared the treatment plan of the baseline

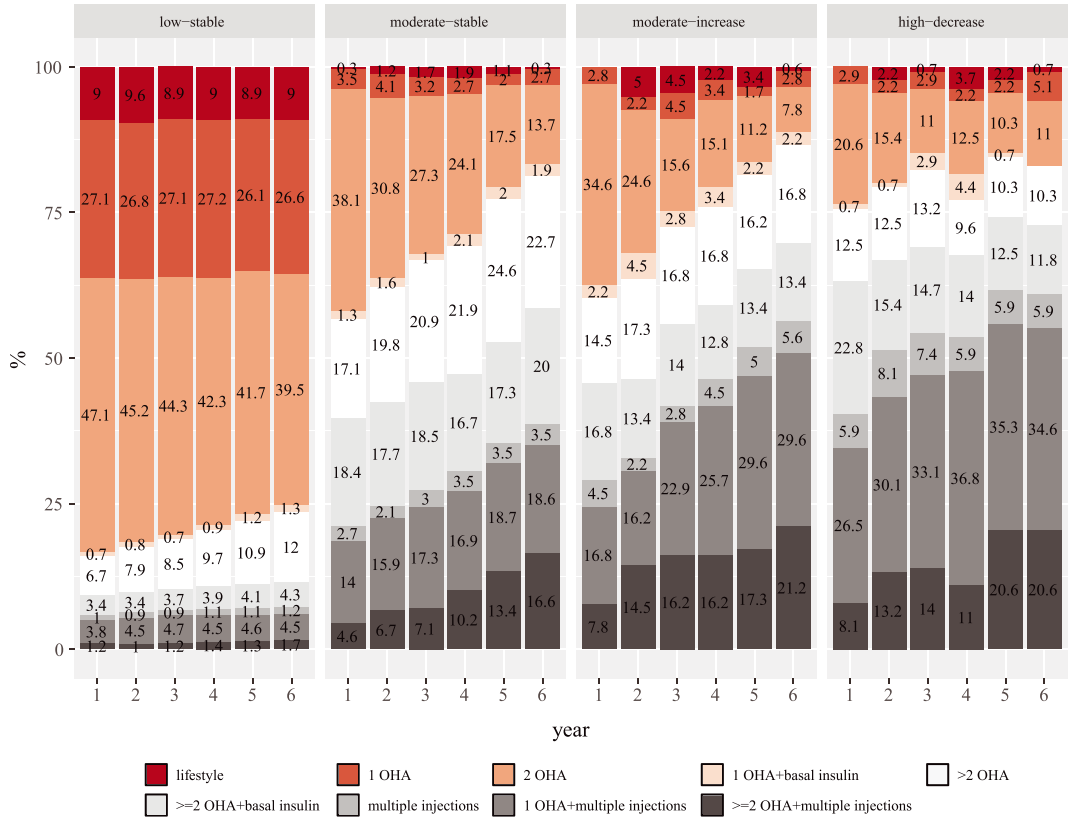

FIGURE 3 Comparison of annual treatment plans between 2011 (year 1) and 2016 (year 6) in the four HbA1c subgroups

(2011) and the last year (2016). In the low-stable group, 62% of subjects had the same treatment plans in 2011 and 2016; 24% and 14% of subjects had intensified or de-intensified treatment, respectively, with addition or removal of OHA being the most common change. In the three poorer control groups, around 45% of subjects had unchanged treatment plans, of whom 45%, 60%, and 76% were already treated with multiple insulin injections in moderate-stable, moderate-increase, and high-decrease groups, respectively; 41% to 50% of subjects in these three groups had intensified treatment plans. In the moderate-stable group, 39% of the intensified subjects added multiple insulin injections, 28% added basal insulin, and 34% added OHA only. In the moderate-increase and high-decrease group, adding multiple insulin injections was the most common type of treatment intensification, accounting for around 60% of intensified subjects.

4 | DISCUSSION

This study examined antidiabetic treatment and treatment changes in association with glycemic control trajectories in a cohort of multi-ethnic Asian patients managed under public primary care clinics in Singapore. Four distinct HbA1c patterns were identified including low-stable, moderate-stable, moderate-increase, and high-decrease, with treatment complexity differing across groups commensurate to the severity of dysglycemia. The majority of patients having poorer glycemic control were either already receiving multiple insulin injections at baseline, or intensified to multiple insulin injections during follow-up.

In this population with an average diabetes duration of 5 years at recruitment, the vast majority of patients managed to maintain low and stable HbA1c. In this group, most patients were using one or two OHAs, while a small proportion of patients transitioned from oral medication to insulin treatment. This increase in the rate of insulin treatment was consistent with previous studies[3,4] and maybe a result of the progressive beta-cell failure along with the increase in duration of diabetes.[10] This step-by-step transitioning of treatment plans was also in accordance with the current recommended sequence of treatment initiation and intensification in clinical guidelines, which suggest starting treatment from OHA mono-therapy, and progressing to more complex therapy combinations when simple treatment fails.[1]

We also identified three other groups of patients with poorer glycemic control and much higher uptake of insulin treatment. While all groups were considered poor control groups with average HbA1c levels greater than 8.0%, we observed different trends of glycemic control in these groups. One group had stable HbA1c at moderately high level; one group had very high initial HbA1c levels that improved substantially over time; the other group, however, had moderately high initial HbA1c levels but deteriorated over time. Clinical inertia is a possible cause for the different trends, and two hypotheses were examined in this study. First, it is possible that patients with deteriorating control did not have treatment intensification during the follow-up period, where timely intervention may have resulted in more rapid attainment of HbA1c goals.[11] Second, it is also likely that these patients were not getting sufficient treatment intensification, where multiple insulin injections could still be added to stop the deteriorating trend. In this study, we found that that 71% of the patients with deteriorating control had experienced treatment intensification during the follow-up period, and time to first intensification of treatment was in average 1 year shorter in this group than the low-stable

TABLE 2 Change in treatment between 2011 and 2016 in the four HbA1c subgroups

	Low-Stable (*n* = 5005)	Moderate-Stable (*n* = 898)	Moderate-Increase (*n* = 179)	High-Decrease (*n* = 136)	*P* Value
During the whole follow-up period (2011 to 2016)					
Ever intensified (N, %)	1994 (39.8)	567 (63.1)	127 (70.9)	82 (60.3)	<0.001
Time to first intensification (median, IQR)	3.00 [2.00, 4.00]	3.00 [1.00, 4.00]	2.00 [1.00, 3.00]	2.00 [1.00, 3.75]	<0.001
Ever de-intensified (N, %)	1505 (30.1)	234 (26.1)	69 (38.5)	47 (34.6)	0.003
Time to first de-intensification (median, IQR)	3.00 [2.00, 4.00]	3.00 [2.00, 4.00]	2.00 [1.00, 4.00]	3.00 [2.00, 3.00]	0.003
Experienced both intensification and de-intensification (N, %)	961 (19.2)	206 (22.9)	65 (36.3)	42 (30.9)	<0.001
Unchanged (N, %)	2467 (49.3)	303 (33.7)	48 (26.8)	49 (36.0)	<0.001
Comparing the first year (2011) and the last year (2016)					
Status (N, %)					<0.001
Intensified	1207 (24.1)	444 (49.4)	87 (48.6)	56 (41.2)	
De-intensified	693 (13.8)	61 (6.8)	10 (5.6)	17 (12.5)	
Unchanged	3105 (62.0)	393 (43.8)	82 (45.8)	63 (46.3)	
Change of treatment among intensified patient (N, %)					<0.001
Add OHA	959 (79.5)	149 (33.6)	17 (19.5)	11 (19.6)	
Add basal insulin	147 (12.2)	123 (27.7)	18 (20.7)	10 (17.9)	
Add multiple injections	101 (8.4)	172 (38.7)	52 (59.8)	35 (62.5)	
Change of treatment among de-intensified patients (N, %)					<0.001
Remove OHA	625 (90.2)	30 (49.2)	5 (50.0)	5 (29.4)	
Remove basal insulin	34 (4.9)	15 (24.6)	2 (20.0)	5 (29.4)	
Remove multiple injections	34 (4.9)	16 (26.2)	3 (30.0)	7 (41.2)	
Treatment plan among unchanged patients (N, %)					<0.001
Lifestyle	281 (9.0)	1 (0.3)	0 (0.0)	0 (0.0)	
OHA	2464 (79.4)	162 (41.2)	26 (31.7)	11 (17.5)	
Basal insulin	96 (3.1)	55 (14.0)	7 (8.5)	4 (6.3)	
Multiple injections	264 (8.5)	175 (44.5)	49 (59.8)	48 (76.2)	

Abbreviations: IQR, interquartile range; OHA, oral hypoglycemic agent; SD, standard deviation.

or moderate-stable groups. Addition of multiple insulin injections was the most common treatment intensification in patients with deteriorating control, and around 60% of those without intensified treatment were already on multiple insulin injections.

These results suggest that only a small proportion of the patients with deteriorating control may potentially suffer clinical inertia manifested as not getting treatment intensified. However, it is important to note that more intensive treatment may not be applicable for these patients in some circumstances. We observed that around 41% of them were diagnosed with diabetic kidney diseases at recruitment. Several studies have suggested that the potential side effects of treatment intensification, such as severe hypoglycemic episodes, may outweigh the benefits of tighter glycemic control in high-risk patients with long diabetes duration and/or severe comorbidities.[12-14] Therefore, current treatment in these patients may actually be optimal based on their clinical profile.

Although deteriorating HbA1c invites treatment intensification, there are factors associated with the HbA1c deterioration which render bringing glycemia under control challenging, despite treatment intensification. Differences in the underlying diabetes biology, such as severe progressive beta-cell failure, may drive the relentless HbA1c deterioration. The patient characteristics of those with deteriorating HbA1c suggests the existence of a more severe form of disease characterized by early beta cell failure and high level of insulin resistance. These patients were more likely to be of Malay and Indian ethnicity and with younger age at diagnosis. Both younger age at diagnosis and ethnicity were associated with poorer glycemic control in previous studies,[15] and it has also been reported that Indians have lower insulin sensitivity and Malays lower beta cell responsiveness than Chinese ethnicity.[16] These non-responsive patients may require more intensive workup to identify effective regimens in clinical practice. Medication adherence is another possible explanation. Previous studies have reported that insulin adherence rate in patients with type 2 diabetes was only around 60%,[17] and barriers in insulin administration, high costs, and side effects could further impede adherence to insulin treatment.[18,19] It is possible that these patients were non-adherent to their prescribed treatment due to health-related, personal, or social reasons. In some patients, the deterioration of glycemic control may be attributable to inappropriate insulin usage.[20] Patients with poor glycemic control are more likely to experience hypoglycemic episodes when using insulin,[21] in part due to failure to follow the strict time window constraints for insulin treatment. Excessive eating due to hypoglycemia and fear of impending hypoglycemic episodes may in turn lead to hyperglycemia and weight gain,[22] resulting in a vicious cycle of insulin intensification and deteriorating glycemic control. These patients may benefit from a wide range of technological advances in diabetes, including user-friendly continuous glucose monitoring for the elucidation of intra-day variations in glycemic levels, testing to identify special diabetes subtypes including latent autoimmune diabetes in adults (LADA), new effective pharmaco-therapeutics, and

greater support for timely and appropriate use of prescribed medication including insulin. Further studies would be necessary to identify the specific reasons behind the deteriorating HbA1c in this group and explore ways to improve glycemic control among these patients. This is especially important because these patients have a substantially higher risk of severe complication and death, as our previous study has shown,[3] and are likely to demand a disproportionate amount of health care resources.

The HbA1c patterns identified in this study were quite consistent with the four patterns identified in our previous study, except that there were more subjects in the low-stable group and fewer subjects in the moderate-group than the previous study.[3] It is important to note that even though both studies were conducted using the same cohort, the population pool was quite different. In our previous analysis, we analyzed patients with data from medical records available before 2010 and included patients managed in specialist outpatient clinics as well. These patients were usually referred from primary care clinics due to advanced disease conditions; thus, they were more likely to have less stringent HbA1c targets and categorized into a group with moderate HbA1c levels. In the current study, on the other hand, the data period was from 2011 to 2016, and all the patients included were managed in primary care settings only.

The different HbA1c trajectory patterns may to some extent reflect the heterogeneity within type 2 diabetes patients. Ahlqvist et al have recently identified five clusters of adult-onset diabetes, including severe autoimmune diabetes (SAID), severe insulin-deficient diabetes (SIDD), severe insulin resistant diabetes (SIRD), mild obesity-related diabetes (MOD), and mild age-related diabetes (MARD).[23] These clusters were differentiated in terms of age of diagnosis, BMI, metabolic control, insulin deficiency, insulin resistance, and presence of glutamic acid decarboxylase antibodies (GADA). We also observed differences in patient profiles among our HbA1c trajectory subgroups. Patients in the low-stable group had the oldest age and lowest rate of insulin treatment, suggesting that the MARD cluster may dominate this trajectory group, while patients in the moderate-increase group had high BMI and poor response to insulin treatment, suggesting they may belong to the SIDD cluster which had high level of insulin resistance. However, we were not able to test this formally in our population, as data on GADA and C-peptide levels were not available.

Our study has several limitations. First, the analysis of medication in this study was based on patients' dispensed medication records, not prescribed medication records; therefore, we were not able to capture the gap between prescribed and dispensed medication. However, the dispensed medication records are more closely related to patient's actual medication usage than prescribed records, thus the annual treatment plan identified using dispensed medical records would better reflect the medication usage in real practice. Second, information on the quantity of medication dispensed and medical adherence was not available in the data; thus, we were not able to quantify medication coverage in this study. Also, diabetic retinopathy was assessed based on self-reported questionnaire and record of physician diagnosis at the time of recruitment. Retinal photography images were not accessible; thus, we may have underestimated the prevalence of diabetic retinopathy. In addition, type 2 diabetes is based on physician diagnosis in this study, and patients with atypical types of diabetes or diabetes with secondary mixed aetiologies, such as glucokinase–maturity-onset diabetes of the young (GCK-MODY) or LADA, might be mis-classified as type 2 diabetes in clinical practice. Such "non-classic type 2 diabetes" may influence HbA1c trajectories and related treatment. The limitation of using the LCGA is also worth noting. LCGA is a simplified reflection of the longitudinal HbA1c profiles in the population. However, the individual HbA1c trajectories may be much more diverse and complicated, and the model may not be able to capture all these different individual patterns.[24] Lastly, this study was conducted in a single network of public primary care clinics in Singapore and we excluded a number of subjects due to lack of complete data for analysis. However, the National Primary Care Survey has shown that public polyclinics covered a large proportion of chronic disease management including diabetes,[25] and the distribution of patients with OHAs and insulin treatment in our study was consistent with other descriptive studies conducted in primary care settings in Singapore.[26]

Our study examined antidiabetic treatment and treatment changes in patients with type 2 diabetes in real clinical practice and analyzed their association with the glycemic control trajectories observed. We found that treatments were generally reflective of and appropriate to the extent of dysglycemia, and in accordance with current clinical care guidelines. A small group of patients continued to manifest deteriorating glycemic control, in spite of being treated with the most complex regimen available, multiple insulin injections with or without other agents. These patients may either be non-responsive or non-adherent to treatment, and further investigation is needed to identify reasons for the deteriorating control observed and design effective interventions for these patients.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest associated with this manuscript.

CONTRIBUTION STATEMENT

K.V. and M.L. designed the study, researched data, and wrote the manuscript. E.S.T. and W.Y.L. contributed to study design, the collection of research data, and edited the manuscript. C.S.T. contributed to data analysis and edited the manuscript. K.S.C. and W.E.T. contributed to data collection and edited the manuscript. All authors read and approved the final manuscript.

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SUPPORTING INFORMATION

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

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