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Prevalence and predictors of clinical inertia in patients with type 2 diabetes who were treated with a single oral antidiabetic drug

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ABSTRACT

Aims/Introduction: Clinical inertia, defined as a failure of healthcare providers to initiate or intensify treatment when indicated, is one of the challenges in achieving glycemic targets in type 2 diabetes patients.

Materials and Methods: Using a Japanese medical database compiled from Diagnostic Procedure Combination hospitals, this retrospective study investigated clinical inertia in type 2 diabetes patients treated with a single oral antidiabetic drug. We analyzed predictors of clinical inertia, measured the time to treatment intensification, and monitored patients' glycemic control and renal function for 2 years. The index date was defined as the first date of hemoglobin A1c ≥7.0% during the 180 (±60) days after the first oral antidiabetic drug was prescribed.

Results: Clinical inertia was identified in 35.3% of patients. The median time to treatment intensification from the index date was 75.5 days. The proportion of patients achieving hemoglobin A1c <7.0% within 2 years was 33.8% with clinical inertia, and 47.9% without clinical inertia. Multivariate logistic regression analysis showed that Charlson Comorbidity Index score and an interval between visits of ≥6 weeks significantly increased the risk of developing clinical inertia, and hyperlipidemia and higher hemoglobin A1c at baseline significantly decreased the risk.

Conclusions: This study showed that clinical inertia in type 2 diabetes patients treated with a single oral antidiabetic drug might have a lasting effect on long-term glycemic control. Our findings will inform clinicians of the characteristics of patients associated with clinical inertia and the importance of providing appropriate treatment under clinical practice guidelines.

INTRODUCTION

Clinical inertia, defined as a failure of healthcare providers to initiate or intensify treatment when indicated, is one of the challenges in achieving glycemic targets in type 2 diabetes[1–4]. The target hemoglobin A1c (HbA1c) of <7.0% (<53 mmol/mol) is recommended in the majority of adult patients with type 2 diabetes by the Japan Diabetes Society, the American Diabetes Association and International Diabetes Federation to minimize the risk of microvascular and macrovascular complications developing later[5–7]. A prospective observational study of 4,585 patients with type 2 diabetes in 23 hospital-based clinics in England, Scotland and Northern Ireland showed that the risk of diabetic complications was strongly associated with previous hyperglycemia, and that any reduction in HbA1c was likely to reduce the risk of those complications[8]. A 10-year post-interventional follow up of the United Kingdom Prospective Diabetes Study survivor cohort showed a continued microvascular benefit from early improved glucose control, as well as emergent risk reductions for myocardial infarction and death from any cause[9]. A retrospective cohort study using primary care level data of 105,477 patients

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in the UK showed that a 1-year delay in receiving treatment intensification was associated with an increased risk of cardiovascular diseases in patients with HbA1c ≥7.0%[10]. However, according to the previous surveys using non-institutionalized data in Japan, the USA and the UK, nearly half of patients with diabetes failed to achieve HbA1c of <7.0%[11–13].

Previous reports classified principal factors contributing to clinical inertia into three categories: (i) physician-related factors, such as failure to set clear goals and reactive rather than proactive care; (ii) patients-related factors, such as denial of having the disease and absence of symptoms; and (iii) healthcare-related factors, such as no clinical guidelines and no decision support[14]. Education programs for prescribing physicians have been shown to effectively remind them of the long-term benefits of aiming at therapeutic targets beyond resolving patient symptoms[1]. Thus, identifying factors and patient characteristics associated with clinical inertia is imperative to understand what causes hesitation to initiate clinical intervention and improve the management of diabetes.

In the present study, using a Japanese medical database compiled from Diagnostic Procedure Combination hospitals, we evaluated the prevalence of clinical inertia in type 2 diabetes patients who had been treated with a single oral antidiabetic drug (OAD), analyzed predictors of clinical inertia, measured the time to treatment intensification, and monitored glycemic control and renal function for 2 years.

MATERIALS AND METHODS

Data source and participants

The present historical cohort study was carried out using the Medical Data Vision (MDV) database (https://en.mdv.co.jp/about-mdv-database/), a hospital-based anonymized database containing health claim data and blood test results of >400 Diagnostic Procedure Combination hospitals compiled between April 2008 and November 2018. Retrieved data included patient demographics, diagnosis date of type 2 diabetes, comorbidities (kidney disease, hypertension, hyperlipidemia, liver disease, heart disease and dementia), Charlson Comorbidity Index (CCI) score, OADs, number of prescription medications, clinical departments that prescribed medications to patients, history of hypoglycemia and blood test results (HbA1c and estimated glomerular filtration rate [eGFR]).

Inclusion and exclusion criteria

Patients were included in the study if they were diagnosed with type 2 diabetes (International Classification of Diseases, 10th revision, code E11 or E14) after December 2010, prescribed a single OAD as the first treatment of diabetes, aged ≥18 years and <75 years at the first OAD prescription, with an HbA1c ≥7.0% recorded within 180 (±60) days after the first OAD prescription. In the present study, the index date was defined as the first date of HbA1c ≥7.0% within 180 (±60) days after the first OAD prescription. To be included in the study, the patient must have had their medical chart recorded for 180 days after the index date, and have had at least one serum creatinine or eGFR determination between the date of the first OAD prescription and the index date. Patients were excluded if they were diagnosed with type 1 diabetes, received other antidiabetic drugs before the index date, OAD was prescribed for less than half the days from the date of the first prescription to the index date, OAD was prescribed for <90 days of the 180 days after the index date, prescribed hemodialysis or erythropoietin-stimulating agents after the first OAD prescription, hospitalized for treatment of type 2 diabetes before the index date or hospitalized for ≥14 days after the first OAD prescription. Clinical inertia was defined as not receiving treatment intensification, such as increasing the dose of the current OAD, adding other OADs and switching to other OADs, within 180 days after the index date. Patients whose HbA1c was maintained <7.0% between 150 and 210 days after the index date were not considered clinical inertia patients, even without treatment intensification. In the present study, we excluded patients aged ≥75 years on the assumption that individual differences, such as complications, activities of daily living and caregiving situations, vary considerably in this stage of life.

End-points

The protocol-specified primary end-point was to identify the baseline risk factors associated with clinical inertia. The secondary end-points were: (i) to measure and compare the time from the index date to the first treatment intensification in the overall population, between patients with or without clinical inertia and among patients treated with different OADs; and (ii) to monitor HbA1c, the proportion of patients achieving target HbA1c (<7.0%), eGFR, hypoglycemic episodes in patients with and without clinical inertia up to 24 months.

Statistical analysis

Data are presented either as the median (interquartile range), number (percentage) or mean ± standard deviation (SD). A baseline cross-sectional summary of patient characteristics at the first prescription of OAD was made for the entire cohort and then stratified by the presence of clinical inertia. Univariate logistic analysis was used to screen for the risk factors associated with clinical inertia. Variables with *P*-values <0.2 in the univariate logistic analysis were used for a stepwise multivariate logistic regression analysis. Subgroup analysis was carried out in patients aged ≥18 and <65 years, and patients aged ≥65 and <75 years to determine and compare the risk factors associated with clinical inertia in each age group. Student's *t*-tests were used to compare HbA1c and eGFR between patients with and without clinical inertia. Kaplan–Meier plots were made until treatment intensification for the entire cohort and then for groups stratified by baseline OADs. A two-tailed *P*-value <0.05 was considered statistically significant. SAS® Enterprise Guide and System Release 9.4 (SAS Institute Inc., Cary, NC, USA) were used for these analyses.

RESULTS

Participants and descriptive statistics

Among 295,131 diabetes patients whose medical data were available in the MDV database between April 2008 and November 2018, patients who met the outlined inclusion and exclusion criteria were analyzed for the primary (n = 1,483) and secondary end-points (n = 1,412), respectively (Figure S1). The baseline descriptive statistics for the entire cohort and patients with and without clinical inertia are presented in Table 1. Among 1,483 patients, 524 (35.3%) experienced clinical inertia. Approximately 60% of the patients in each group were men, the median age at the first OAD initiation was approximately 60 years and one-third of the patients were aged ≥65 years. The median baseline HbA1c level was 7.3% for both groups, and 10.3% of patients with clinical inertia and 21.5% without clinical inertia had an HbA1c value of ≥8.0%. The prevalence of clinical inertia was 38.4% (470 of 1,223) in patients with an HbA1c value of ≥7.0% and <8.0%, 19.7% (36 of 183) in patients with an HbA1c value of ≥8.0% and <9.0%, and 23.4% (18 of 77) in patients with an HbA1c value of ≥9.0% (Figure S2). The median eGFR level was approximately 80 mL/min/1.73 m^2 in both groups. In both groups, half of the patients were prescribed dipeptidyl peptidase-4 inhibitors, and one-third were prescribed biguanides. More than 80% of the patients were not treated by doctors whose specialty was diabetes mellitus. Regarding complications, 53.4% of the patients with clinical inertia and 57.6% without clinical inertia had hyperlipidemia, and 28.2% of the patients with clinical inertia and 22.2% without clinical inertia had heart disease. None of the patients developed hypoglycemia.

Factors associated with clinical inertia

In univariate logistic regression analysis, age (odds ratio [OR] 1.01, 95% confidence interval [CI] 1.00–1.03), age categories (vs ≥minimum and ≤first quartile [Q1]: OR 1.39 for > Q1 and ≤median, 1.49 for >median and ≤quartile 3 [Q3], and 1.38 for >Q3 and ≤maximum), every 1% increase in HbA1c (OR 0.69, 95% CI 0.58–0.82), HbA1c value ≥8.0% (vs ≥7.0% and <7.5%: OR 0.40, 95% CI 0.29–0.55), CCI score (OR 1.07, 95% CI 1.01–1.13), a concomitant heart disease (OR 1.38, 95% CI 1.08–1.76) and the interval between visits (vs <6 weeks: OR 1.46 for ≥6 weeks and <8 weeks, 1.41 for ≥8 weeks and

Table 1 | Baseline descriptive statistics for the entire cohort and patients with and without clinical inertia

Variables	Overall, n = 1,483	With clinical inertia, n = 524 (35.3%)	Without clinical inertia, n = 959 (64.7%)
Sex			
Male	952 (64.2)	327 (62.4)	625 (65.2)
Female	531 (35.8)	197 (37.6)	334 (34.8)
Age (years)	59 (50–66)	60 (52–66)	59 (49–66)
≥65	478 (32.2)	177 (33.8)	301 (31.4)
HbA1c, %	7.3 (7.1–7.7)	7.3 (7.1–7.6)	7.3 (7.1–7.8)
≥ 8.0	260 (17.5)	54 (10.3)	206 (21.5)
eGFR (mL/min/1.73 m^2)	79.5 (67.5–92.8)	78.4 (66.2–91.4)	79.9 (68.5–93.2)
≥60	1,281 (86.4)	440 (84.0)	841 (87.7)
Oral antidiabetic drugs			
DPP-4 inhibitors	762 (51.4)	283 (54.0)	479 (49.9)
Biguanides	504 (34.0)	158 (30.2)	346 (36.1)
Sulfonylureas	106 (7.1)	42 (8.0)	64 (6.7)
α-Glucosidase inhibitors	44 (3.0)	14 (2.7)	30 (3.1)
SGLT2 inhibitors	39 (2.6)	17 (3.2)	22 (2.3)
Thiazolidinediones	16 (1.1)	5 (1.0)	11 (1.1)
Meglitinides	12 (0.8)	5 (1.0)	7 (0.7)
Not treated by DM specialists	1,249 (84.2)	446 (85.1)	803 (83.7)
Charlson Comorbidity Index	2 (1–3)	2 (1–3)	2 (0–3)
No. prescribed medications	3 (2–6)	3 (2–6)	3 (2–6)
Kidney disease	125 (8.4)	45 (8.6)	80 (8.3)
Hypertension	821 (55.4)	289 (55.2)	532 (55.5)
Hyperlipidemia	832 (56.1)	280 (53.4)	552 (57.6)
Liver disease	353 (23.8)	129 (24.6)	224 (23.4)
Heart disease	361 (24.3)	148 (28.2)	213 (22.2)
Dementia	3 (0.2)	3 (0.6)	0 (0.0)
History of hypoglycemia	0 (0.0)	0 (0.0)	0 (0.0)

Data are presented as n (%) or the median (interquartile range). DM, diabetes mellitus; DPP-4, dipeptidyl peptidase IV; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; SGLT2, sodium–glucose cotransporter 2.

<10 weeks, and 1.71 for ≥10 weeks) were associated with the development of clinical inertia (Table 2). In stepwise multivariate logistic regression analysis using variables with *P*-values <0.2 in the preceding univariate analysis, an HbA1c value ≥8.0% (vs ≥7.0% and <7.5%: OR 0.41, 95% CI 0.29–0.56), CCI score (OR 1.07, 95% CI 1.01–1.13), hyperlipidemia (OR 0.76, 95% CI 0.61–0.95) and the interval between visits (vs <6 weeks: OR 1.45 for ≥6 weeks and <8 weeks, 1.45 for ≥8 weeks and <10 weeks, and 1.74 for ≥10 weeks) were associated with the development of clinical inertia (Table 2). When stratified by

Table 2 | Factors predictive of clinical inertia (n = 1,483)

Variables	Unadjusted OR (95% CI)	*P*-value
Female	1.13 (0.90–1.41)	0.2881
Age (years)	1.01 (1.00–1.03)	0.0047
Age, categories (vs ≥minimum and ≤Q1)		
>Q1 and ≤median	1.39 (1.03–1.89)	0.0342
>median and ≤Q3	1.49 (1.10–2.00)	0.0094
>Q3 and ≤maximum	1.38 (1.02–1.88)	0.0385
HbA1c, every 1% increase	0.69 (0.58–0.82)	<0.0001
HbA1c, % (vs ≥7.0 and <7.5)		
≥7.5 and <8.0	0.78 (0.60–1.03)	0.0763
≥8.0	0.40 (0.29–0.55)	<0.0001
eGFR (every 5 mL/min/1.73 m^2 increase)	0.98 (0.95–1.00)	0.0595
≥60 vs <30	0.52 (0.13–2.10)	0.3613
Not treated by DM specialists	1.11 (0.83–1.49)	0.4856
Charlson Comorbidity Index	1.07 (1.01–1.13)	0.0137
Number of prescribed medications		
≥ 5 vs 0–2	1.03 (0.81–1.32)	0.8116
Kidney disease	1.03 (0.71–1.51)	0.8702
Hypertension	0.99 (0.80–1.22)	0.9051
Hyperlipidemia	0.85 (0.68–1.05)	0.1261
Liver disease	1.07 (0.84–1.37)	0.5859
Heart disease	1.38 (1.08–1.76)	0.0098
Interval between visits, weeks (vs <6)		
≥6 and <8	1.46 (1.09–1.95)	0.0111
≥8 and <10	1.41 (1.06–1.89)	0.0197
≥10	1.71 (1.26–2.31)	0.0005
Oral antidiabetic drugs (vs sulfonylureas)		
DPP-4 inhibitors	0.90 (0.59–1.37)	0.6207
Biguanides	0.70 (0.45–1.07)	0.1002
α-Glucosidase inhibitors	0.71 (0.34–1.50)	0.3693
SGLT2 inhibitors	1.18 (0.56–2.48)	0.6665
Thiazolidinediones	0.69 (0.23–2.14)	0.5229
Meglitinides	1.09 (0.32–3.66)	0.891

Variables	adjusted OR (95% CI)	*P*-value
HbA1c, categories (vs ≥7.0 and <7.5)		
≥ .5 and <8.0	0.80 (0.61–1.06)	0.1177
≥ 8.0	0.41 (0.29–0.56)	<0.0001
Charlson Comorbidity Index	1.07 (1.01–1.13)	0.0227
Hyperlipidemia	0.76 (0.61–0.95)	0.0179
Heart disease	1.29 (1.00–1.67)	0.0534
Interval between visits, weeks (vs <6)		
≥6 and <8	1.45 (1.07–1.94)	0.0151
≥8 and <10	1.45 (1.08–1.95)	0.0144
≥10	1.74 (1.28–2.38)	0.0005

Univariate logistic regression analysis was used to estimate the unadjusted odds ratio (OR) and 95% confidence interval (CI). Stepwise multivariate logistic regression analysis was used to estimate the adjusted OR and 95% CI. Variables with *P*-values <0.2 in univariate logistic analysis were included. DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; Q1, first quartile; Q3, third quartile.

age, an HbA1c value ≥8.0% (vs ≥7.0% and <7.5%: OR 0.44, 95% CI 0.22–0.87), hypertension (OR 0.64, 95% CI 0.42–0.96), heart disease (OR 1.62, 95% CI 1.05–2.50) and the interval between visits (vs <6 weeks: OR 1.70 for ≥6 weeks and <8 weeks, 2.04 for ≥8 weeks and <10 weeks, and 2.17 for ≥10 weeks) among older patients (≥65 and <75) were associated with clinical inertia (Table 3). In younger patients (aged ≥18 and <65 years), age categories (vs ≥minimum and ≤Q1: OR 1.38 for >Q1 and ≤median, 1.57 for >median and ≤Q3, and 1.58 for >Q3 and ≤maximum), an HbA1c value ≥8.0% (vs ≥7.0% and <7.5%: OR 0.42, 95% CI 0.29–0.62) and the interval between visits (vs <6 weeks: OR 1.34 for ≥6 weeks and <8 weeks, 1.19 for ≥8 weeks and <10 weeks, and 1.57 for ≥10 weeks) were associated with clinical inertia (Table 3).

Time to treatment intensification

The proportion of patients whose treatment was intensified continued to increase steadily up until 24 months after the index date (Figures 1a, b, Figure S3). From the index date to treatment intensification, the median time was 75.5 days, 306.5 days and 57.0 days in all patients, in clinical inertia patients and in patients without clinical inertia, respectively (Table 4). When stratified by the first prescribed OADs, the median time to treatment intensification ranged from 60.5 days (α-glucosidase inhibitors) to 85.0 days (sulfonylureas) in the overall population (Table 4).

Table 3 | Factors predictive of clinical inertia in subgroup analysis

Patients ≥65 and <75 (n = 478)		
Variables	adjusted OR (95% CI)	P-value
HbA1c, categories (vs ≥7.0 and <7.5)		
≥7.5 and <8.0	1.07 (0.66–1.74)	0.7883
≥8.0	0.44 (0.22–0.87)	0.0178
Hypertension	0.64 (0.42–0.96)	0.0310
Heart disease	1.62 (1.05–2.50)	0.0305
Interval between visits, weeks (vs <6)		
≥6 and <8	1.70 (1.00–2.89)	0.0484
≥8 and <10	2.04 (1.22–3.42)	0.0066
≥10	2.17 (1.22–3.86)	0.0083
Patients ≥18 and <65 (n = 1,005)		
Variables	adjusted OR (95% CI)	P-value
Age, categories (vs ≥ minimum and ≤Q1)		
>Q1 and ≤median	1.38 (0.95–2.02)	0.0932
>median and ≤Q3	1.57 (1.08–2.28)	0.0187
>Q3 and ≤maximum	1.58 (1.06–2.34)	0.0247
HbA1c, categories (vs ≥ 7.0 and <7.5)		
≥7.5 and <8.0	0.72 (0.52–1.01)	0.0562
≥8.0	0.42 (0.29–0.62)	<0.0001
Charlson Comorbidity Index	1.07 (1.00–1.15)	0.0657
Hyperlipidemia	0.79 (0.60–1.03)	0.0782
Interval between visits, weeks (vs <6)		
≥6 and <8	1.34 (0.94–1.93)	0.1102
≥8 and <10	1.19 (0.83–1.73)	0.3465
≥10	1.57 (1.08–2.27)	0.0168

Stepwise multivariate logistic regression analysis was used to estimate the adjusted odds ratio (OR) and 95% confidence interval (CI). HbA1c, hemoglobin A1c; Q1, first quartile; Q3, third quartile.

Follow-up HbA1c and eGFR assessment

At the index date, the mean HbA1c was 7.4% (SD 0.6) in patients with clinical inertia and 7.6% (SD 0.8) in patients without clinical inertia (P < 0.0001; Figure 2a). Six and 12 months from the index date, patients with clinical inertia had significantly higher HbA1c values: 7.6% (SD 0.7) versus 7.2% (SD 1.0) (P < 0.0001) and 7.4% (SD 0.8) versus 7.2% (SD 0.9; P = 0.0001), respectively. At 24 months, there was no significant difference between the groups: 7.3% (SD 0.9) versus 7.2% (SD 1.0; P = 0.1158). The mean eGFR (standard deviation) was 79.7 mL/min/1.73 m^2 (SD 20.7) in patients with clinical inertia and 82.2 mL/min/1.73 m^2 (SD 21.1) in patients without clinical inertia (P = 0.0312; Figure 2b). At 12 and 24 months, there was no significant difference in eGFR between the groups.

The proportion of patients achieving HbA1c <7.0% at 6 months was 4.6% in patients with clinical inertia and 48.1% in those without clinical inertia. The disparity between the groups still existed at 24 months, and the proportion of patients achieving target HbA1c was 33.8% in patients with clinical inertia and 47.9% in those without clinical inertia (Figure 3a, b). There were no reported hypoglycemic events throughout the study period.

DISCUSSION

The present study analyzed the medical data of approximately 1,500 patients with type 2 diabetes treated in Diagnostic Procedure Combination hospitals in Japan, and found that 35.3% of the patients experienced clinical inertia in the treatment. The interval from the index day to the first treatment intensification was 75.5 days in the overall population. After 2 years of treatment, the proportion of patients achieving HbA1c <7.0% was consistently smaller in patients with clinical inertia than those without clinical inertia. Multivariate logistic regression analysis showed that baseline CCI score (OR 1.07) and an interval between visits of ≥6 weeks (OR 1.45–1.74) significantly increased the risk of clinical inertia, and concomitant hyperlipidemia (OR 0.76) and higher HbA1c at baseline (OR 0.41) significantly decreased the risk of clinical inertia.

The prompt initiation of treatment intensification in patients with newly diagnosed type 2 diabetes is necessary to prevent future complications of type 2 diabetes to reduce mortality[15,16]. Therefore, we included a cohort of patients in whom a single OAD was administered as the first diabetes treatment to determine the prevalence of clinical inertia during the early stage of diabetes. The Japanese Clinical Practice Guideline for Diabetes 2019 states that the treatment strategy and the choice of glucose-lowering agents for diabetes should be individualized

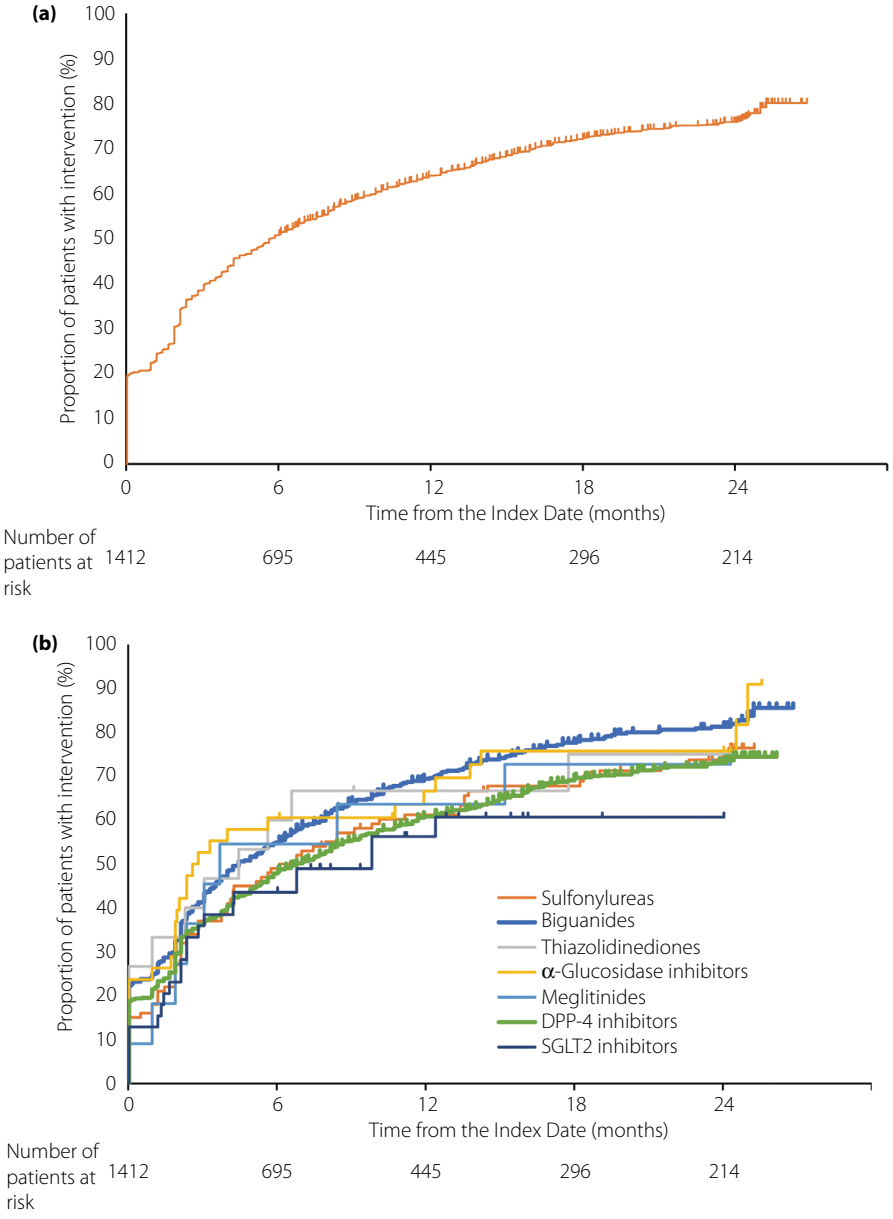

Figure 1 | Time to treatment intensification. The proportion of patients who underwent treatment intensification steadily increased until 24 months after the index date in (a) overall population and (b) groups stratified by first prescribed oral antidiabetic drugs. DPP-4, dipeptidyl peptidase-4; SGLT2, sodium–glucose cotransporter 2.

for each patient depending on the type, disease condition, age, metabolic abnormality and status of diabetic complications[5]. At the same time, it advises controlling glucose levels to be as close to normal as possible, as achieving and maintaining reasonable glycemic control earlier is likely to lead to favorable long-term outcomes. The guideline recommends increasing the dose of the agent, switching to a more potent agent or combining a current agent with another agent with a different mechanism of action when patients fail to achieve their glycemic target with first-line medication. The American Diabetes Association recommends re-evaluating the medication regimen every 3–6 months and adjusting as required to incorporate new patient factors while pharmacologically treating type 2 diabetes[17].

The result of our present study that 35.3% of the patients experienced clinical inertia in the treatment is consistent with the previous findings. A recent retrospective study in Japan utilized data from the Computerized Diabetes Care (CoDiC®) database, which contains the data of patients treated by diabetes specialists in 61 institutions participating in the Japan Diabetes Clinical Data Management Study Group nationwide. It reported on the existence of clinical inertia, identifying patients whose treatment was not intensified despite poor glycemic control[12].

Table 4 | Time to treatment intensification

First prescribed OAD	Overall population	Patients with clinical inertia	Patients without clinical inertia
Overall	75.5 (1.0–228.0), *n* = 1,032	306.5 (239.0–449.0), *n* = 256	57.0 (1.0–106.0), *n* = 776
DPP-4 inhibitors	78.0 (1.0–239.0), *n* = 501	321.5 (239.0–477.0), *n* = 130	57.0 (1.0–113.0), *n* = 371
Biguanides	78.0 (1.0–225.0), *n* = 387	295.5 (233.0–414.0), *n* = 94	54.0 (1.0–104.0), *n* = 293
Sulfonylureas	85.0 (36.0–239.0), *n* = 73	304.0 (224.0–547.0), *n* = 19	60.0 (1.0–120.0), *n* = 54
α-Glucosidase inhibitors	60.5 (1.0–169.0), *n* = 30	420.5 (358.0–736.0), *n* = 6	57.0 (1.0–74.5), *n* = 24
SGLT2 inhibitors	67.5 (36.0–128.0), *n* = 22	249.5 (204.0–333.5), *n* = 4	57.0 (1.0–85.0), *n* = 18
Thiazolidinediones	69.0 (1.0–169.0), *n* = 11	198.0 (198.0–198.0), *n* = 1	49.0 (1.0–134.0), *n* = 10
Meglitinides	81.5 (43.0–182.0), *n* = 8	354.5 (253.0–456.0), *n* = 2	64.0 (29.0–92.0), *n* = 6

Data are presented as the median days (interquartile range). DPP-4, dipeptidyl peptidase-4; OAD, oral antidiabetic drug; SGLT2, sodium–glucose cotransporter 2.

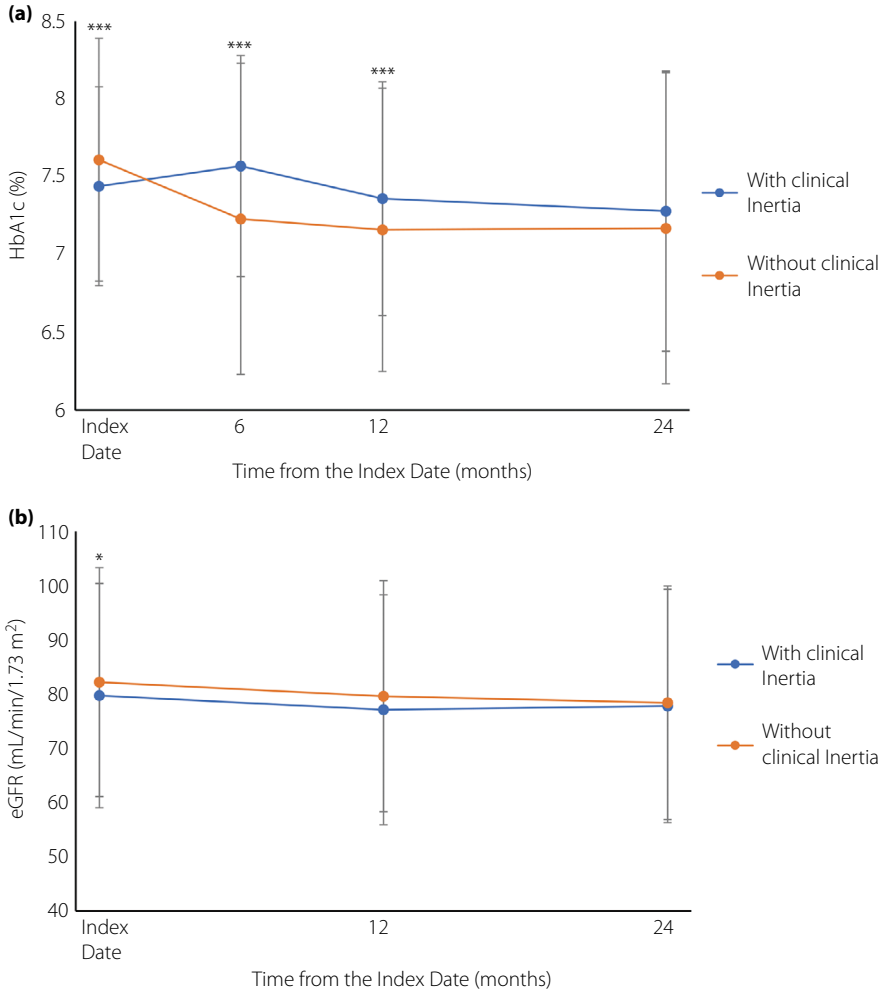

Figure 2 | Follow-up hemoglobin A1c (HbA1c) and estimated glomerular filtration rate (eGFR) stratified by intervention status. (a) The mean HbA1c was significantly lower in patients with clinical inertia at the index date, and significantly higher at 6 and 12 months than in patients without clinical inertia. (b) The mean eGFR was significantly lower at the index date in the patients with clinical inertia. Data are presented as mean ± standard deviation. ***$P < 0.001$; *$P < 0.05$.

A group in the USA using the electronic health records held by the Cleveland Clinic analyzed patients with newly diagnosed type 2 diabetes receiving metformin monotherapy who failed to reach HbA1c 7.0%, and found that treatment was not intensified within 6 months of metformin failure in 38% of the patients[4]. The analysis of the same database showed that 62.9%

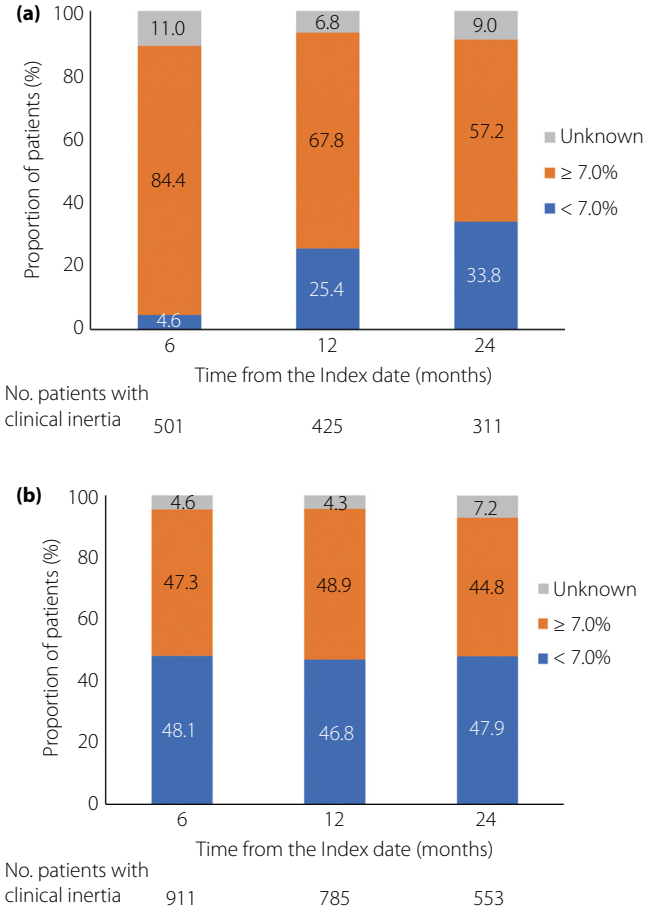

Figure 3 | The proportion of patients achieving target hemoglobin A1c (HbA1c). (a) The proportion of patients with clinical inertia achieving target HbA1c (<7.0%) increased over time, but remained one-third of the population at 24 months. (b) HbA1c (<7.0%) was observed in approximately half of the patients without clinical inertia up to 24 months.

of patients on a stable regimen of two OADs did not undergo treatment intensification during the 6 months after HbA1c ≥7%[18].

The present study shows that the CCI score, which predicts the 1-year mortality for a patient who might have a range of comorbid conditions[19,20], was chosen as one of the risk factors for clinical inertia in the multivariate logistic regression analysis of the study. Therefore, we presume that vulnerable patients might trigger an unwillingness by physicians to intensify treatment. In addition, heart disease increased the risk of clinical inertia in the overall population (OR 1.38) in the univariate logistic analysis. Although the database we utilized did not provide further details of heart disease, we assume many patients had coronary artery disease. Epidemiological evidence consistently links diabetes and cardiovascular disease[21,22]. At the same time, previous reports have shown that hypoglycemia is associated with cardiovascular disease[23] and cardiac events[24]. Thus, we assume the treating physicians might have been reluctant to intensify treatment in patients with known heart disease. In contrast, concomitant hyperlipidemia led to a decreased risk of clinical inertia (OR 0.76); further study is necessary to clarify the patient- or physician-related factors that underly this association.

Regular doctor visits are an essential part of type 2 diabetes management. The results of the present study showed that the risk of clinical inertia increased in patients where the interval between visits was ≥6 weeks; the risk is especially higher in those where the interval between visits was ≥10 weeks (OR 1.74). Therefore, encouraging patients to visit hospital regularly would decrease the risk of developing clinical inertia.

The subgroup analysis showed different risk factors between two age groups: older patients (aged ≥65 and <75 years) versus younger patients (aged ≥18 and <65 years). In the former group, heart disease increased the risk of clinical inertia (OR 1.62), as in the overall population, and hypertension decreased its risk (OR 0.64). As hypertension and hyperlipidemia are known risk factors for cardiovascular disease, physicians might set stricter goals for patients with these comorbidities. In the latter group, the risk of clinical inertia was increased with higher age and decreased with higher HbA1c (Table 3). Age itself has been reported to be a risk factor for poor glycemic control[25]. In a study of 1,109 adults aged ≥45 years with an established diagnosis of diabetes, those aged ≥65 years had better glycemic control than those aged 45–64 years[25]. Furthermore, these two age groups had distinct metabolic characteristics. The proportion of patients with HbA1c ≥8.0%, hypertension, hyperlipidemia and heart disease is 12.3%, 58.2%, 53.8% and 30.1% in the older patients, and 20.0%, 54.0%, 57.2% and 21.6% in the younger patients. Although the difference in risk factors between older and younger patients in the present study is not fully explicable, retirement might change a patient's lifestyle. Younger persons are often too occupied with work to incorporate a healthy lifestyle. Many full-time employees in Japan retire at age 60–65 years[26,27], leading to a change in diet and physical activity that might considerably affect their metabolic parameters.

The present study showed that the median time to treatment intensification was 75.5 days (2.5 months) in the overall population. In a previous study in Japan, the median time from the first reported HbA1c ≥7% to treatment intensification with OAD add-on or insulin was 3.7 and 3.3 months, respectively, among patients taking one OAD[12]. It took 14 months to treatment intensification among patients with newly diagnosed type 2 diabetes who failed to reach HbA1c 7.0% after 3 months of metformin therapy[4]. Compared with these studies, the patients in the present study received treatment relatively early. However, the median time to treatment intensification was 306.5 days in patients with clinical inertia, which was fivefold longer than those without clinical inertia (57.0 days). It shows that patients who miss the early treatment intensification might undergo fewer interventions throughout the course of their treatment. Among different OADs, sulfonylureas had the

longest median time to treatment intensification of 85.0 days (Table 4). Sulfonylureas stimulate insulin secretion independently of serum glucose levels and increase the risk of hypoglycemia[28]. The risk of hypoglycemia has shown to be further elevated when sulfonylureas are used in combination with dipeptidyl peptidase-4 inhibitors or glucagon-like peptide-1 receptor agonists[29,30]. Therefore, physicians might feel hesitant to add another OAD to patients treated with sulfonylureas to avoid hypoglycemia. At the same time, dipeptidyl peptidase-4 inhibitors and biguanides were the most popular first-line treatment in the present study, and secretagogues, including sulfonylureas and meglitinides, were much less common. This prescribing trend might explain why there were no reported hypoglycemic events in this study.

The clinical course of patients with and without clinical inertia was significantly different in terms of the mean HbA1c levels and the proportion of patients who achieved the target HbA1c of <7.0%. The mean HbA1c was significantly lower in patients with clinical inertia than in those without clinical inertia at the index date, but significantly higher 6 and 12 months from the index date. Some patients with clinical inertia underwent treatment intensification after 6 months from the index date, which might lead to an increase in the number of patients who achieved HbA1c <7.0%. Patients without clinical inertia, in contrast, were not likely to undergo another treatment intensification for a long time, which might lead to the number of patients who achieved HbA1c <7.0% remaining unchanged. At the same time, the proportion of patients achieving target HbA1c was smaller among those with clinical inertia throughout the study period, with just 33.8% of patients achieving the HbA1c target within 2 years. In contrast, approximately half of the patients without clinical inertia (47.9%) achieved HbA1c <7.0%.

There was no relationship between clinical inertia and deterioration of kidney function at 2 years. The kidney function of patients included in the present study was relatively well preserved at baseline. As the participants were patients who started with a single agent, it is estimated that few patients would have developed diabetic nephropathy.

The present study had several limitations. First, the MDV database only covers healthcare received in participating hospitals, and visits to emergency care or other hospitals were omitted. We did not obtain patients' medical record from hospitals or clinics they attended previously, if any, and patients who had been treated at other institutions might have been included in this study. In addition, because the data were from an acute care hospital, the study contain a large number of patients who are in poor condition. Second, the results of the present study were based on a database compiled between 2008 and 2018, and the current prescription habits of physicians and the OADs used might differ from those in this study. Third, only variables available in the database were entered into the regression analysis. The MDV database does not provide patients' body mass index, social status (occupation, wealth and education), lifestyle factors such as smoking and drinking or physicians' age and sex.

In conclusion, the present study shows that clinical inertia in type 2 diabetes patients treated with a single OAD might have a lasting effect on long-term glycemic control. To provide appropriate, timely treatment under the clinical guideline recommendations, clinicians need to be aware of the characteristics of patients at higher risk of experiencing clinical inertia.

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Approval of the research protocol: The study was approved by the ethics committee of Tokyo Medical University (T2021-0030).

Informed consent: As the study only involved analysis of pre-existing data in the databases, written informed consent from the study participants was not required.

Registry and the registration no. of the study/trial: Clinical trial registration was not required for this study, because it was not a prospective study and did not involve any intervention.

Animal studies: N/A.

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SUPPORTING INFORMATION

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

Figure S1 | Patient selection.

Figure S2 | Prevalence of clinical inertia in each hemoglobin A1c category.

Figure S3 | Probability of remaining free from intervention.