CLINICAL RESEARCH STUDY

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Impact of Medication Adherence and Glycemic Control on the Risk of Micro- and Macrovascular Diseases in Patients with Diabetes

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ABSTRACT

PURPOSE: Our purpose in the research was to clarify the impact of medication adherence to oral hypoglycemic agents during a 1-year period and subsequent glycemic control on the risk of micro- and macrovascular diseases.

METHODS: Examined was a nationwide claims database on 13,256 individuals with diabetic eye disease without requiring prior treatment, 7,862 without prior initiation of dialysis, 15,556 without prior coronary artery disease, 16,243 without prior cerebrovascular disease, and 19,386 without prior heart failure from 2008 to 2016 in Japan. Medication adherence was evaluated by the proportion of days covered. Patients were considered to have poor adherence if the proportion of days covered was <80%. Multivariate Cox regression model identified risks of micro- and macrovascular diseases.

RESULTS: In each group, mean age was 53 to 54 years, HbA1c was 7.1% to 7.2%, and median follow-up period was 4.6 to 5.1 years, and the percentage of poor adherence was approximately 30%. During the study period, 532 treatment-requiring diabetic eye disease, 75 dialysis, 389 coronary artery disease, 316 cerebrovascular disease, and 144 heart failure events occurred. Multivariate Cox regression model revealed that the hazard ratio (95% confidence interval) of dialysis in the poor adherence group was 2.04 (1.27-3.30) compared with the good adherence group. The hazard ratios in the poor adherence/poor glycemic control group were 3.34 (2.63-4.24) for treatment-requiring diabetic eye disease, 4.23 (2.17-8.26) for dialysis, 1.69 (1.23-2.31) for coronary artery disease, and 2.08 (1.25-3.48) for heart failure compared with the good adherence/good glycemic control group.

CONCLUSIONS: Poor medication adherence was an independent risk factor for the initiation of dialysis, suggesting that clinicians must pay close attention to these patients.

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KEYWORDS: Diabetic mellitus; Medication adherence; Proportion of days covered

INTRODUCTION

Poor medication adherence is a persistent problem in clinical practice,[1] especially among patients with asymptomatic chronic diseases such as diabetes,[2-4] because it is not only associated with economic burdens[5,6] but also limits the effectiveness of drug therapy.[7] A study that evaluated medication adherence using a claims database that included 218,384 patients with diabetes who were prescribed oral

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hypoglycemic agents (OHAs) in the United States showed that 31% of patients had poor medication adherence.[8] Similarly, we reported that 33% of Japanese patients with diabetes poorly adhered to their medication regimens.[9]

Previous studies showed that poor medication adherence was associated with poor glycemic control and increased risks of all-cause mortality and hospitalization.[4,9,10] On the other hand, although medication adherence is thought to be associated with the risk of micro- and macrovascular diseases through variations in glycemic control, such relationships were unexpectedly inconsistent.[11-14] Data in previous reports were not adjusted for glycemic control[11,13,14] or were only adjusted for HbA1c before and after the initiation of OHAs and did not take into account long-term glycemic control after the initiation of OHAs.[12]

CLINICAL SIGNIFICANCE

- The association between medication adherence for OHAs and micro/macrovascular diseases is still unclear
- The risk of micro/macrovascular diseases varied according to medication adherence for OHAs and subsequent glycemic control.
- Poor adherence for OHAs was an independent risk factor for the initiation of dialysis

In clinical practice, although some patients have poor medication adherence and good glycemic control and others have good medication adherence and poor glycemic control, no reports have examined the risk of micro- and macrovascular diseases in those patients separately. However, considering these patients according to patterns of medication adherence and glycemic control is extremely important for clinicians in devising treatment strategies. In addition, although the impact of these patterns on micro- and macrovascular diseases may differ in clinical settings, little is known about these differences.

Therefore, we investigated the impact of medication adherence to OHAs for a 1-year period and subsequent glycemic control and their combinations on the risk of micro- and macrovascular diseases among Japanese using nationwide claims data.

METHODS

Overview

For this retrospective study, we reviewed data on employees and their dependents in Japan derived from health insurance claims provided by the Japan Medical Data Center Co., Ltd. (JMDC). The JMDC database contains monthly claims submitted to health insurance societies from medical institutions beginning in January 2005. This database includes patient characteristics, medical diagnoses, drug prescriptions, and medical procedures. Details of the claims data and classifications were described elsewhere.[15-22]

Study Participants

The index date was defined as the earliest annual check-up day from April 1, 2008 to July 31, 2016 (index period). We examined data on 805,986 patients aged 18-72 years who were continuously enrolled in the database during the 12 months preceding the index date (baseline period) (Figure 1). Data on age, sex, body mass index (BMI), blood pressure, laboratory values such as HbA1c, and information on questionnaires were acquired on the earliest annual check-up day (index date). Patients were excluded for the following reasons: no diabetes mellitus diagnosis (n = 745,429); not prescribed OHA from 365 days to 340 days before the index date (n = 35,508); missing values for age, gender, BMI, systolic blood pressure (SBP), diastolic blood pressure, laboratory data such as HbA1c, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and smoking status (n = 5216); extremely high values for SBP, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and BMI (n = 75); and patients with type 1 diabetes (n = 196).

Finally, diabetic eye disease requiring treatment, coronary artery disease, cerebrovascular disease, and heart failure were analyzed in 13,256, 15,556, 16,243, and 19,386 individuals, respectively. Excluded were individuals in whom each event occurred at baseline or within 30 days after the index date. The initiation of dialysis was analyzed in 7862 individuals; those with missing values for serum creatinine and whose dialysis occurred at baseline or within 30 days after the index date were excluded. We excluded individuals who were not followed for more than 36 months from the index date (Supplemental Figure, available online).

Adherence Assessment

We assessed adherence only to OHAs that were prescribed from 365 days to 340 days before the index date without distinguishing between prevalent users and new users. The observation period for medication adherence was 1 year (365 days) before the index date. Medication adherence was evaluated by the proportion of days covered (PDC). The proportion of days covered was calculated as the number of days with the drug on hand during the observation period divided by 365 days. For fixed-dose combinations, the proportion of days covered was calculated for each component. In these calculations, inpatient and outpatient prescriptions were not differentiated. Patients were considered to have poor adherence if their PDC was <80%.[23]

Definitions

The diagnosis of diabetes was defined as fasting plasma glucose ≥7.0 mmol/L, HbA1c ≥6.5%, or both and no OHA prescription, or with an OHA prescription regardless of fasting plasma glucose or HbA1c. Estimated glomerular filtration rate was calculated based on serum creatinine values.[24]

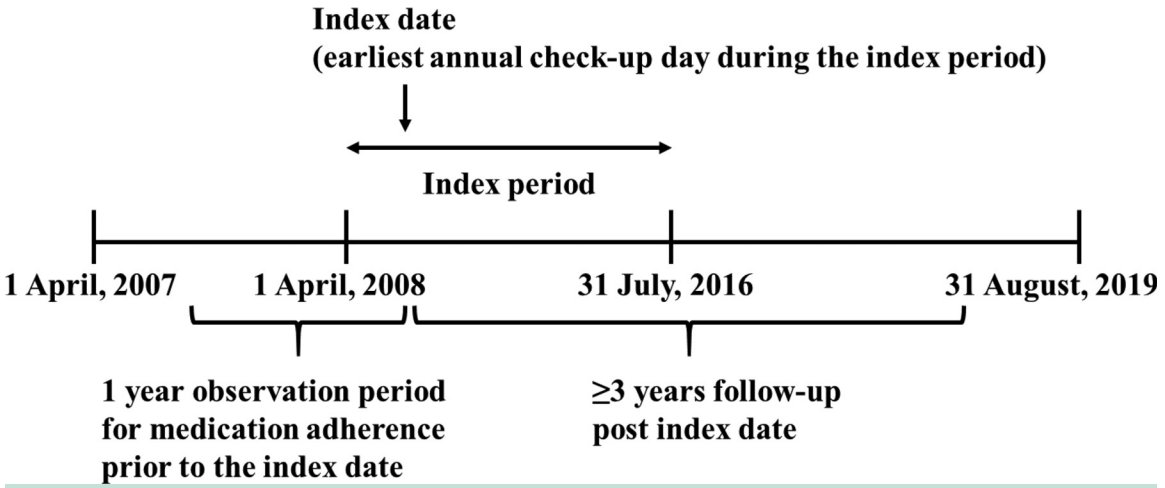

Figure 1 Study baseline and observation period. Data on age, sex, body mass index, blood pressure, and laboratory values such as HbA1c and information on questionnaires were acquired for the earliest annual check-up day (index date).

The presence of diabetic eye disease requiring treatment was determined according to claims using the *International Statistical Classification of Diseases and Related Health Problems, 10th revision* (ICD-10) codes that included 1 or more terms for diabetic retinopathy, maculopathy or macular edema and a procedure code for intravitreal injection of antivascular endothelial growth factor or a steroid drug, or retinal photocoagulation, or vitreous surgery.[21,22]

The initiation of dialysis was defined by claims using ICD-10 codes for either the 4 or 5 class of diabetic nephropathy in E10 or E11 and medical procedures for the initiation of peritoneal dialysis or hemodialysis.[19] The presence of coronary artery disease was determined according to claims using ICD-10 codes for cardiac events but excluding heart failure and procedure codes for medical interventions, such as percutaneous coronary intervention and coronary artery bypass grafting.[15-18] Determination of cerebrovascular disease was indicated by claims using ICD-10 codes for cerebrovascular events and procedure codes for medical interventions, such as thrombolytic therapy and endovascular recanalization.[16] The presence of heart failure was determined according to claims using ICD-10 codes that included heart failure and medication use.

In the following analysis, we used HbA1c values that were measured immediately after the 1-year evaluation of the proportion of days covered. First, we analyzed the risk of micro- and macrovascular diseases by dividing study participants into a poor adherence group (PDC<0.8) and good adherence group (PDC≥0.8). Second, we divided participants into the following 4 groups according to PDC and HbA1c and examined the risk of micro- and macrovascular diseases by Cox regression analysis: 1) PDC≥0.8%, HbA1c <8.0%, good adherence/good glycemic control group; 2) PDC<0.8%, HbA1c <8.0%, poor adherence/good glycemic control group; 3) PDC≥0.8%, HbA1c≥8.0%, good adherence/poor glycemic control group; and 4) PDC<0.8%, HbA1c≥8.0, poor adherence/poor glycemic control group. The same analysis was performed with the HbA1c cut off changed to 7.0% or 9.0%. Also, this analysis was performed in 9 groups according to combinations of PDC and HbA1c; PDC was divided into PDC<0.8, 0.8≤ PDC<0.9, 0.9 ≤ PDC and HbA1c was divided into HbA1c <8.0%, 8.0% ≤ HbA1c <9.0%, 9.0%≤ HbA1c.

Statistical Analysis

Categorical variables were expressed as numerals and percentages and were compared with the χ^2 test. Continuous variables were expressed as means and standard deviations or median and interquartile range. Continuous variables were compared using the unpaired Student *t*-test or the Mann-Whitney U test for 2-group comparisons based on their distributions. Cox regression model identified associations with micro- and macrovascular diseases. Analyses were performed using SPSS (version 19.0). Statistical significance was considered for $P < .05$. The Ethics Committee of the Niigata University approved this study.

RESULTS

Table 1 shows the baseline characteristics of study participants according to the presence or absence of each micro- and macrovascular disease examined. In each group, the mean age was approximately 53 years (53 to 54 years), male sex was 83% (82 to 86%), HbA1c was 7.2% (7.1% to 7.2%), median follow-up period was 4.9 years (4.6 to 5.1 years), and the percentage of poor adherence was approximately 30% (29 to 30%), which was almost similar. The percentage of poor adherence tended to be higher in those with than without the event examined. SBP was significantly higher in those groups that experienced the event

Table 1 Baseline Characteristics of Our Study Participants

A) Microvascular Disease

	Treatment-required diabetic eye disease (n = 13,256)				Initiation of dialysis (n = 7862)			
	Total	(-) n = 12,724	(+) n = 532	*P* Value	Total	(-) n = 7787	(+) n = 75	*P* Value
Age (years)	53 ± 8	53 ± 8	53 ± 8	.14	54 ± 8	54 ± 8	52±8	0.19
Male sex, n (%)	11,348 (85.6)	10,903 (85.7)	445 (83.6)	.19	6416 (81.6)	6346 (81.5)	70(93.3)	0.01
BMI (kg/m^2)	26.6 ± 4.6	26.6 ± 4.6	26.3 ± 4.4	.20	26.3 ± 4.5	26.3 ± 4.5	27.4±5.3	0.03
SBP (mm Hg)	129 ± 16	129 ± 16	135 ± 18	<.01	129 ± 16	129 ± 16	140±17	<0.01
DBP (mm Hg)	80 ± 11	80 ± 11	81 ± 12	.01	79 ± 11	79 ± 11	82±11	<0.01
TG (mmol/L)	1.4 (0.9-2.0)	1.4 (0.9-2.0)	1.4 (0.9-2.1)	.42	1.3 (0.9-1.9)	1.3 (0.9-1.9)	1.8(1.2-2.6)	<0.01
HDL-C (mmol/L)	1.4 ± 0.4	1.4 ± 0.4	1.4 ± 0.4	.38	1.4 ± 0.4	1.4 ± 0.4	1.3±0.4	<0.01
LDL-C (mmol/L)	3.0 ± 0.8	3.0 ± 0.8	3.1 ± 0.8	.03	3.0 ± 0.8	3.0 ± 0.8	3.0±1.0	0.60
HbA1c (%)	7.1 ± 1.2	7.1 ± 1.2	8.1 ± 1.8	<.01	7.2 ± 1.3	7.2 ± 1.3	7.4±2.1	0.33
Smoking, n (%)	4793 (36.2)	4607 (36.2)	186 (35.0)	.56	2568 (32.7)	2534 (32.5)	34 (45.3)	.02
Creatinine (mg/dl)	NA	NA	NA	NA	0.82 ± 0.31	0.80 ± 0.20	2.3 ± 2.0	<.01
eGFR (mL/min/1.73m^2)	NA	NA	NA	NA	78.3 ± 18.1	78.6 ± 17.7	44.1 ± 27.7	<.01
Number of OHAs (%)				<.01				.81
1	5956 (44.9)	5794 (45.5)	162 (30.5)		3357 (42.7)	3323 (42.7)	34 (45.3)	
2	4185 (31.6)	4003 (31.5)	182 (34.2)		2470 (31.4)	2449 (31.4)	21 (28.0)	
3 or more	3115 (23.5)	2927 (23.0)	188 (35.3)		2035 (25.9)	2015 (25.9)	20 (26.7)	
Use of insulin (%)	488 (3.7)	417 (3.3)	71 (13.3)	<.01	430 (5.5)	419 (5.4)	11 (14.7)	<.01
Use of GLP-1RA (%)	50 (0.4)	44 (0.3)	6 (1.1)	<.01	59 (0.8)	59 (0.8)	0 (0.0)	.45
Lipid-lowering medication (%)	6601 (49.8)	6365 (50.0)	236 (44.4)	.01	3904 (49.7)	3859 (49.6)	45 (60.0)	.07
Use of statins (%)	5303 (40.0)	5124 (40.3)	179 (33.6)	<.01	3180 (40.4)	3144 (40.4)	36 (48.0)	.18
Hypertension medication (%)	6519 (49.2)	6284 (49.4)	235 (44.2)	.02	3636 (46.2)	3578 (45.9)	58 (77.3)	<.01
Use of ACEIs (%)	592 (4.5)	556 (4.4)	36 (6.8)	.01	346 (4.4)	339 (4.4)	7 (9.3)	.04
Use of ARBs (%)	4769 (36.0)	4599 (36.1)	170 (32.0)	.05	2663 (33.9)	2617 (33.6)	46 (61.3)	<.01
Antiplatelet medication (%)	1087 (8.2)	1037 (8.1)	50 (9.4)	.30	665 (8.5)	654 (8.4)	11 (14.7)	.05
Mean PDC	0.81 ± 0.21	0.81 ± 0.21	0.80 ± 0.22	.08	0.82 ± 0.20	0.82 ± 0.20	0.77 ± 0.24	.09
PDC < 0.8, n (%)	4026 (30.4)	3840 (30.2)	186 (35.0)	.02	2292 (29.2)	2258 (29.0)	34 (45.3)	<.01

B) Macrovascular Disease

	Coronary artery disease (n = 15,556)				Cerebrovascular disease (n = 16,243)				Heart failure (n = 19,386)			
	Total	(-) n = 15,167	(+) n = 389	*P* Value	Total	(-) n = 15,927	(+) n = 316	*P* Value	Total	(-) n = 19,242	(+) n = 144	*P* Value
Age (years)	54 ± 8	54 ± 8	54 ± 7	.42	54 ± 8	54 ± 8	55 ± 8	<.01	54 ± 8	54 ± 8	55 ± 7	.03
Male sex, n (%)	12,936 (83.2)	12,572 (82.9)	364 (93.6)	<.01	13,590 (83.7)	13,309 (83.6)	281 (88.9)	.01	16,339 (84.3)	16,209 (84.2)	130 (90.3)	.05
BMI (kg/m^2)	26.4 ± 4.6	26.4 ± 4.6	26.6 ± 4.3	.37	26.5 ± 4.5	26.5 ± 4.5	26.2 ± 4.1	.35	26.5 ± 4.6	26.5 ± 4.6	27.2 ± 5.0	.05
SBP (mm Hg)	129 ± 16	129 ± 16	135 ± 16	<.01	129 ± 16	129 ± 16	135 ± 17	<.01	129 ± 16	129 ± 16	137 ± 22	<.01
DBP (mm Hg)	79 ± 11	79 ± 11	82 ± 11	<.01	79 ± 11	79 ± 11	82 ± 12	<.01	79 ± 11	79 ± 11	81 ± 14	.29
TG (mmol/L)	1.3 (0.9-2.0)	1.3 (0.9-1.9)	1.6 (1.1-2.2)	<.01	1.3 (0.9-2.0)	1.3 (0.9-2.0)	1.5 (1.0-2.2)	<.01	1.3 (0.9-2.0)	1.3 (0.9-2.0)	1.6 (1.1-2.1)	<.01
HDL-C (mmol/L)	1.4 ± 0.4	1.4 ± 0.4	1.3 ± 0.3	<.01	1.4 ± 0.4	1.4 ± 0.4	1.3 ± 0.4	<.01	1.4 ± 0.4	1.4 ± 0.4	1.3 ± 0.4	<.01
LDL-C (mmol/L)	3.0 ± 0.8	3.0 ± 0.8	3.4 ± 0.9	<.01	3.0 ± 0.8	3.0 ± 0.8	3.1 ± 0.9	.33	3.0 ± 0.8	3.0 ± 0.8	2.9 ± 0.8	.20
HbA1c (%)	7.2 ± 1.3	7.2 ± 1.3	7.7 ± 1.6	<.01	7.2 ± 1.3	7.2 ± 1.3	7.4 ± 1.5	.02	7.2 ± 1.3	7.2 ± 1.3	7.4 ± 1.6	.08
Smoking, n (%)	5359 (34.4)	5166 (34.1)	193 (49.6)	<.01	5524 (34.0)	5390 (33.8)	134 (42.4)	<.01	6632 (34.2)	6575 (34.2)	57 (39.6)	.17
Number of OHAs				.09				.19				.50
1	6447 (41.4)	6305 (41.6)	142 (36.5)		6708 (41.3)	6588 (41.4)	120 (38.0)		8043 (41.5)	7982 (41.5)	61 (42.4)	
2	5019 (32.3)	4876 (32.1)	143 (36.8)		5250 (32.3)	5133 (32.2)	117 (37.0)		6249 (32.2)	6198 (32.2)	51 (35.4)	
3 or more	4090 (26.3)	3986 (26.3)	104 (26.7)		4285 (26.4)	4206 (26.4)	79 (25.0)		5094 (26.3)	5062 (26.3)	32 (22.2)	
Use of insulin (%)	857 (5.5)	821 (5.4)	36 (9.3)	<.01	910 (5.6)	891 (5.6)	19 (6.0)	.75	1098 (5.7)	1078 (5.6)	20 (13.9)	<.01
Use of GLP-1RA (%)	98 (0.6)	97 (0.6)	1 (0.3)	.35	107 (0.7)	102 (0.6)	5 (1.6)	.04	128 (0.7)	127 (0.7)	1 (0.7)	.96
Lipid-lowering medication (%)	7472 (48.0)	7263 (47.9)	209 (53.7)	.02	8046 (49.5)	7884 (49.5)	162 (51.3)	.53	9610 (49.6)	9542 (49.6)	68 (47.2)	.57
Use of statins (%)	5951 (38.3)	5795 (38.2)	156 (40.1)	.45	6503 (40.0)	6374 (40.0)	129 (40.8)	.77	7795 (40.2)	7750 (40.3)	45 (31.3)	.03
Hypertension medication (%)	7251 (46.6)	7025 (46.3)	226 (58.1)	<.01	7800 (48.0)	7607 (47.8)	193 (61.1)	<.01	9434 (48.7)	9329 (48.5)	105 (72.9)	<.01
Use of ACEIs (%)	587 (3.8)	561 (3.7)	26 (6.7)	<.01	693 (4.3)	678 (4.3)	15 (4.7)	.67	878 (4.5)	861 (4.5)	17 (11.8)	<.01
Use of ARBs (%)	5431 (34.9)	5263 (34.7)	168 (43.2)	<.01	5780 (35.6)	5625 (35.3)	155 (49.1)	<.01	6976 (36.0)	6907 (35.9)	69 (47.9)	<.01
Antiplatelet medication (%)	708 (4.6)	674 (4.4)	34 (8.7)	<.01	1152 (7.1)	1096 (6.9)	56 (17.7)	<.01	1665 (8.6)	1626 (8.5)	39 (27.1)	<.01
Mean PDC	0.82 ± 0.20	0.82 ± 0.20	0.79 ± 0.22	.02	0.82 ± 0.20	0.82 ± 0.20	0.80 ± 0.22	.06	0.82 ± 0.20	0.82 ± 0.20	0.79 ± 0.21	.11
PDC < 0.8, n (%)	4636 (29.8)	4499 (29.7)	137 (35.2)	.02	4790 (29.5)	4685 (29.4)	105 (33.2)	.14	5711 (29.5)	5658 (29.4)	53 (36.8)	.05

ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin II receptor blockers; BMI = body mass index; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; GLP-1RA = glucagon like peptide-1 receptor agonist; LDL-C = low-density lipoprotein cholesterol; OHA, oral hypoglycemic agents; PDC = proportion of days covered; SBP = systolic blood pressure; TG = triglycerides.

Data are presented as n (%), mean± SD or median (interquartile range).

The number of concomitant medications was defined as the total number of antihypertensive medications, dyslipidemia medications, and antiplatelet agents.

studied than in those who did not, as was HbA1c with the exception of dialysis and heart failure. The percentage of patients in the poor adherence/poor glycemic control group was higher in those with than without the event.

Supplemental Table 1, available online, shows the result of mean PDC and percentage of poor adherence for each OHA. The percentage of poor adherence for sodium-glucose transport protein 2 (SGLT2) inhibitors, glinides, α-glucosidase inhibitors tended to be high.

Table 2 shows the incidence rates of each micro- and macrovascular disease examined per 1000 person-years. Poor medication adherence caused up to 1.6 more cases per 1000 person-years of treatment-requiring diabetic eye disease, 1.5 cases per 1000 person-years of initiation of dialysis, 1.1 more cases per 1000 person-years of coronary artery disease, 0.6 more cases per 1000 person-years of cerebrovascular disease, and 0.5 more cases per 1000 person-years of heart failure. Results of Cox proportional hazard models for each micro- and macrovascular disease were divided into 2 groups: poor adherence and good adherence. Compared with patients with good adherence, only the adjusted HR for dialysis was significantly higher in patients with poor adherence. The risk of dialysis was about twice that in those with poor adherence than good adherence.

Table 3 shows the incidence rates of each micro- and macrovascular disease per 1000 person-years and the results of Cox proportional hazard models for each micro- and macrovascular disease divided into 4 groups according to combinations of PDC and 2 stratified HbA1c values. Compared with the group with good adherence/good glycemic control, the risks of treatment-requiring diabetic eye disease and coronary artery disease were significantly higher in the 2 groups with poor glycemic control regardless of PDC. When the cutoff for HbA1c was 9.0%, the risk of cerebrovascular disease was significantly higher in the 2 groups with poor glycemic control group as were risks of treatment-requiring diabetic eye disease and coronary artery disease. The risk of dialysis was significantly higher in the poor adherence/poor glycemic control group regardless of the HbA1c cutoff. When the cutoff for HbA1c was 9.0%, the risk of dialysis was significantly higher in the poor adherence/good glycemic control group. The risk of heart failure was significantly higher in the poor adherence/poor glycemic control group when the cutoff of HbA1c was either 8.0% or 9.0%.

Figure 2 shows the results of Cox proportional hazard models for each micro- and macrovascular disease for 9 groups divided according to combinations of 3 stratified PDC values and three stratified HbA1c values. In the 9-group study, the results were similar to those of the 4-group study according to PDC and HbA1c.

DISCUSSION

This is the first study that we are aware of to evaluate the risks of micro- and macrovascular diseases according to medication adherence for OHAs for 1 year and subsequent

Table 2 The Incidence Rates of Each Event per 1000 Person-Years and the Multivariate-Adjusted Hazard Ratio for Each Event According to Medication Adherence

A) Microvascular Disease

	Treatment-required diabetic eye disease (n = 13,256)				Dialysis (n = 7862)			
	Event count/N	Event rate, per 1000 person-years	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)	Event count/ N	Event rate, per 1000 person-years	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
PDC ≥ 0.8	346/9230	8.3	ref	ref	41/5570	1.4	ref	ref
PDC < 0.8	186/4026	9.9	1.21 (1.01-1.44)	0.84 (0.69-1.02)	34/2292	2.9	1.90 (1.21-3.00)	2.04 (1.27-3.30)

B) Macrovascular Disease

	Coronary artery disease (n = 15,556)				Cerebrovascular disease (n = 16,243)				Heart failure (n = 19,386)			
	Event count/N	Event rate, per 1000 person-years	Crude Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)	Event count/N	Event rate, per 1000 person-years	Crude Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)	Event count/N	Event rate, per 1000 person-years	Crude Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
PDC ≥ 0.8	252/10,920	4.8	ref	ref	211/11,453	3.8	ref	ref	91/13,675	1.4	ref	ref
PDC < 0.8	137/4636	5.9	1.22 (0.99-1.50)	1.03 (0.83-1.28)	105/4790	4.4	1.13 (0.89-1.43)	1.16 (0.91-1.47)	53/5711	1.9	1.31 (0.93-1.83)	1.40 (0.99-1.99)

ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin II receptor blockers; BMI = body mass index; CI = confidence interval; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; PDC = proportion of days covered; SBP = systolic blood pressure; TG = triglycerides.
Adjusted for age, sex, HbA1c, SBP, TG, HDL-C, LDL-C, current smoking, BMI, eGFR (only dialysis), use of statins, use of ACEIs, use of ARBs, number of concomitant medications

Table 3 The Incidence Rates of Each Complication per 1000 Person-Years and the Results of Cox Proportional Hazard Models for Each Complication for 4 Groups Divided According to Combinations of Proportion of Days Covered and 2 Stratified Hba1c Values.

A) Microvascular Disease

	Treatment-required diabetic eye disease (n = 13,256)				Initiation of dialysis (n = 7862)			
	Event count/N	Event rate, per 1000 person-years	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)	Event count/N	Event rate, per 1000 person-years	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
PDC ≥ 0.8, HbA1c<7	113/5082	4.9	ref	ref	22/2901	1.5	ref	ref
PDC < 0.8, HbA1c<7	29/1810	3.3	0.70(0.47-1.05)	0.69(0.46-1.05)	15/962	3.0	1.95(1.01-3.76)	1.79(0.89-3.63)
PDC ≥ 0.8, HbA1c≥7	233/4148	12.5	2.57(2.05-3.22)	2.50(1.99-3.14)	19/2669	1.4	0.88(0.48-1.63)	1.31(0.67-2.57)
PDC < 0.8, HbA1c≥7	157/2216	15.5	3.19(2.51-4.07)	2.96(2.30-3.81)	19/1330	2.8	1.67(0.90-3.10)	3.39(1.73-6.63)
PDC ≥ 0.8, HbA1c<8	223/7836	6.3	ref	ref	31/4595	1.3	ref	ref
PDC < 0.8, HbA1c<8	72/2887	5.2	0.85(0.65-1.11)	0.86(0.66-1.12)	19/1598	2.3	1.67(0.94-2.96)	1.71(0.93-3.12)
PDC ≥ 0.8, HbA1c≥8	123/1394	19.3	3.13(2.51-3.89)	3.17(2.53-3.97)	10/975	1.9	1.35(0.66-2.75)	1.39(0.64-3.01)
PDC < 0.8, HbA1c≥8	114/1139	21.8	3.53(2.82-4.43)	3.34(2.63-4.24)	15/694	4.1	2.78(1.50-5.17)	4.23(2.17-8.26)
PDC ≥ 0.8, HbA1c<9	285/8764	7.2	ref	ref	36/5213	1.4	ref	ref
PDC < 0.8, HbA1c<9	106/3450	6.5	0.92(0.74-1.15)	0.92(0.73-1.15)	23/1936	2.3	1.62(0.96-2.74)	1.75(1.01-3.04)
PDC ≥ 0.8, HbA1c≥9	61/466	29.0	4.12(3.12-5.43)	4.35(3.28-5.78)	5/357	2.6	1.76(0.69-4.50)	2.07(0.78-5.51)
PDC < 0.8, HbA1c≥9	80/576	30.8	4.36(3.40-5.59)	4.02(3.09-5.24)	11/356	6.0	3.98(2.02-7.84)	6.50(3.12-13.52)

B) Macrovascular Disease

	Coronary artery disease (n = 15,556)				Cerebrovascular disease (n = 16,243)				Heart failure (n = 19,386)			
	Event count/N	Event rate, per 1000 person-years	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)	Event count/N	Event rate, per 1000 person-years	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)	Event count/N	Event rate, per 1000 person-years	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
PDC ≥0.8, HbA1c<7	100/5713	3.6	ref	ref	103/5995	3.6	ref	ref	45/7123	1.3	ref	ref
PDC <0.8, HbA1c<7	37/1955	3.7	1.02 (0.70-1.49)	0.98 (0.67-1.43)	40/2018	4.0	1.09 (0.76-1.57)	1.17 (0.81-1.69)	23/2404	1.9	1.41 (0.85-2.33)	1.58 (0.95-2.62)
PDC ≥0.8, HbA1c≥7	152/5207	5.9	1.61 (1.25-2.07)	1.44 (1.11-1.86)	108/5458	4.0	1.12 (0.85-1.46)	1.11 (0.85-1.46)	46/6552	1.5	1.06 (0.70-1.60)	1.08 (0.72-1.65)
PDC <0.8, HbA1c≥7	100/2681	7.5	1.99 (1.51-2.62)	1.66 (1.24-2.22)	65/2772	4.7	1.27 (0.93-1.73)	1.34 (0.97-1.85)	30/3307	1.8	1.30 (0.82-2.07)	1.48 (0.92-2.39)
PDC ≥0.8, HbA1c<8	171/9084	3.9	ref	ref	161/9523	3.5	ref	ref	68/11,348	1.2	ref	ref
PDC <0.8, HbA1c<8	79/3234	4.9	1.24 (0.95-1.62)	1.19 (0.91-1.56)	69/3339	4.1	1.16 (0.88-1.54)	1.24 (0.94-1.65)	32/3955	1.6	1.27 (0.83-1.93)	1.42 (0.93-2.18)
PDC ≥0.8, HbA1c≥8	81/1836	8.8	2.17 (1.67-2.83)	1.91 (1.46-2.51)	50/1930	5.2	1.42 (1.04-1.96)	1.4 5(1.05-2.01)	23/2327	2.0	1.50 (0.94-2.41)	1.53 (0.95-2.48)
PDC <0.8, HbA1c≥8	58/1402	8.1	2.02 (1.50-2.72)	1.69 (1.23-2.31)	36/1451	4.9	1.34 (0.93-1.92)	1.46 (1.00-2.13)	21/1756	2.4	1.78 (1.09-2.90)	2.08 (1.25-3.48)
PDC ≥0.8, HbA1c<9	224/10,280	4.5	ref	ref	186/10,780	3.6	ref	ref	81/12,851	1.3	ref	ref
PDC <0.8, HbA1c<9	100/3906	5.1	1.12 (0.88-1.42)	1.08 (0.85-1.37)	81/4032	4.0	1.11 (0.85-1.44)	1.20 (0.92-1.56)	40/4797	1.7	1.24 (0.85-1.81)	1.40 (0.95-2.05)
PDC ≥0.8, HbA1c≥9	28/640	8.3	1.80 (1.22-2.67)	1.67 (1.12-2.49)	25/673	7.2	1.97 (1.30-2.99)	2.19 (1.43-3.34)	10/824	2.4	1.72 (0.89-3.32)	1.91 (0.98-3.72)
PDC <0.8, HbA1c≥9	37/730	10.0	2.15 (1.52-3.04)	1.70 (1.18-2.45)	24/758	6.2	1.68 (1.10-2.57)	1.88 (1.21-2.93)	13/914	2.8	2.02 (1.12-3.63)	2.49 (1.35-4.58)

ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin II receptor blockers; BMI = body mass index; CI = confidence interval; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; PDC = proportion of days covered; SBP = systolic blood pressure; TG = triglycerides.

Adjusted for age, sex, SBP, TG, HDL-C, LDL-C, current smoking, BMI, eGFR (only dialysis), use of statins, use of ACEIs, use of ARBs, number of concomitant medications

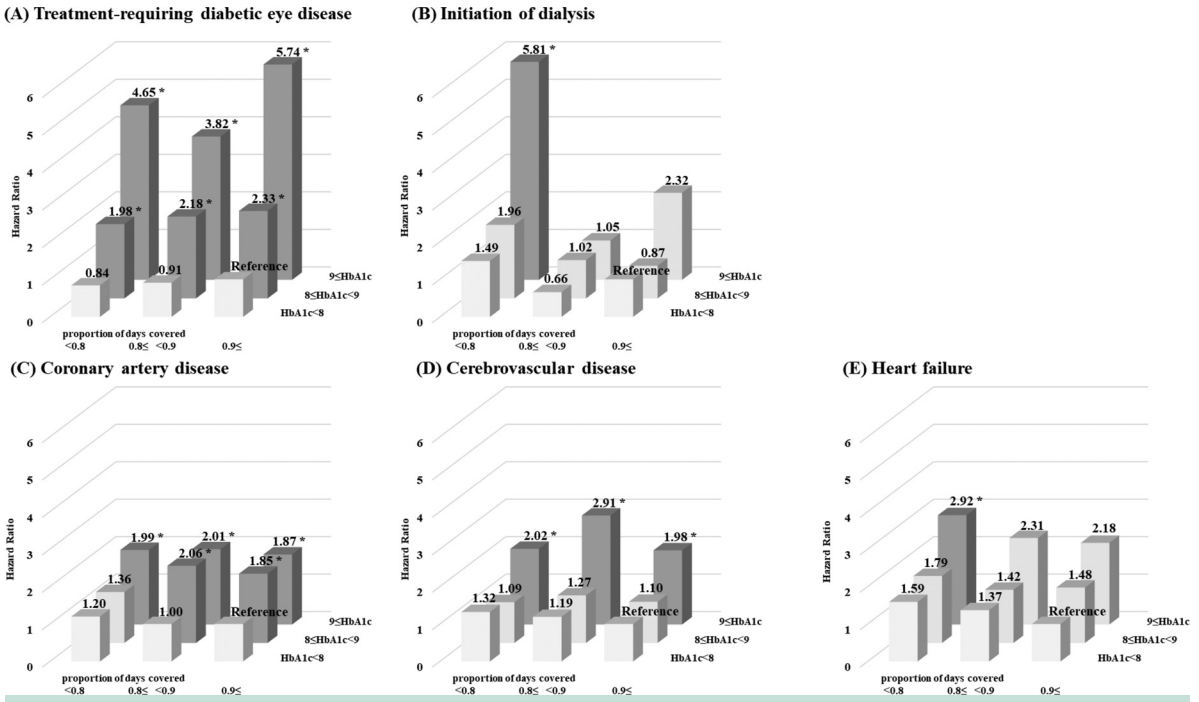

Figure 2 Hazard ratios for each analyzed event according to combinations of proportion of days covered and HbA1c. Each of the 9 bars shows the hazard ratio for each event compared with the combination of 0.9 ≤ proportion of days covered and HbA1c <8% as the reference group. HbA1c was measured immediately after the 1-year evaluation of proportion of days covered. Adjustments were made for age, sex, systolic blood pressure, triglycerides, high-density lipoprotein-C, low-density lipoprotein-C, current smoking, body mass index, and estimated glomerular filtration rate (only dialysis), use of statins, use of angiotensin-converting enzyme inhibitors, use of angiotensin Ⅱ receptor blockers, and number of concomitant medications.
*P <.05.

glycemic control. Poor adherence was an independent risk factor for dialysis. When participants were divided into 4 groups according to proportion of days covered and HbA1c, the risks of treatment-requiring diabetic eye disease, coronary artery disease, and cerebrovascular disease in the 2 poor glycemic control groups were significantly higher regardless of proportion of days covered. The risks of dialysis and heart failure in the poor adherence/poor glycemic control group were significantly higher by 3.9-fold and 1.9-fold, respectively, than in the good adherence/good glycemic control group when the cutoff of HbA1c was 8.0%.

Previous reports showed inconsistent results regarding the relationship between medication adherence for OHAs and micro- and macrovascular diseases.[11-14] Teresa et al[11] reported that poor medication adherence was significantly associated with the increased risk of micro- and macrovascular diseases, whereas Han et al[13] reported no significant associations. A study of 1695 patients with diabetes in Taiwan reported that poor medication adherence increased the risk of end-stage renal disease.[14] However, because these studies did not adjust for HbA1c, which is the most important confounding factor, it was unclear how glycemic control affected the relationship between medication adherence and micro- and macrovascular diseases.

Recently, in the United States, a study of 159,032 patients with diabetes who were prescribed OHAs for the first time showed that poor medication adherence increased the risk of myocardial infarction and ischemic stroke but reduced the risk of neuropathy and retinopathy.[12] Although this study adjusted for HbA1c, it is unclear whether glycemic control improved or worsened after the initiation of OHAs because HbA1c values were measured 90 days before and after the first OHA was prescribed. In the present study, we clarified the risk of micro- and macrovascular diseases according to medication adherence for OHAs for 1 year and subsequent HbA1c values.

In the analysis of medication adherence for each OHA, the proportion of days covered for SGLT2 inhibitors, glinides, and α-glucosidase inhibitors was low compared with those for sulfonylureas, metformin, and DPP-4 inhibitors. Because SGLT2 inhibitors are more expensive than sulfonylureas and metformin, their cost could be responsible for poor medication adherence,[11,25] whereas timing of usage (ie, just before eating) and frequency of dosage for glinides and α-glucosidase inhibitors could lead to poor medication adherence.[26] In our previous study, current smoking, younger age, skipping breakfast, and late-night eating were associated with poor adherence.[9] Smoking history and meal frequency were associated with socioeconomic factors.[27,28]

Taken together, socioeconomic factors influence poor adherence and impact the risk of micro- and macrovascular diseases. Thus, these results suggest the necessity for clinicians to review prescriptions considering socioeconomic factors among patients.

Poor adherence was shown to be an independent risk factor for dialysis after adjustment for known risk factors such as the estimated glomerular filtration rate, HbA1c, and SBP.[24,29-31] We reported that poor adherence to OHAs was associated with lifestyle factors.[9] A meta-analysis of 104 cohort studies reported that lifestyle factors such as potassium intake, vegetable intake, and exercise habits were associated with the risk of chronic kidney disease and the initiation of renal replacement therapy.[32] Moreover, poor medication adherence was independently associated with the initiation of dialysis after adjustments for use and adherence to statins, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers. These reports suggested that patients with poor medication adherence may engage in many lifestyle factors that lead to the initiation of dialysis.

The UK Prospective Diabetes Study showed that good glycemic control clearly reduced the incidence of micro- and macrovascular diseases[33,34] and that persistent hyperglycemia was closely related to the risk of developing macrovascular diseases.[35] In our study, the good adherence/poor glycemic control group was associated with a higher risk of treatment-requiring diabetic eye disease, coronary artery disease, and cerebrovascular disease. These groups may include many patients with so-called clinical inertia, in which there is failure to initiate intensified treatment according to evidence-based guidelines.[36] Clinical inertia was reported to increase cardiovascular events[37] and retinopathy,[38] and our results may also support the possibility that clinical inertia increases the occurrence of these complications. In these patients, it thought to be important to change drug therapy or strengthen diet and exercise therapy.

The poor adherence/poor glycemic control group was associated with a higher risk of treatment-requiring diabetic eye disease, dialysis, coronary artery disease, and heart failure. In these patients, because medication adherence is associated with glycemic control,[4,9,10] it is thought to be important to seek strategies to improve medication adherence to reduce the risk of these complications.

This study's strengths were accurate definitions of treatment-requiring diabetic eye disease, dialysis, coronary artery disease, cerebrovascular disease, and heart failure using data from health examinations, medical practice, and the claims database, which allowed us to precisely identify almost all patients having each event during the follow-up.

Limitations

Several limitations should be considered. First, we have no data on several of the confounders. Although socioeconomic factors such as income or economic status and patients' family support are closely associated with medication adherence to OHAs,[11,25,39] we have no data on these factors. In addition, we could not use a diabetes comorbidity severity index such as the Charlson Comorbidity Index as a covariate as that information was not available in the database. However, we used the number of concomitant medications, which was reported to be associated with medication adherence,[9,40] as a covariate and confirmed the association between medication adherence and micro- and macrovascular diseases. Secondly, the prescription periods were too short to assess a relationship between medication adherence and subsequent complications due to SGLT2 inhibitors. Third, because of the nature of employer-sponsored health care plans, patients older than age 75 were not included, and the study population was largely male. The results of this study cannot be applied to patients with diabetes older than age 75, and caution must be used in applying these results to women with diabetes. Fourth, proportion of days covered, which was calculated based on pharmacy records, measured only refill behavior and not actual consumption of the medications. We evaluated the proportion of days covered only for OHAs that were taken 340-365 days before the index date. Thus, proportion of days covered was underestimated in those who discontinued OHAs in the presence of improving glycemic control or side effects. Finally, our study may have a prevalent user bias because we did not distinguish between prevalent users and new users.

CONCLUSION

The risk of micro- and macrovascular disease varies according to medication adherence for OHAs and subsequent glycemic control, suggesting that clinicians should determine treatment strategies, considering adherence and glycemic control separately. In addition, poor medication adherence was an independent risk factor for the initiation of dialysis, suggesting that clinicians must pay close attention to these patients.

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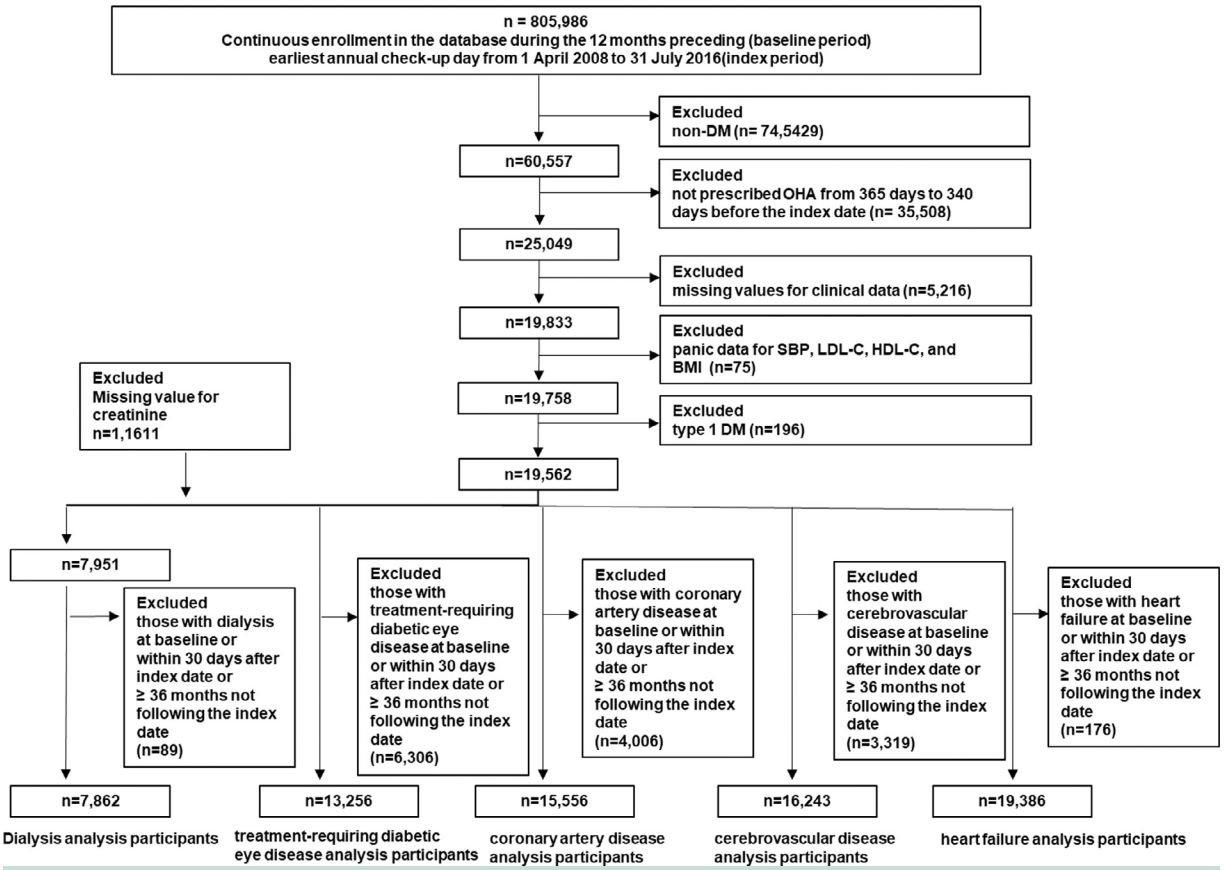
SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjmed.2021.10.018.



Supplemental Figure Inclusion-exclusion criteria and sample size.

Supplemental Table 1 Mean Proportion of Days Covered and percent poor adherence for each oral hypoglycemic agent

	Treatment-required diabetic eye disease (n=13256)		Initiation of dialysis(n=7,862	
	PDC (mean ± SD)	PDC <0.8 (%)	PDC (mean ± SD)	PDC <0.8 (%)
Sulfonylureas	0.82±0.21	27.1	0.82±0.21	26.5
Biguanides	0.82±0.21	27.4	0.83±0.21	26.4
Thiazolidines	0.80±0.23	31.4	0.80±0.23	30.3
α-glucosidase inhibitors	0.79±0.24	33.5	0.81±0.22	29.4
Glinides	0.74±0.27	38.8	0.75±0.27	37.4
DPP-4 inhibitors	0.85±0.19	22.2	0.86±0.18	21.1
SGLT2 inhibitors	0.77±0.26	34.7	0.72±0.29	39.3

	Coronary artery disease (n=15,556)		Cerebrovascular disease (n=16,243)		Heart failure (n=19,386)	
	PDC (mean ± SD)	PDC <0.8 (%)	PDC (mean ± SD)	PDC <0.8 (%)	PDC (mean ± SD)	PDC <0.8 (%)
Sulfonylureas	0.83±0.21	26.3	0.83±0.21	25.9	0.83±0.21	26.0
Biguanides	0.83±0.20	26.4	0.83±0.20	25.9	0.83±0.20	25.8
Thiazolidines	0.80±0.23	30.4	0.80±0.23	30.1	0.80±0.23	30.5
α-glucosidase inhibitors	0.80±0.23	31.3	0.80±0.23	30.9	0.80±0.23	31.1
Glinides	0.75±0.28	37.1	0.75±0.27	37.1	0.75±0.27	36.9
DPP-4 inhibitors	0.85±0.19	21.0	0.85±0.19	20.8	0.86±0.19	20.7
SGLT2 inhibitors	0.77±0.27	33.9	0.77±0.26	33.1	0.77±0.26	34.2

PDC = proportion of days covered; SD = standard deviation; DPP-4 = dipeptidyl peptidase 4; SGLT2 = sodium glucose co-transporter 2