Factors associated with the degree of glycemic deterioration among patients with type 2 diabetes who dropped out of diabetes care: A longitudinal analysis using medical claims and health checkup data in Japan

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INTRODUCTION
Diabetes is a chronic disease that requires lifelong treatment and management. Patient-centered care and continuous follow-up are essential to prevent acute hyperglycemic and chronic diabetic complications such as neuropathy, retinopathy, nephropathy, and cardiovascular comorbidities1. Because diabetes is not a curable disease, periodic consultation is recommended even though the patient does not need their antidiabetic medication at that moment. However, some
patients drop out of diabetes care during the lifelong treatment, which consists of discontinuation of regular visits for diabetic medication or glycemic measurement. Previous cohort studies reported that the dropout rate among patients with type 2 diabetes ranged from 5.5 to 10%2,3. It has been reported that some factors such as age, sex, income, and race were associated with a higher dropout rate2,4,5. A meta-analysis of diabetes disease-management programs showed that 1.1–39.0% of patients dropped out6.

Owing to medication interruptions and lifestyle disruptions during the dropout, blood glucose control can be expected to deteriorate. Therefore, the degree to which blood glucose levels worsen from baseline during dropout is worth investigating to identify patients who especially need to resume treatment. However, no study has investigated the predictors of the degree of glycemic deterioration during treatment dropout, presumably due to the generally missing laboratory data for dropout patients.

In Japan, employer-sponsored health insurers cover employees of large-scale companies and their dependents, mandating yearly health checkups for their employees. Given that insurers have access to health checkup results, as well as health care claims information, such a collection of information may be a promising data source for investigating the worsening glucose levels among patients with diabetes who have dropped out of care.

As such, the present study aimed to investigate the effects of treatment discontinuation on glycemic control among patients with type 2 diabetes and to identify factors associated with worsening glycemic control during the dropout using combined claims and health checkup data in Japan.

MATERIALS AND METHODS

Study design, settings, and participants

This retrospective cohort study utilized a combination of medical claims and health checkup data between January 2005 and April 2018 from employer-sponsored health insurances in Japan provided by JMDC Inc. Japan has a universal health care system with approximately 3,500 insurers7 that provides coverage to individuals mostly based on their unique characteristics (e.g., age, region, job). Employees of large companies, as well as their dependents, are often insured by employer-sponsored health insurance. Employers and insurers are also required to conduct annual health checkups for all employees and their dependents to maintain employees’ health. Claims data include the names of diseases, examination provided, tests performed, and prescription contents, whereas health checkup data include examination results and questionnaire results. Insurers collect these data and combine them according to the insured person’s identification number. JMDC Inc. safely and anonymously collects the combined data for more than 7 million persons from insurers as described previously8.

This study focused only on adult employees (aged 20 years or more) with type 2 diabetes rather than their families, given that employees had much higher health checkup participation rates than their families and that differences in many aspects could exist between employees and their families. Because the subjects were mostly company employees, they were more likely to be males, of working-age, and presumably healthy enough to work. Patients with type 2 diabetes were defined as those who continuously received diabetes care and did not have insulin-dependent diabetes mellitus (ICD-10: E10), malnutrition-related diabetes mellitus (ICD-10: E12), or other specified types of diabetes mellitus (ICD-10: E13) (Table S1)9.

An outline of how we defined dropout patients and collected health checkup information before and after is provided in Figure S1. Consecutive diabetes care was defined as hospital/clinic visits with HbA1c/glycoalbumin measurements, antidiabetic medication, or both, with the longest interval between visits of 4 months or less. On the other hand, dropout from diabetes care was defined as not receiving glycemic examinations or antidiabetic medication for more than 4 months. In Japan, most patients usually receive glycemic tests or antidiabetic medication at medical facilities at a maximum interval of 4 months, with 99% of the prescription days for antidiabetic medication in the present dataset being 90 days. Based on the established definitions, adult employees who received continuous diabetes care for 18 months or more and dropped out thereafter were initially included. Given that this study included data from health checkups within 12 months before dropping out, we focused on those who had received continuous diabetes care for at least 6 months before the health checkup so that the health checkup results would reflect prior non-intermittent diabetes care. This would explain our selection of a duration of 18 months.

The flowchart of subject selection is presented in Figure 1. Among the patients who received continuous diabetes care for 18 months or more and who dropped out of diabetes care during the observation period, those who withdrew from their insurance within 4 months after dropping out were then excluded because we could not determine whether they received care within those 4 months as beneficiaries of their subsequent insurance. Patients without health checkup information before dropout in terms of HbA1c level were also excluded. Similarly, patients who had never received antidiabetic medications despite having undergone continuous HbA1c/glycoalbumin measurements and low baseline HbA1c levels (<6.5%) upon health checkup were excluded because they may not have been diagnosed with diabetes. In addition, patients who returned to a hospital/clinic before the follow-up health checkup were excluded because they were outside the scope of this study in that they received medical diabetes care in the end. Some patients in this group may have spontaneously returned to diabetes care without any symptoms, while others may have sought care for symptoms or events (such as heart attack and dry mouth and/or polyuria due to hyperglycemia). Therefore, patients for whom follow-up information in terms of the HbA1c level was missing were excluded. Some of them may
have changed their insurance before the follow-up health checkup due to job change or skipped the health checkups in addition to medical care.

This study was approved by the ethics committees of the National Center of Global Health and Medicine Center Hospital (NCGM-G-002096-01), Graduate School of Medicine, the University of Tokyo (11520), and University of Tsukuba (1393-1). As the data were anonymized, it was impossible to re-identify patients in this study; opt-out or opt-in was therefore impossible and not required according to the ethical guidelines.

Outcome variable
The outcome variable was a change in HbA1c levels between baseline and follow-up health checkups. Baseline medical data were extracted from health checkups closest to 12 months before the dropout. Health checkup data during the dropout period were determined between 4 and 24 months from the dropout month. When multiple health checkups were conducted during the dropout period, the closest one to the dropout was selected (Figure S1).

Predictors and covariates
Predictors and covariates included in the multiple logistic regression analysis consisted of age on the day of baseline health checkup, sex, baseline HbA1c level, baseline body mass index (BMI), and type of antidiabetic medication received during the last month before the dropout. Antidiabetic medications were determined based on pharmaceutical claims data using the codes A10A (insulins and analogs) and A10B (blood glucose-lowering drugs, excluding insulins) in the anatomical therapeutic chemical (ATC) classification, excluding voglibose 0.2 mg tablets due to their possible use for diabetes prevention. The type of antidiabetic medication prescribed was also extracted and categorized as follows: sulfonylurea or insulin; other antidiabetic medication, excluding sulfonylurea and insulin; and no antidiabetic medication. This study focused on these two antidiabetic medications given that discontinuing insulin and sulfonylurea would have more influence on glycemic control compared with discontinuing other antidiabetic medications.

For descriptive analyses, laboratory and questionnaire data of the health checkups were also extracted. Patients’ characteristics
and glycemic levels were extracted from medical claims data, while prescription information was extracted from medical and pharmaceutical claims data. Moreover, measured values of HbA1c, BMI, other biochemical tests, physical examination values, and medication history except for antidiabetics or smoking history were derived from health checkup data (Table S1).

Statistical analyses
The current study initially described the characteristics of the patients included herein. Categorical variables were presented as n (%), while continuous variables were presented as mean (standard deviation, SD). Only complete data were included in the analyses. Thereafter, multiple linear regression analysis was used to identify factors that contributed to the change in HbA1c level after the dropout. Specifically, baseline HbA1c, baseline BMI category (≥25 or less), age, sex, and type of antidiabetic medication were included. Moreover, a stratified analysis according to the type of antidiabetic medicine (all patients; no antidiabetic medicine; antidiabetic medicine excluding sulfonylurea and insulin; sulfonylurea and/or insulin) was also conducted.

Furthermore, considering that the association between baseline HbA1c and change in HbA1c using linear regression analyses could differ according to the type of antidiabetic medication used, the association between baseline HbA1c and change in HbA1c stratified according to the type of antidiabetic medication was plotted using restricted cubic spline (RCS) curves, which were depicted using four knots located at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles of the baseline HbA1c. Patient groups stratified based on antidiabetic medications were adjusted for baseline HbA1c, baseline BMI, age, and sex. The duration between baseline health checkup and dropout month and that between the dropout month and follow-up health checkups were not included in the main RCS analysis, given that these variables could potentially mediate the changes in HbA1c. Sensitivity analysis was conducted including these variables in the patients’ groups.

All statistical analyses were performed using Stata 15.0 software (StataCorp, College Station, TX, USA), with \( P < 0.05 \) indicating statistical significance.

RESULTS
Among the 101,773 adult beneficiaries with type 2 diabetes who continued diabetic treatment for more than 18 months between January 2005 and April 2018, 62,900 continued diabetic treatment, whereas 22,668 ended the observation period (Figure 2). Accordingly, patients without antidiabetic medications exhibited minimal changes in HbA1c (+0.5% at a baseline HbA1c of 7.0%), which decreased as the baseline HbA1c increased. Moreover, the change in HbA1c became negative when the baseline HbA1c was about 8% or more (Figure 2b). Conversely, patients receiving prescriptions other than sulfonylurea and insulin had an approximately 1.2% worse HbA1c at a baseline HbA1c of 6.8%, with higher baseline blood glucose levels causing more severe worsening of blood glucose levels during the dropout period (Figure 2c). Patients prescribed sulfonylureas or insulin had a peak at a baseline HbA1c of 7.0%, with a deterioration of approximately 2.4%, followed by the slight decline in the change in HbA1c as baseline HbA1c increased (Figure 2d).

Ultimately, 1,125 patients were included in the current study (Figure 1).

Clinical characteristics
The 1,125 patients who discontinued diabetic treatment had a mean age, baseline HbA1c, and baseline BMI of 51.2 years, 6.8%, and 26.4 kg/m². The mean duration of continuous diabetic treatment before dropout was 31.5 months. During the discontinuation period, HbA1c levels and BMI were 7.6% and 26.1 kg/m², respectively. The mean duration between discontinuation and follow-up health checkups was 9.3 months. With regard to antidiabetic medication use before discontinuation, 41.7%, of the patients received no antidiabetic medication, whereas 12.5, 4.3, and 41.5% received sulfonylurea, insulin, and antidiabetic medication excluding sulfonylurea and insulin, respectively (Table 1).

Risk factors for change in HbA1c during the dropout period
The results of multiple linear regression analysis with the continuous outcome variable (i.e., change in HbA1c) are detailed in Table 2. Our analysis showed that a 1% increase in baseline HbA1c was associated with a 1.03% increase in the change in HbA1c (95% CI, 0.55–1.51; \( P < 0.001 \)). Sulfonylurea and insulin use was associated with a 1.40% (95% CI, 1.12–1.69; \( P < 0.001 \)) and 1.46% (95% CI, 1.04–1.87; \( P < 0.001 \)) increase in HbA1c, respectively. Stratified analyses according to antidiabetic medication showed that a 1% increase in baseline HbA1c levels was associated with a 0.12% decrease in HbA1c (95% CI, −0.21 to −0.02; \( P = 0.015 \)) among those who did not receive antidiabetic medication and a 0.32% increase in HbA1c (95% CI, 0.19–0.45; \( P < 0.001 \)) among those who received antidiabetic medication except for sulfonylurea and insulin. Among patients who received sulfonylurea or insulin, baseline HbA1c was not associated with a change in HbA1c (−0.11%, 95% CI, −0.36 to 0.14; \( P = 0.402 \)).

Baseline HbA1c and type of diabetic medication
The RCS curves illustrated that the associations between baseline HbA1c and change in HbA1c differed according to the prescribed antidiabetic (Figure 2). Accordingly, patients without antidiabetic medications exhibited minimal changes in HbA1c (+0.5% at a baseline HbA1c of 7.0%), which decreased as the baseline HbA1c increased. Moreover, the change in HbA1c became negative when the baseline HbA1c was about 8% or more (Figure 2b). Conversely, patients receiving prescriptions other than sulfonylurea and insulin had an approximately 1.2% worse HbA1c at a baseline HbA1c of 6.8%, with higher baseline blood glucose levels causing more severe worsening of blood glucose levels during the dropout period (Figure 2c). Patients prescribed sulfonylureas or insulin had a peak at a baseline HbA1c of 7.0%, with a deterioration of approximately 2.4%, followed by the slight decline in the change in HbA1c as baseline HbA1c increased (Figure 2d).
Table 1 | Characteristics of patients who discontinued diabetic treatment by type of medication

| Characteristics of patients who discontinued diabetic treatment by type of medication | All patients (n = 1,125) | Patients without antidiabetic medication (n = 469) | Patients with any antidiabetic medication excluding sulfonylurea and insulin (n = 467) | Patients with sulfonylurea or insulin (n = 189) |
|---|---|---|---|---|
| **Baseline data** | | | | |
| Sex, male | 1,047 (93.7) 1,047 (93.7) | 436 (93.0) 436 (93.0) | 435 (93.2) 435 (93.2) | 176 (93.1) 176 (93.1) |
| Age, year | 51.2 (7.7) 51.2 (7.7) | 52.2 (7.7) 52.2 (7.7) | 50.5 (7.5) 50.5 (7.5) | 506 (81.1) 506 (81.1) |
| Baseline HbA1c, % | 6.8 (1.2) 6.8 (1.2) | 6.4 (0.92) 6.4 (0.92) | 6.7 (1.0) 6.7 (1.0) | 7.9 (1.6) 7.9 (1.6) |
| Baseline BMI | 26.4 (4.5) 26.4 (4.5) | 25.8 (4.3) 25.8 (4.3) | 26.8 (4.5) 26.8 (4.5) | 27.1 (4.7) 27.1 (4.7) |
| Systolic blood pressure, mmHg | 129.1 (15.3) 129.1 (15.3) | 128.5 (15.2) 128.5 (15.2) | 128.4 (15.1) 128.4 (15.1) | 132.3 (16.1) 132.3 (16.1) |
| Diastolic blood pressure, mmHg | 80.3 (10.1) 80.3 (10.1) | 79.5 (10.0) 79.5 (10.0) | 80.5 (10.0) 80.5 (10.0) | 81.7 (10.3) 81.7 (10.3) |
| Triglyceride, mg/dL | 149.8 (118.2) 149.8 (118.2) | 140.9 (109.0) 140.9 (109.0) | 150.6 (123.3) 150.6 (123.3) | 170.1 (125.4) 170.1 (125.4) |
| HDL cholesterol, mg/dL | 54.4 (14.8) 54.4 (14.8) | 56.3 (15.7) 56.3 (15.7) | 53.6 (13.6) 53.6 (13.6) | 51.9 (15.0) 51.9 (15.0) |
| LDL cholesterol, mg/dL | 119.9 (31.9) 119.9 (31.9) | 118.9 (32.1) 118.9 (32.1) | 120.7 (31.8) 120.7 (31.8) | 120.6 (31.4) 120.6 (31.4) |
| Antihypertensive agent | 376 (35.8) 376 (35.8) | 158 (36.2) 158 (36.2) | 154 (35.2) 154 (35.2) | 64 (36.4) 64 (36.4) |
| Hypolipidemic agent | 326 (31.5) 326 (31.5) | 125 (28.6) 125 (28.6) | 154 (35.2) 154 (35.2) | 47 (26.7) 47 (26.7) |
| Smoking | 430 (40.5) 430 (40.5) | 141 (31.9) 141 (31.9) | 199 (45.2) 199 (45.2) | 90 (50.0) 90 (50.0) |
| Consecutive term of diabetic treatment before dropout, month | 31.5 (15.8) 31.5 (15.8) | 31.0 (16.8) 31.0 (16.8) | 31.0 (14.7) 31.0 (14.7) | 33.6 (15.9) 33.6 (15.9) |
| Interval from the baseline health checkup to dropout point, month | 5.3 (3.0) 5.3 (3.0) | 5.6 (2.9) 5.6 (2.9) | 5.1 (3.0) 5.1 (3.0) | 5.3 (3.1) 5.3 (3.1) |
| Types of antidiabetic medication | | | | |
| Without antidiabetic medication | 469 (41.7) 469 (41.7) | – – | – – | – – |
| Any antidiabetic medications | 656 (58.3) 656 (58.3) | – – | 141 (74.6) 141 (74.6) | 48 (25.4) 48 (25.4) |
| Sulfonylurea | 141 (12.5) 141 (12.5) | – – | – – | – – |
| Insulin | 48 (4.3) 48 (4.3) | – – | – – | – – |
| Both sulfonylurea and insulin | 0 (0) 0 (0) | – – | – – | – – |
| Antidiabetic medication excluding | 467 (41.5) 467 (41.5) | – – | 467 (100) 467 (100) | – – |
| Sulfonylurea and insulin | | | | |
| Biguanide | 279 (24.8) 279 (24.8) | – – | – – | – – |
| DPP4 | 390 (34.2) 390 (34.2) | – – | – – | – – |
| SGLT2 | 62 (5.5) 62 (5.5) | – – | – – | – – |
| aGI | 106 (9.4) 106 (9.4) | – – | – – | – – |
| Thiazolizine | 98 (8.7) 98 (8.7) | – – | – – | – – |
| glinide | 29 (2.6) 29 (2.6) | – – | – – | – – |
| GLP1 | 10 (0.9) 10 (0.9) | – – | – – | – – |
| Follow-up data | | | | |
| HbA1c during dropout, % | 7.6 (2.1) 7.6 (2.1) | 6.7 (1.3) 6.7 (1.3) | 7.6 (2.0) 7.6 (2.0) | 9.8 (2.7) 9.8 (2.7) |
| BMI during dropout | 26.1 (4.4) 26.1 (4.4) | 25.8 (4.2) 25.8 (4.2) | 26.6 (4.6) 26.6 (4.6) | 260 (4.4) 260 (4.4) |
| Systolic blood pressure during dropout, mmHg | 132.3 (17.5) 132.3 (17.5) | 130.3 (15.8) 130.3 (15.8) | 132 (17.7) 132 (17.7) | 135.7 (20.0) 135.7 (20.0) |
| Diastolic blood pressure during dropout, mmHg | 82.5 (11.3) 82.5 (11.3) | 80.5 (10.2) 80.5 (10.2) | 83.5 (11.6) 83.5 (11.6) | 84.8 (12.3) 84.8 (12.3) |
| Triglyceride during dropout, mg/dL | 170.5 (139.2) 170.5 (139.2) | 150.8 (115.6) 150.8 (115.6) | 183.3 (150.0) 183.3 (150.0) | 187.9 (158.4) 187.9 (158.4) |
| HDL cholesterol during dropout, mg/dL | 54.4 (15.0) 54.4 (15.0) | 55.8 (15.4) 55.8 (15.4) | 53.1 (14.6) 53.1 (14.6) | 53.7 (14.9) 53.7 (14.9) |
| LDL cholesterol during dropout, mg/dL | 133.3 (38.1) 133.3 (38.1) | 126.7 (37.5) 126.7 (37.5) | 137.2 (36.8) 137.2 (36.8) | 140 (40.4) 140 (40.4) |
| Interval from the dropout point to follow-up health checkup, month | 9.3 (3.6) 9.3 (3.6) | 9.4 (3.6) 9.4 (3.6) | 9.3 (3.7) 9.3 (3.7) | 9.0 (3.8) 9.0 (3.8) |

Mean (standard deviation) or n (%). aGI, alpha glucosidase inhibitors; BMI, body mass index; DPP4, dipeptidyl peptidase-4 inhibitors; GLP1, glucagon-like peptide-1 receptor agonist; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SGLT2, sodium glucose cotransporter 2 inhibitors.
Table 2 | Multiple regression analysis for change in HbA1c in patients who discontinued diabetic treatment by type of medication

|                                | All patients (n = 1,125) | Patients without antidiabetic medication (n = 469) | Patients with any antidiabetic medicine excluding sulfonylurea or insulin (n = 467) | Patients with sulfonylurea or insulin (n = 189) |
|--------------------------------|--------------------------|---------------------------------------------------|---------------------------------------------------------------------------------|-----------------------------------------------|
|                                | Coeff. 95% Conf. Interval | P value                                           | Coeff. 95% Conf. Interval | P value                                  | Coeff. 95% Conf. Interval | P value                                  | Coeff. 95% Conf. Interval | P value                                  |
| Baseline HbA1c                 | 1.03 0.55–1.51           | < 0.001                                           | -0.12 -0.21–0.02 | 0.015                                    | 0.32 0.19–0.45            | < 0.001                                   | -0.11 -0.36–0.14            | 0.402                                    |
| Baseline BMI  ≥ 25             | 0.11 -0.06–0.28          | 0.205                                             | 0.00 -0.18–0.17 | 0.964                                    | 0.16 -0.11–0.44           | 0.247                                    | 0.27 -0.53–1.06            | 0.509                                    |
| Sex, female                    | 0.07 -0.25–0.39          | 0.664                                             | 0.17 -0.17–0.51 | 0.327                                    | 0.27 -0.66–0.38           | 0.597                                    | 0.22 -1.24–1.68            | 0.765                                    |
| Age                            |                          |                                                   |                          |                                          |                          |                                          |                          |                                          |
| 20-39 (Ref)                    | - -                      |                                                   | - -                     | - -                                     | - -                     | - -                                     | - -                     | - -                                     |
| 40-49                          | 0.13 -0.23–0.50          | 0.473                                             | -0.15 -0.63–0.33 | 0.531                                    | -0.13 -0.70–0.44          | 0.660                                    | -0.49 -0.155–1.25            | 0.833                                    |
| 50-59                          | -0.01 -0.37–0.36         | 0.972                                             | -0.21 -0.69–0.26 | 0.377                                    | -0.24 -0.82–0.32          | 0.396                                    | -0.24 -1.64–1.16            | 0.737                                    |
| 60-                            | -0.17 -0.08–0.24         | 0.408                                             | -0.31 -0.83–0.19 | 0.217                                    | -0.51 -1.17–0.15          | 0.132                                    | -0.28 -1.98–1.41            | 0.742                                    |
| Antidiabetic medication        |                          |                                                   |                          |                                          |                          |                                          |                          |                                          |
| No medication (Ref)            | - -                      |                                                   | - -                     | - -                                     | - -                     | - -                                     | - -                     | - -                                     |
| Any medication excluding       | 0.56 0.38–0.74           | < 0.001                                           | - -                     | - -                                     | - -                     | - -                                     | - -                     | - -                                     |
| sulfonylurea and insulin       |                          |                                                   |                          |                                          |                          |                                          |                          |                                          |
| Sulfonylurea                   | 1.40 1.12–1.69           | < 0.001                                           | - -                     | - -                                     | - -                     | - -                                     | - -                     | - -                                     |
| Insulin                        | 1.46 1.04–1.87           | < 0.001                                           | - -                     | - -                                     | - -                     | - -                                     | - -                     | - -                                     |

All patients (n = 1,125): the association was adjusted for baseline HbA1c, baseline BMI ≥ 25, sex, age, and type of antidiabetic medications in all the subjects. Patients without antidiabetic medication (n = 469): the association was adjusted for baseline HbA1c, baseline BMI ≥ 25, sex, and age in the subjects. Patients who received any antidiabetic medication excluding sulfonylurea and insulin (n = 467): the association was adjusted for baseline HbA1c, baseline BMI ≥ 25, sex, and age in the subjects. Patients receiving sulfonylurea and/or insulin (n = 189): the association was adjusted for baseline HbA1c, baseline BMI ≥ 25, sex, and age in the subjects. BMI, body mass index; HbA1c, hemoglobin A1c; Ref, Reference.
Sensitivity analysis
Sensitivity analysis showed the same tendencies in the change in HbA1c regardless of whether adjustment for the interval between baseline health examination and dropout point and that between dropout and follow-up health checkup was conducted (Figure S2). Moreover, a stratified analysis of patients with sulfonylurea and insulin showed the same tendencies in the change in HbA1c (Figure S3).

DISCUSSION
This retrospective study investigated factors associated with more insufficient glycemic control during discontinuation of diabetes care among patients who received 18 months or more of continuous diabetes care. Accordingly, our results found that, overall, patients who dropped out of treatment exhibited deteriorating glycemic levels, with the degree of change differing according to prescription type. As such, further care is needed for patients at higher risk for worsening glycemic levels among those who received antidiabetic medication, specifically sulfonylurea or insulin. To the best of our knowledge, this has been the first study to analyze glycemic levels during the dropout period of diabetic treatment.

The current study focused on baseline HbA1c levels and the type of antidiabetic medication before dropping out as factors for glycemic deterioration. First, multiple regression analysis showed that the degree to which blood glucose control deteriorated during the dropout period depended on the diabetes medication. Furthermore, inconsistent results with regard to the influence of baseline HbA1c had been observed depending on the type of antidiabetic medication received (Table 2). Interestingly, the coefficient for the change in HbA1c in all patients did not fall within the range of that in other patient groups stratified based on antidiabetic medications, which suggests the existence of both confounding and statistical interactions according to medication type. Therefore, more precise analysis of the influence of baseline HbA1c and type of antidiabetic medication on the change in HbA1c during the dropout period was conducted using the RCS curves. Notably, the change in HbA1c levels did not differ considerably according to baseline HbA1c levels among patients who received no antidiabetic medication, while a higher baseline HbA1c (>8%) was associated with a decline in HbA1c (Figure 2b). In contrast, among those who received antidiabetic medication except for sulfonylurea or insulin (Figure 2c), the degree to which HbA1c increased became greater as baseline HbA1c increased. Moreover, patients who received sulfonylurea and/or insulin (Figure 2d) showed large changes in HbA1c even when they previously had maintained good glycemic control; however, the degree to which HbA1c increase became slightly smaller as baseline HbA1c increased. Given our assumption that higher
Baseline HbA1c levels were associated with a greater deterioration in HbA1c, especially among those who received sulfonylurea or insulin, the observed results were interesting. One potential explanation for this discrepancy could be that those with greater HbA1c deterioration may have been more likely to revisit physicians before the follow-up health checkup and were therefore excluded from analysis.

Our findings, which showed that medication type mediated the degree to which discontinuation of diabetes care caused worsening of glycemic control, provides clinically significant information that can guide the medical management of patients at higher risk for dropping out. However, this study could not determine the risk factors of dropping out given that it had no control subjects. Some studies have indicated an association between the risk of dropping out and the lack of diabetic medication, younger age, distance from home to the clinic, smoking, and lack of diabetes knowledge. Another study comparing the discontinuation rates among newly diagnosed patients with diabetes reported that patients who received guideline-recommended practices, defined as nutritional guidance or ophthalmological examination, had lower discontinuation rates in subsequent visits. These factors should also be considered when clinicians manage patients with diabetes.

This study has several limitations. First, our data were obtained from claims and regular health checkup data of relatively large companies, so workers were mainly male (over 90%), young, and healthy. Patients with other characteristics were not included in this study. As such, we should be careful when attempting to generalize the results of this study to the general population. Moreover, we excluded patients without follow-up health checkup information due to missing data. Among 680 dropout patients who did not receive follow-up health checkups, 233 withdrew from insurance within 6 months after dropout. In Japan, insurance is decided on the basis of job, region, or age; therefore, changes in insurance along with lifestyle changes may present a risk of not receiving medical care and checkups. However, as the claims data were linked to regular health checkups, which were independently conducted at medical care hospitals or clinics, we could analyze the degree of glycemic deterioration during the dropout period that could not be disclosed normally. Second, with regard to the characteristics of antidiabetic medication among those who dropped out with health checkup data, the most prescribed drugs were DPP-4 inhibitors followed by biguanide (Table 1), which differed from that reported in previous studies. DPP-4 inhibitors are the most prescribed antidiabetic medication in Japan, unlike that in Western countries. Third, although we excluded patients with type 1 diabetes based on ICD-10 classification, some patients with type 1 diabetes may have remained in the study sample. Fourth, when interpreting the results of this study, we should note that the dropout patients did not visit a hospital/clinic because of hyperglycemia or other diseases and received health checkups after dropout from diabetes care. In other words, patients whose glycemic control worsened and started to suffer from symptoms due to dropout were more likely to return to medical care before health checkups and were excluded from the present study. The medical claims and health checkup data analysis design precluded us from obtaining patients’ HbA1c information after returning to medical care; if we had extended the scope of this study to include such patients, the results may have underestimated the adverse effects of dropout on glycemic control. Lastly, considering that our prescription information was derived from claims data, information regarding medication adherence or medical expenses was not included. As some patients might have had leftover medicines or might have purchased medicines outside insurance coverage, the increase in HbA1c after dropout might have been underestimated. However, 99% of the patients received their antidiabetic tablets within 90 days, as described previously. As such, they are unlikely to continue leftover medicine over 4 months after dropout. Furthermore, given the medical insurance system in Japan, patients who receive continuous medication despite not being covered under insurance are exceptionally rare.

The current study investigated the impact of diabetes care discontinuation among the working population. Overall, dropout patients showed worsening blood glucose control during treatment interruptions, while changes in HbA1c differed according to antidiabetic medication and baseline HbA1c. The stratification of patient groups highlighted those at higher risk. Accordingly, patients without diabetes prescriptions showed no significant increase in HbA1c levels, whereas those receiving sulfonylurea or insulin showed a 2% or greater increase in HbA1c during the drop out despite maintaining reasonable glycemic control before dropping out. As such, preventing patients from dropping out of the diabetes care, especially those at high risk for deteriorating glycemic control after dropping out, is imperative.

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Informed Consent: As the data were anonymized, it was impos-
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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 | Definition of variables
Table S2 | The RECORD statement-checklist of items, extended from the STROBE statement
Figure S1 | Outline of defining dropout patients and collecting before and follow-up health checkup information.
Figure S2 | Regression restricted cube spline analysis in patients who dropped out adjusted for health checkup intervals.
Figure S3 | Regression restricted cube spline analysis in patients using sulfonylurea or insulin before dropping out.