Master's Thesis of Science in Medicine

Clinical characteristics associated with adherence and persistence in patients with type 2 diabetes mellitus treated with dulaglutide

Dulaglutide로 치료받는 제2형 당뇨병 환자의 치료 순응도에 영향을 주는 임상적 요인 분석

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이 데이비드 승우

Clinical characteristics associated with adherence and persistence in patients with type 2 diabetes mellitus treated with dulaglutide

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Abstract

OBJECTIVE

Dulaglutide is a Glucagon-like Peptide-1 Receptor Agonist (GLP-1RA) indicated for the treatment of type 2 diabetes mellitus (T2DM). However, as an injectable therapy, treatment with dulaglutide has been complicated by suboptimal adherence and persistence rates. The objective of this study was to identify clinical characteristics associated with adherence and persistence in T2DM patients treated with dulaglutide.

METHODS

This retrospective observational cohort study used electronic medical records transformed into the Observational Medical Outcomes Partnership Common Data Model (OMOP CDM, version 5.3.1) of Seoul National University Hospital (SNUH), Seoul, South Korea. Patients with T2DM who initiated treatment with dulaglutide (0.75 mg or 1.5 mg) between January 1st, 2018 and December 31st, 2019 were included and followed for one year since treatment initiation. Adherence was evaluated by using proportion of days covered (PDC) and adherence status (PDC$\geq$ 0.8 or PDC<0.8). Persistence was assessed with treatment duration (the number of days on treatment without >60 days prescription gap) and continuation status (continuer or discontinuer). Multivariate linear regression and multivariate logistic regression were used to identify the factors associated with continuous and categorical outcome measures, respectively. Subgroup analysis was conducted involving patients with high cardiovascular disease (CVD) risk (i.e., having $\geq$2 identifiable risk factors for cardiovascular disease). Sensitivity analysis was conducted by 1) changing the permissible prescription gap for continuous treatment to >90 days and 2) defining subjects with high CVD risk as having $\geq$3 identifiable CVD risk factors.

RESULTS

A total of 236 patients met the eligibility criteria and were included in the analyses. In multivariate logistic regression analyses, a year increase in age and a unit increase in estimated glomerular filtration rate significantly increased the likelihood of adherence and treatment continuation. In contrast, patients with baseline obesity and

baseline use of sulfonylurea and insulin were significantly less likely to continue treatment with dulaglutide. In multivariate linear regression analyses, a year increase in age, switching dulaglutide dose, and baseline neuropathy were significantly associated with higher PDC and longer treatment duration, while baseline use of insulin and sulfonylurea were associated with lower PDC and shorter treatment duration. In subgroup analysis, there was no significant differences in dulaglutide adherence and persistence between patients with high CVD risk and those with low CVD risk. Sensitivity analyses showed no statistically significant difference in the adherence and persistence results.

CONCLUSIONS

This study found clinical characteristics of dulaglutide users who are more likely to be adherent and persistent to dulaglutide. It is expected that the findings of this study can be used in guiding prescriptions for T2DM patients considering to initiate treatment with dulaglutide.

Keyword: type 2 diabetes mellitus, medication adherence, medication persistence, dulaglutide

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Chapter 1. Introduction

1.1 Study Background

Adequate management of chronic disease is difficult. Patients are often required to take one or more medications over the entire lifespan of the disease[1]. Management of chronic disease is further complicated by two patterns of medication non-use: 1) missed medication doses (termed non-adherence in this study) and 2) abrupt discontinuation or substantial medication gap (termed non-persistence or discontinuation in this study)[2]. In developed countries, average adherence to medications for chronic diseases is as low as 50%, while the measure is lower in developing countries due to limited access to healthcare resources[3, 4]. Medication non-use aggravates the burden of chronic diseases and clinical outcomes of patients[4, 5]. Therefore, ensuring adherence and persistence of medications is key to successful management of chronic disease.

Poor adherence and persistence are a barrier to optimal care for patients with type 2 diabetes mellitus (T2DM)[6-9]. A systematic review found that only 56.2% in T2DM patients continued treatment one year after treatment initiation[10]. Adherence and persistence to injection drugs are even lower. The persistence rate of insulin glargine in the first year after initiation is below 50%[11]. Suboptimal persistence undermines clinical outcomes, leading to poor glycemic control[12, 13] and increases mortality and comorbidity burden[14, 15]. Moreover, low adherence to antidiabetic medications increases healthcare costs and diminishes quality of life[5, 14, 16].

The causes of low adherence and persistence to T2DM medications are multifactorial[17]. The World Health Organization classified reasons for medication non-use into five categories: patient-related (e.g., age), socioeconomic (e.g., medication costs), condition-related (e.g., presence of complications), health-system-related (e.g., level of continuity of care), and medication-related (e.g., adverse effects)[4]. Similarly, motivations behind medication non-use in T2DM patients on injection therapies are multifaceted. Ineffective communication between

patients and providers, inadequate knowledge about medications, and confusing directions for medication use simultaneously undermine treatment processes[18]. Moreover, the classes of antidiabetic medication are known to influence the adherence and persistence to the treatment[1, 19].

Dulaglutide (brand name: Trulicity®) is a Glucagon-like Peptide-1 Receptor Agonist (GLP-1RA) indicated for the treatment of type 2 diabetes mellitus (T2DM). Dulaglutide consists of two identical, disulfide-linked chains of modified GLP-1 sequence, which are covalently linked to the modified human immunoglobulin G4 Fc chain via a small peptide linker[20]. Unlike endogenous GLP-1, dulaglutide resists degradation by dipeptidyl peptidase-4 (DPP4) and has a molecular size large enough to reduce renal clearance[21]. These molecular characteristics extend the half-life of dulaglutide to approximately 5 days, making it suitable for once-weekly dosing[20].

Glucagon-like peptide-1 receptor agonists (GLP-1RA) including dulaglutide improve glycemic control and cardiovascular factors, reduce body weight, and rarely induce hypoglycemia[22]. GLP-1RA agents are preferred second-line treatment options for T2DM patients with cardiovascular comorbidities[23]. Furthermore, GLP-1RA agents are recommended as the first injectable medication before insulin[24]. As of 2021, nine formulations of injectable GLP-1RA agents have been approved worldwide (Table 1). Oral semaglutide (brand name: Rybelsus) was the first oral formulation of GLP-1RA approved by the US Food and Drug Administration for the treatment of T2DM[25].

Table 1 List of injectable GLP-1RA agents currently in clinical use worldwide

Drug	Dosing frequency
Exenatide	twice a day (BID)
Liraglutide	once a day (QD)
Exenatide	once a week (QW)
Albiglutide	once a week (QW)
Dulaglutide	once a week (QW)
Exenatide pen	once a week (QW)
Lixisenatide	once a day (QD)
Exenatide auto-injector	once a week (QW)
Semaglutide	once a week (QW)

GLP-1RAs are administered by subcutaneous injection except for oral semaglutide. As with many injectable therapies, GLP-1RAs are prone to medication non-use[26]. For example, when adherence was assessed using the average proportion of days covered (PDC) or the number of days covered by prescription fills divided by the total number of days[27], PDC for injectable GLP-1RAs at six months was only 0.61-0.76[28], lower than 0.8, a PDC of optimal treatment adherence. Furthermore, the proportion of non-persistent patients with injectable GLP-1RA in six months ranged between 26.0% and 67.9%[29].

Injectable GLP-1RA agents differ in dosing regimens, need for dose titration and reconstitution, and administration device features[30]. These differences led to differences in adherence and persistence rates among individual GLP-1RA agents. Within this medication class, dulaglutide has demonstrated significantly higher adherence and persistence rates than other GLP-1RAs[26, 30-32](HR [95% CI] of discontinuation compared with dulaglutide: 2.5 [2.1-3.0] for exenatide QW, 1.6 [1.5-1.8] for liraglutide, 1.4 [1.3-1.5] for semaglutide, and 2.8 [2.3-3.3] for lixisenatide; all $p<0.001$)[24, 30]. Similarly, dulaglutide was associated with significantly higher adherence than other GLP-1RA agents (OR [95% CI] of adherence compared with dulaglutide: 0.63 [0.55-0.73] for albiglutide, 0.32 [0.28-0.37] for exenatide BID, 0.48 [0.43-0.53] for exenatide QW, and 0.65 [0.59-0.71] for liraglutide; all $p<0.05$)[31]. Additionally, a recent claims-based study has found that patients treated with dulaglutide were significantly more adherent and persistent than those treated with oral semaglutide at six-month follow-up[33]. Nevertheless, the adherence and persistence rates in dulaglutide users still fell short of being optimal (mean PDC 0.76; 37% discontinuation rate)[28].

This result can be explained, at least partly, by dosing frequency and ease of use. In general, GLP-1RA agents with QW regimen demonstrated significantly better adherence and persistence than GLP-1RA agents with QD or BID regimen[22, 31, 34, 35]. In terms of delivery method, GLP-1RA agents using simple delivery systems (single-use pen or auto-injector device) had significantly higher adherence and persistence than GLP-1RA using multi-use pen or syringe[22, 28, 30, 31, 36]. Furthermore, treatment-related factors, such as experiencing early response (defined as improvements in HbA1c and body weight within six months after treatment initiation),

was known to be associated with significantly higher adherence and persistence in GLP-1RA users[29]. However, a comprehensive analysis of clinical characteristics associated with treatment adherence and persistence has been lacking.

Optimizing treatment adherence and persistence is an important determinant of clinical outcome[37]. In this sense, it is beneficial to investigate which clinical characteristics are associated with increased adherence and persistence. However, such analysis on dulaglutide users remain understudied. Previous studies mostly limited their scopes to comparative purposes, with the goal of showing higher adherence and persistence in dulaglutide users than users of other antidiabetic medications or other GLP-1RAs[10, 26, 28, 30-33]. Moreover, most of previous studies have used claims data, assembled primarily for reimbursement purposes and therefore not providing important clinical data such as laboratory test results. There are also concerns about inaccuracy and missingness of information in claims data due to lack of billing codes for some conditions or up-coding comorbidities[38, 39].

1.2 Purpose of Research

The objective of this study was to identify clinical characteristics associated with adherence and persistence in T2DM patients treated with dulaglutide. To this end, electronic medical records (EMR) transformed into the Common Data Model (CDM) at Seoul National University Hospital (SNUH), Seoul, South Korea were used.

Chapter 2. Methods

2.1 Data Source

Patient EMRs were collected by using the Observational Medical Outcomes Partnership Common Data Model (OMOP CDM, version 5.3.1) of Seoul National University Hospital (SNUH), Seoul, South Korea. SNUH is a university-affiliated, tertiary-care hospital. The OMOP CDM of SNUH contains over 2.3 billion medical records of more than 3 million patients, including patient demographics, diagnosis, drug exposures, laboratory test orders and results, surgeries, family histories, and past medical histories[40, 41]. Since w individually identifiable data were not used or collected, the SHUH Institutional Review Board (IRB) granted a waiver for obtaining informed consent.

2.2 Study Subjects

This was a retrospective observational cohort study. Eligible patients were those who were diagnosed with T2DM and initiated treatment with once-weekly dulaglutide (0.75 mg or 1.5 mg) between January 1st, 2018 and December 31st, 2019. The index date was defined as the first date of dulaglutide prescription with ≥6 months of identifiable past clinical history (i.e., baseline). Each eligible patient was followed for one year after the index date. Patients were excluded if they were <18 years of age at the index date, without ≥1 record of baseline HbA1c, diagnosed with type 1 diabetes or gestational diabetes, or with a record of bariatric surgery. Additionally, patients who were lost to follow-up (i.e., without clinical history) were considered disenrolled from SNUH and therefore excluded.

2.3 Clinical Characteristics

Records on demographics, comorbidities, concomitant antidiabetic medications, and

laboratory test results at baseline were extracted. Baseline comorbidities recorded in SNOMED CT were converted into corresponding International Classification of Diseases 10th Revision (ICD-10) codes by using Interactive Map-Assisted Generation of ICD Codes (I-MAGIC)[42]. After conversion, baseline comorbidities were categorized into composite events by using the diagnosis designation of the ICD-10 codes. Likewise, individual concomitant antidiabetic medications were grouped according to drug class. In addition, adverse events (AEs) were defined as any of the following conditions during follow up: nausea, vomiting, diarrhea, indigestion, abdominal pain, lower abdominal pain, foot ulcer, impaired fasting glucose, hyperglycemia, hypoglycemia, gastroparesis, and pancreatitis[43]. Finally, missingness was handled by imputing values for laboratory tests results and demographics with missingness <15% using the multiple imputation with chained equation (MICE) [44] ,whereas those with ≥15% missing data were excluded from analysis[45].

2.4 Outcome Measures

Adherence was measured by PDC and adherence status. Adherence status was a categorical variable, in which patients with ≥0.8 PDC were classified as adherent and those with <0.8 PDC were non-adherent. Similarly, persistence was assessed using treatment duration and continuation status. Treatment duration represents the number of days on treatment without discontinuation (i.e., >60 days gap between any two consecutive prescriptions). Continuation status was a categorical variable, in which patients were classified as either continuer or discontinuer based on the operational definition of discontinuation. If patients had overlapping days' supply, this study disregarded residual supply from the previous fill. The timeline of this study is depicted in Figure 1.

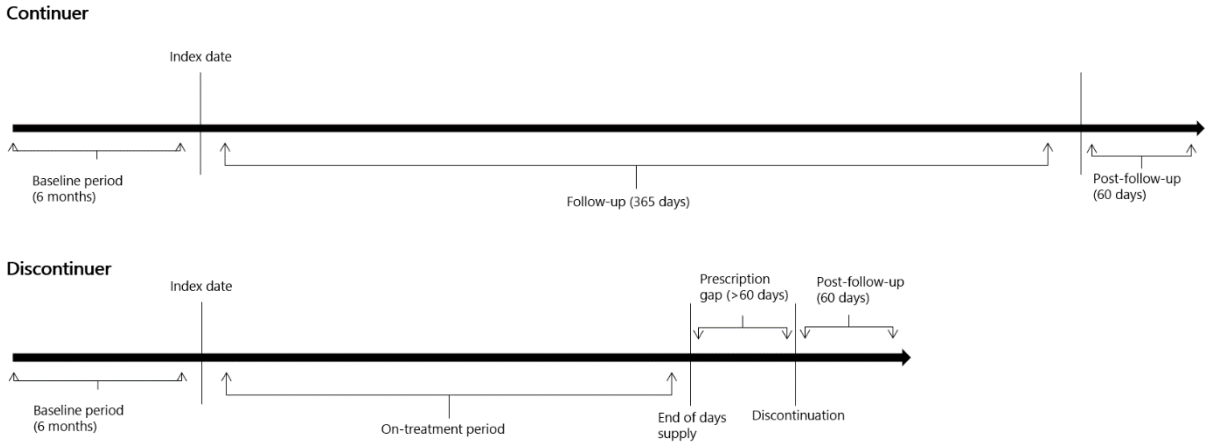

Figure 1 The timeline of the study for continuer (top) and discontinuer (bottom). The index date was the first date of dulaglutide prescription with ≥6 months of identifiable past clinical history (i.e., baseline). Each patient was followed for one year after the index date. Disenrollment was evaluated in post-follow-up period.

2.5 Statistical Analysis

Multivariate linear regression and multivariate logistic regression were conducted to identify the factors associated with continuous and categorical outcome measures, respectively. Important independent variables were selected per the highest adjusted R^2 value and the lowest Akaike Information Criterion (AIC) for the linear regression and the logistic regression models, respectively.

Because dulaglutide is also indicated for the treatment of T2DM patients with cardiovascular disease (CVD) risks, a subgroup analysis was performed involving patients with high CVD risk defined as having ≥2 identifiable CVD factor(s) (Table 2)[46, 47]. The cutoff of 2 identifiable CVD factor(s) was determined based on the median number of CVD risk factors in the study subjects. Propensity score (PS) was used to match subjects with high CVD risk with those with low CVD risk based on baseline characteristics (i.e., demographics, comorbidities, concomitant medications, and lab test results). In the analysis, matching with replacement was conducted because there were not enough controls (i.e., those without a CVD risk) to fully provide one-to-one match. On matched cohorts, the Student's t-test and Chi-squared (χ^2) test were used to analyze differences between those with high CVD risk and those with low CVD risk in continuous and categorical outcome measures,

respectively. For treatment duration, log-rank test was conducted, in which event was defined as discontinuing dulaglutide.

Table 2 List of identifiable risk factors for CVD

Identifiable risk factor	Criteria
LDL-C	≥100 mg/dL
TG	≥150 mg/dL
HDL-C	<40 mg/dL (men), <50 mg/dL (women)
Blood Pressure	≥140 mmHg (systolic) and/or ≥90 mmHg (diastolic)
Baseline hypertension†	Diagnosis record exists at baseline
Baseline obesity	Diagnosis record exists at baseline
Baseline dyslipidemia‡	Diagnosis record exists at baseline
Baseline CVD	Diagnosis record exists at baseline

†Counted only the subjects who did not meet the criteria for blood pressure; ‡Counted only the subjects who did not meet the criteria for LDL-C, TG, and HDL-C; Abbreviations: LDL-C, low density lipoprotein Cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol ;CVD, cardiovascular disease

In addition, a separate subgroup analysis was conducted to investigate significant differences in the four outcome measures with respect to the specialty of prescribers. Analysis of Variance (ANOVA) and χ^2 test were used for continuous outcome variables (i.e., PDC and treatment duration) and categorical outcome variables (i.e., adherence and continuation status), respectively.

To determine the robustness of the results, sensitivity analyses were performed by 1) changing the permissible prescription gap for continuous treatment to >90 days and 2) defining subjects with high CVD risk as having ≥3 identifiable CVD risk factors.

A p-value <0.05 was considered statistically significant. Statistical analysis was conducted using R (version 4.2.1).

Chapter 3. Results

3.1 Subjects

A total of 38,094 patients with T2DM were identified, of whom 236 patients were eligible for this study (Figure 2).

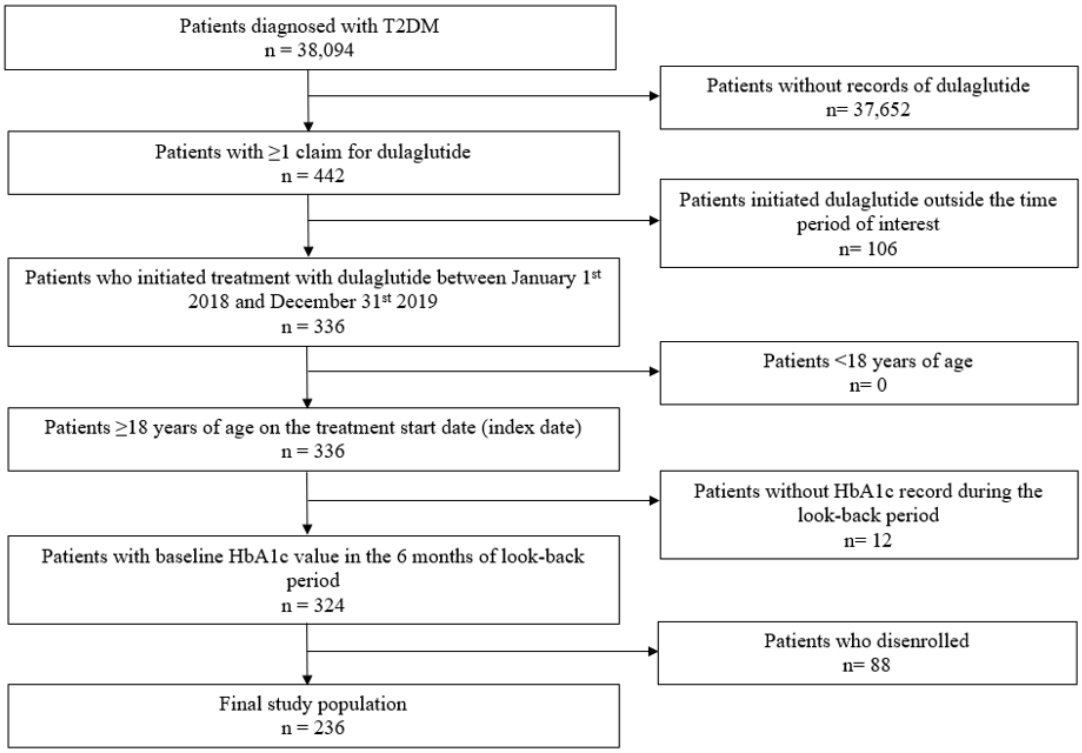

Figure 2 Flowchart for study population selection. Abbreviations: T2DM, type 2 diabetes mellitus; HbA1c, glycated hemoglobin A1c

The mean age was 55.5 years with sex being evenly distributed (50.4% male), and dyslipidemia was the most frequent baseline comorbidity (44.9%) followed by hypertension (37.7%) (Table 1). A total of 169 subjects had ≥2 risk factors for CVD at baseline and thus were classified as having high risk of CVD. More than two-thirds or 76.6% of patients (n=181) initiated treatment with low dose (0.75 mg) dulaglutide (Table 3).

Table 3 Baseline characteristics of total study population and subjects with high CVD risk (≥ 2 identifiable CVD risk factors)

Variables	Total (n = 236)	Subjects with ≥2 identifiable CVD risk factors (n = 169)
Sex		
Male, n (%)	119 (50.4%)	76 (45.0%)
Female, n (%)	117 (49.6%)	93 (55.0%)
Age at index date, mean (SD)	55.5 (13.7)	55.2 (14.1)
Baseline lab test results		
HbA1c, % (SD)	8.3 (1.4)	8.2 (1.5)
Systolic BP, mmHg (SD)	132.1(15.8)	134.4(16.4)
Diastolic BP, mmHg (SD)	80.0 (11.3)	81.7 (11.6)
Total cholesterol, mg/dL (SD)	158.7 (37.2)	157.1 (37.5)
LDL, mg/dL (SD)	86.5 (30.4)	89.6 (31.1)
HDL, mg/dL (SD)	47.1 (12.1)	45.0 (11.1)
Triglyceride, mg/dL (SD)	171.8 (105.3)	187.6 (114.5)
eGFR (MDRP), mL/min/1.73 m2 (SD)	85.6 (27.0)	86.8 (26.5)
eGFR (CKDEPI), mL/min/1.73 m2 (SD)	88.5 (25.1)	85.9 (26.5)
Postprandial glucose, mg/dL (SD)	158.6 (54.2)	159.1 (54.6)
Starting Dose		
0.75 mg, n (%)	181 (76.7%)	129 (76.3%)
1.5 mg, n (%)	55 (23.3%)	40 (23.7%)
Baseline concomitant antidiabetic medication		
Metformin, n (%)	217 (91.9%)	157 (94.1%)
Insulin, n (%)	88 (37.3%)	66 (39.1%)
Meglitinide, n (%)	1 (0.4%)	0 (0%)
DPP4 inhibitor, n (%)	42 (17.8%)	29 (17.2%)
SGLT2 inhibitor, n (%)	46 (19.5%)	33 (19.5%)
Alpha glucosidase, n (%)	2 (0.8%)	2 (1.2%)
Thiazolinedione, n (%)	9 (3.8%)	4 (2.4%)
Sulfonylurea, n (%)	149 (63.1%)	101 (59.8%)
DPP4 inhibitor plus metformin combination drug, n (%)	50 (21.2%)	38 (22.5%)
SGLT2 inhibitor plus metformin combination drug, n (%)	3 (1.3%)	2 (1.2%)
Sulfonylurea plus metformin combination drug, n (%)	6 (2.5%)	4 (2.4%)
Pioglitazone plus DPP4 inhibitor combination drug, n (%)	2 (0.8%)	1 (0.6%)
Injection History	134 (56.8%)	102 (60.4%)
Previously treated with insulin, n (%)	126 (53.4%)	96 (56.8%)
Previously treated with GLP-1RA other than dulaglutide, n (%)	28 (11.9%)	24 (14.2%)
Baseline comorbidity		
Hypertension, n (%)	89 (37.7%)	84 (49.7%)

Obesity, n (%)	21 (8.9%)	21 (12.4%)
Dyslipidemia, n (%)	106 (44.9%)	83 (49.1%)
Cardiovascular disease, n (%)	29 (12.3%)	26 (15.4%)
Kidney disease, n (%)	50 (21.2%)	38 (22.5%)
Eye disease, n (%)	72 (30.5%)	49 (29.0%)
Neuropathy, n (%)	29 (12.3%)	20 (11.8%)
Mental or memory impairment, n (%)	10 (4.2%)	10 (5.9%)
Disease history		
Previously diagnosed with myocardial infarction, n (%)	12 (5.1%)	9 (5.3%)
Previously diagnosed with heart failure, n (%)	4 (1.7%)	3 (1.8%)
Previously diagnosed with lesion in thyroid, n (%)	23 (9.7%)	13 (7.7%)
CVD Risk at Baseline		
Low (<2 CVD risk factor(s))	67 (28.4%)	0 (100%)
High (≥2 CVD risk factors)	169 (71.6%)	169 (0%)

SD, standard deviation; PDC, proportion of days covered; HbA1c, glycated hemoglobin A1c; BP, blood pressure; LDL, low density lipoprotein; HDL, high density lipoprotein; eGFR, estimated glomerular filtration rate; MDRP, modification of diet in renal disease; CKDEPI, chronic kidney disease epidemiology collaboration; DPP4, dipeptidyl peptidase 4; SGLT2, sodium glucose cotransporter 2; GLP1-RA, glucagon-like peptide 1 receptor agonist; CVD, cardiovascular disease

Furthermore, 41.1% of patients (n=97) switched dose after treatment initiation with dulaglutide, among whom 92.8% (n=90) switched to high dose (1.5 mg). Dulaglutide was well-tolerated; <1% of subjects experienced one or more pre-defined AEs except abdominal pain (1.3%)(Table 4).

Table 4 Treatment adherence and persistence results

Variables	Total (n = 236)	Subjects with ≥2 identifiable CVD Risk Factor(s) (n = 169)
Continuation status		
Continued, n (%)	119 (50.4%)	80 (47.3%)
Discontinued, n (%)	117 (49.6%)	89 (52.7%)
Treatment duration, mean days (SD)	236.8 (124.9)	230.5 (125.0)
PDC, mean (SD)	0.6 (0.3)	0.63 (0.34)
Adherence, n (%)		
Yes (PDC≥0.8)	115 (48.7%)	78 (46.2%)
No (PDC<0.8)	121 (51.3%)	91 (53.8%)
Switching		
Yes, n (%)	97 (41.1%)	63 (37.3%)
1.5 mg to 0.75 mg in 1st switching	7 (7.2%)	4 (6.3%)
0.75 mg to 1.5 mg in 1st switching	90 (92.8%)	59 (93.7%)
No, n (%)	139 (58.9%)	106 (62.7%)
Adverse events		

Nausea, n (%)	1 (0.4%)	0 (0%)
Vomiting	0 (0.0%)	0 (0.0%)
Diarrhea	0 (0.0%)	0 (0.0%)
Indigestion, n (%)	2 (0.8%)	1 (0.6%)
Abdominal pain, n (%)	3 (1.3%)	3 (1.8%)
Lower abdominal pain, n (%)	1 (0.4%)	1 (0.6%)
Hyperglycemia, n (%)	2 (0.8%)	2 (1.2%)
Hypoglycemia, n (%)	1 (0.4%)	0 (0%)
Impaired fasting glucose, n (%)	1 (0.4%)	1 (0.6%)
Foot ulcer, n (%)	1 (0.4%)	0 (0%)
Gastroparesis, n (%)	1 (0.4%)	1 (0.6%)
Pancreatitis, n (%)	0 (0.0%)	0 (0.0%)

SD, standard deviation; PDC, proportion of days covered

3.2 Adherence

The mean PDC was 0.6, and 48.7% of subjects were adherent (Table 4). Increase in age, switching dose, and having neuropathy at baseline significantly increased PDC (β−coefficients [95% Confidence Interval, or CI]: 0.006 [0.002, 0.010], 0.09 [0.003, 0.18], 0.14 [0.01, 0.27], respectively; all $p<0.05$) (Table 5). In contrast, baseline uses of sulfonylurea or insulin significantly decreased PDC (β−coefficients [95% CI]: −0.13 [−0.23, −0.022] and −0.11 [−0.21, −0.005], respectively). On the other hand, subjects were 4% more likely adherent as age increased (Odds Ratio or OR [95% CI]: 1.04 [1.010, 1.074], $p<0.05$). Moreover, increase in estimated glomerular filtration rate (eGFR) was significantly associated with increased adherence (OR [95% CI]: 1.02 [1.002, 1.030], $p<0.05$) (Figure 3).

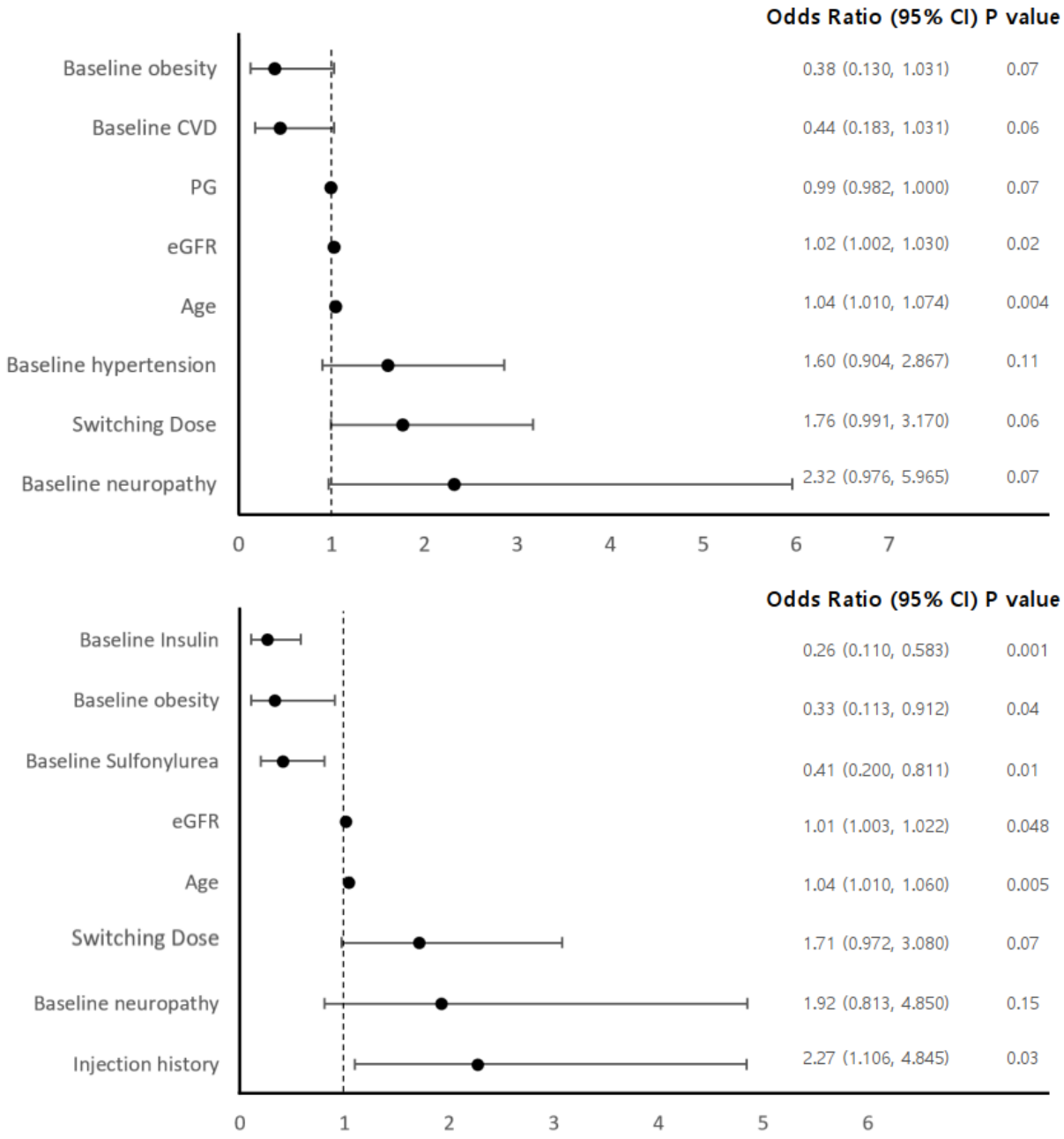

Figure 3 Factors affecting adherence status (top) and continuation status (bottom) of all subjects (n=236). P values were determined by multivariate logistic regression. Abbreviations: 95% CI, 95% confidence interval; CVD, cardiovascular disease; PG, postprandial glucose; eGFR, estimated glucose filtration rate (CKD-EPI)

Table 5 Clinical factors affecting PDC and treatment duration

	PDC			Treatment duration		
	Factor	β−coefficient (95% CI)	P value	Factor	β−coefficient (95% CI)	P value
All patients (n=236)	Age	0.006 (0.002, 0.010)	0.002	Age	2.17 (0.78, 3.55)	0.002
	eGFR	0.002 (−0.0003, 0.0003)	0.11	eGFR	0.55 (−0.12, 1.23)	0.11
	Switching dose	0.09 (0.003, 0.18)	0.04	Switching dose	32.9 (0.81, 64.9)	0.04
	Baseline Insulin	−0.11 (−0.21, −0.005)	0.04	Baseline Insulin	−38.9 (−76.1, −1.68)	0.04
	Baseline Sulfonylurea	−0.13 (−0.23, −0.022)	0.02	Baseline Sulfonylurea	−43.6 (−83.2, −8.08)	0.02
	Baseline obesity	−0.12 (−0.27, 0.03)	0.12	Baseline obesity	−43.4 (−98.3, 11.5)	0.12
	Baseline neuropathy	0.14 (0.01, 0.27)	0.04	Baseline neuropathy	50.6 (2.94, 98.3)	0.04
	Baseline CVD	−0.11 (−0.24, 0.03)	0.12	Baseline CVD	−39.2 (−88.4, 10.0)	0.12
Patients with ≥2 identifiable CVD Risk(s) (n=169)	Age	0.006 (0.001, 0.011)	0.009	Age	2.23 (0.54, 3.91)	0.001
	Male sex	0.079 (−0.023, 0.180)	0.129	Male sex	28.48 (−8.69, 65.66)	0.132
	TG	0.0004 (−0.00008, 0.0009)	0.103	TG	0.147 (−0.03, 0.323)	0.103
	eGFR	0.0028 (0.0006, 0.0049)	0.015	eGFR	1.017 (0.205, 1.830)	0.014
	Switching dose	0.1304 (0.0022, 0.243)	0.019	Switching dose	48.2 (7.74, 88.66)	0.020
	Baseline Insulin	−0.143 (−0.277, −0.0089)	0.037	Baseline Insulin	−52.24 (−101.28, −3.20)	0.037
	Baseline Sulfonylurea	−0.158 (−0.275, −0.0416)	0.008	Baseline Sulfonylurea	−57.75 (−100.31, −15.19)	0.008
	Injection history	0.0905 (−0.037, 0.219)	0.166	Injection history	32.92 (−13.99, 79.83)	0.168
	Baseline neuropathy	0.1415 (−0.0145, 0.297)	0.075	Baseline neuropathy	51.57 (−5.44, 108.58)	0.076
	Baseline obesity	−0.1453(−0.300, 0.0094)	0.065	Baseline obesity	−53.02 (−109.54, 3.52)	0.066

PDC, proportion of days covered; eGFR, estimated glomerular filtration rate; CVD, cardiovascular disease; TG, triglyceride; P value determined by the multivariate linear regression after variables were removed from the model using backward selection method

3.3 Persistence

The mean treatment duration was 236.8 days, and 50.4% of subjects were continuously treated with dulaglutide during follow up (Table 4). Increase in age, switching dose, and having neuropathy at baseline significantly increased treatment duration by 2.17 days (95% CI: 0.78, 3.55 days), 32.9 days (95% CI: 0.81, 64.9 days), and 50.6 days (95% CI: 2.94, 98.3 days), respectively (all $p<0.05$) (Table 5). In contrast, baseline uses of sulfonylurea or insulin significantly reduced treatment duration (β-coefficients [95% CI]: −43.6 days [−83.2, −8.80 days] and −38.9 days [−76.1, −1.68 days], respectively; both $p<0.05$). On the other hand, subjects who had experience with injectable therapies were over twice more likely to continue treatment than those who did not (OR [95% CI]: 2.27 (1.106, 4.845), $p<0.05$) (Figure 3). Furthermore, subjects were significantly more likely to be continuously treated as age increased (OR [95% CI]: 1.04 [1.010, 1.060], $p<0.05$). Contrastingly, subjects using sulfonylurea or insulin or who had obesity at baseline were significantly less likely to continue treatment with dulaglutide (OR [95% CI]: 0.41 (0.200, 0.811), 0.26 (0.110, 0.583), 0.33 (0.113, 0.912), respectively; all $p<0.05$). Those results in adherence and persistence did not significantly change in the sensitivity analysis using 90-day of permissible prescription gap (Table 6).

Table 6 Sensitivity analysis results (using cutoff as 90-day prescription gap)

Endpoint	60-day prescription gap (n=236)	90-day prescription gap (n=236)	P value
PDC, mean (SD)	0.65 (0.3)	0.67 (0.3)	0.46
Treatment duration, mean (SD)	236.8 (124.9)	244.9 (116.7)	0.46
Adherence, n (%)	115 (48.7)	115 (48.7)	0.93
Continuation, n (%)	119 (50.4)	131 (55.5)	0.27

SD, standard deviation; PDC, proportion of days covered; P value determined by Student's t-tests for PDC and treatment duration and by χ^2 tests for adherence and continuation

3.4 Impact of CVD Risk on Dulaglutide Adherence and Persistence

After propensity scores were calculated based on baseline demographics, comorbidities, laboratory test results, and concomitant medications, 67 subjects with <2 identifiable CVD risk factor with 169 subjects with ≥2 identifiable CVD risk factors were matched (Table 7).

Table 7 Comparison of baseline characteristics between matched cohorts

Variable	Subjects with ≥2 identifiable CVD risk factors (n=169)	Subjects with <2 identifiable CVD risk factor (n=67)	p value
Demographics			
Age (years), mean (SD)	55.2 (14.1)	56.3 (12.8)	0.594
Sex (male, %)	45.0	52.2	0.120
Laboratory test results			
HbA1c (%), mean (SD)	8.2(1.4)	8.4 (1.4)	0.310
eGFR (mL/min/1.72 m2), mean (SD)	85.9 (26.5)	85.0 (28.4)	0.810
PG (mg/dL), mean (SD)	159.1 (54.6)	157.3 (53.7)	0.820
Concomitant medication			
Metformin users (%)	94.0	89.6	0.557
Insulin users (%)	39.5	32.8	0.459
DPP4 inhibitor users (%)	17.4	19.4	0.828
SGLT2 inhibitor users (%)	19.8	19.4	1.000
Sulfonylurea users (%)	60.5	71.6	0.120
Comorbidities			
Kidney disease (%)	22.5	17.9	0.549
Eye disease (%)	29.0	34.3	0.518
Neuropathy (%)	11.8	13.4	0.907

CVD, Cardiovascular disease; SD, standard deviation; HbA1c, glycated hemoglobin A1c; GFR, glomerular filtration rate; PG, postprandial glucose; DPP4, dipeptidyl peptidase 4; SGLT2, sodium glucose co-transporter 2; p values were calculated using Student's t-tests and χ^2 tests for continuous and categorical variables, respectively.

The outcome measures were compared using Student's t-tests and $\chi 2$ tests between the matched cohorts. There was no statistically significant difference (all p>0.05) (Table 8).

Table 8 Comparative analysis of endpoints in patients with ≥2 identifiable CVD risk factors and those with <2 identifiable CVD risk factors

Endpoint	Subjects with ≥2 identifiable CVD risk factors (n=169)	Subjects with <2 identifiable CVD risk factors (n=67)	P value
PDC, mean (SD)	0.63 (0.34)	0.69 (0.34)	0.219
Treatment duration, mean (SD)	230.5 (125.0)	252.6 (123.9)	0.221
Adherence, n (%)	78 (46.2)	37 (55.2)	0.210
Continuation, n (%)	80 (47.3)	39 (58.2)	0.132

SD, standard deviation; PDC, proportion of days covered; CVD, cardiovascular disease; P value determined by Student's t-tests for PDC and treatment duration and by χ^2 tests for adherence and continuation

Furthermore, regression analysis results showed that the outcome measures of subjects with ≥2 CVD risk(s) were affected by similar factors in addition to the clinical characteristics associated with CVD, such as the low density lipoprotein cholesterol (LDL-C) level and the presence of hypertension or obesity at baseline (Figure 4).

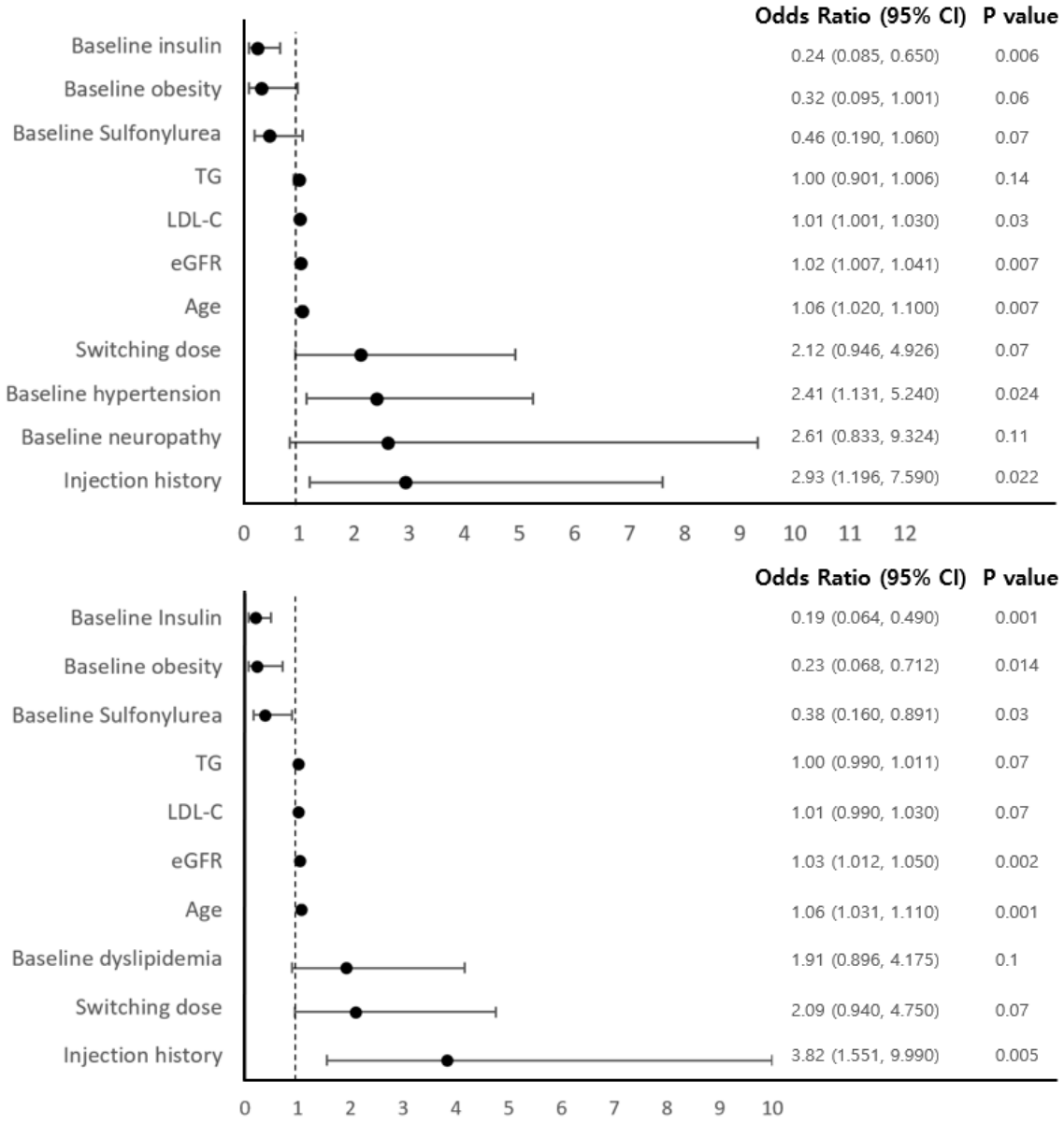

Figure 4 Factors affecting adherence status (top) and continuation status (bottom) of subjects with ≥2 CVD risk(s) (n=169). P values determined by multivariate logistic regression. Abbreviations: 95% CI, 95% confidence interval; CVD, cardiovascular disease; TG, triglyceride; HbA1c, glycated hemoglobin A1c; LDL-C, low density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate (CKD-EPI)

Finally, the result of log-rank test showed there was no significant difference in the time to discontinue dulaglutide between the matched cohorts (p=0.16) (Figure 5). Sensitivity analysis comparing subjects with ≥3 CVD risk factors to those with <3 CVD risk factors showed no significant difference in the results (Table 9, Figure 6).

Table 9 Comparative analysis of endpoints in patients with and without CVD risk (sensitivity analysis)

Endpoint	Patients with ≥3 CVD risk (n = 77)	Patients with <3 CVD risk (n = 159)	P value
PDC, mean (SD)	0.66 (0.35)	0.64 (0.34)	0.62
Treatment duration, mean (SD)	242.5 (125.6)	233.9 (124.8)	0.62
Adherence, n (%)	39 (50.6)	76 (47.8)	0.68
Continuation, n (%)	40 (51.9)	79 (49.7)	0.74

SD, standard deviation; PDC, proportion of days covered; CVD, cardiovascular disease; P value determined by Student's t-tests for PDC and treatment duration and by χ^2 tests for adherence and continuation

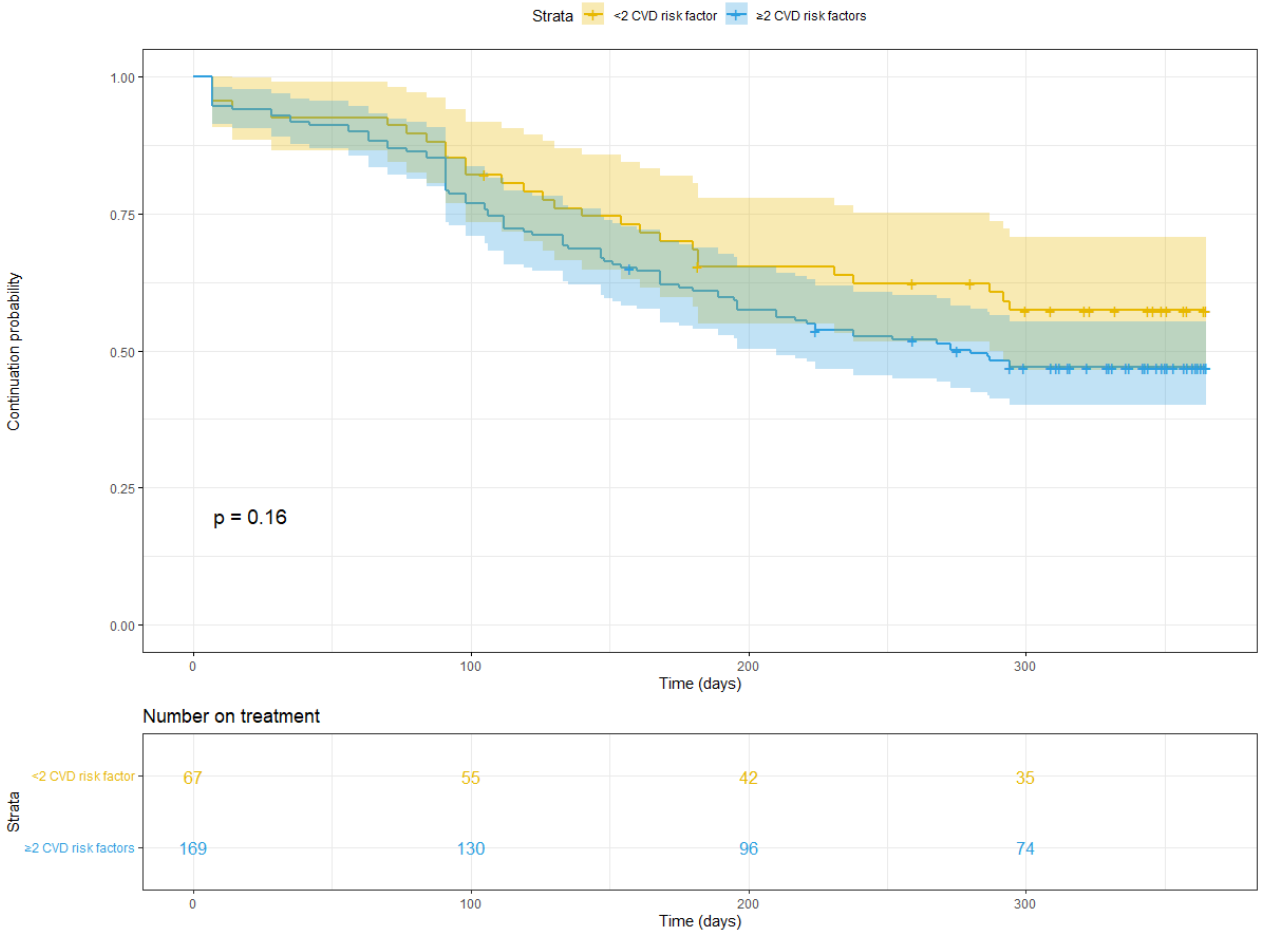

Figure 5 Kaplan–Meier curve for the comparison of time to treatment discontinuation on the matched cohorts between subjects with <2 CVD risk factor (n=67) and subjects with ≥2 CVD risks (n=169). Median was 280 days for subjects with ≥2 CVD risks and was not reached for subjects with <2 CVD risk factor. P value was determined by log–rank test (χ^2=2, 1 degree of freedom). Abbreviations: CVD, cardiovascular disease

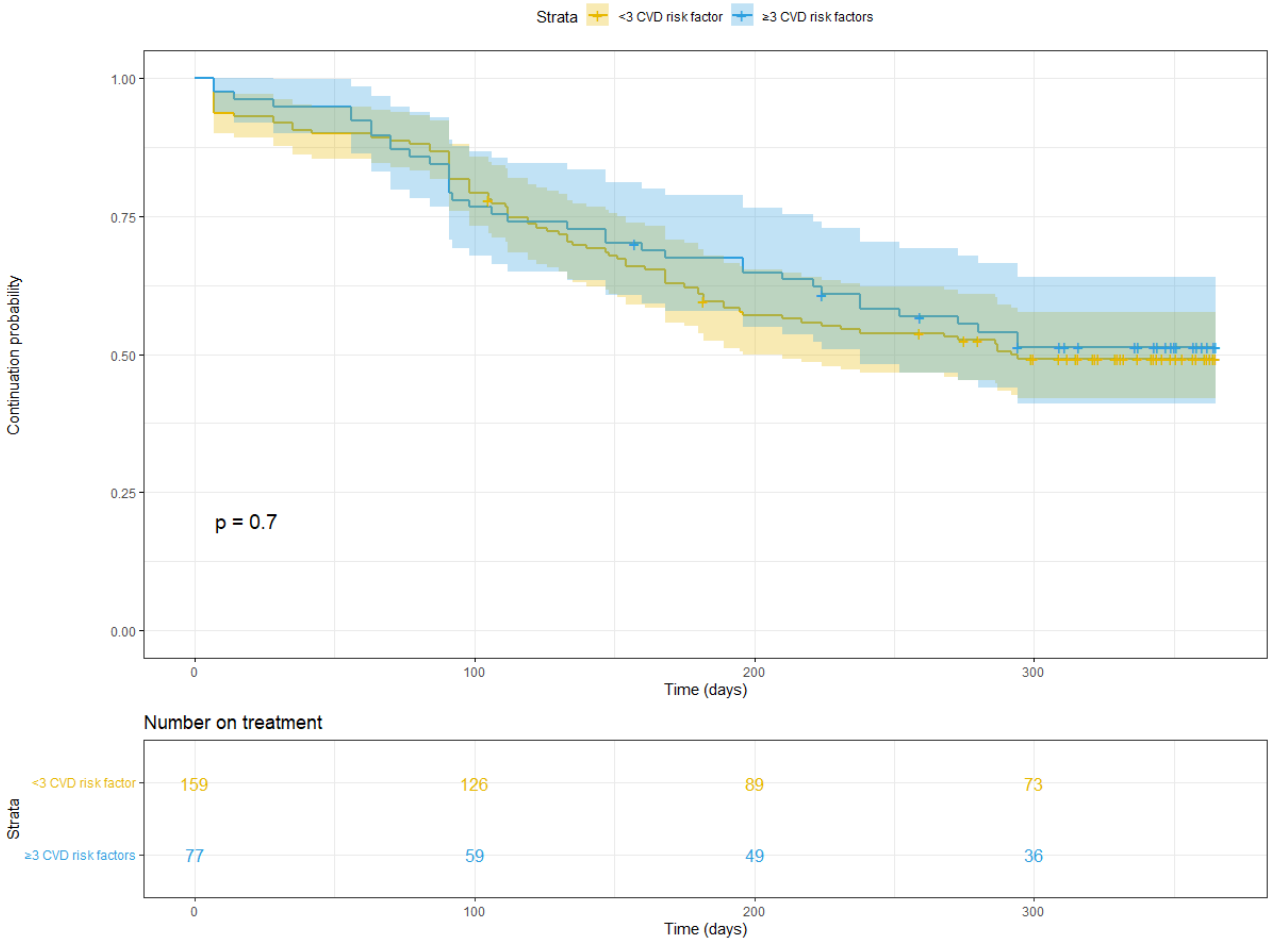

Figure 6 Kaplan–Meier curve for the comparison of time to treatment discontinuation on the matched cohorts between subjects with 3< CVD risk (n=159) and subjects with ≥3 CVD risk(s) (n=77). Median was not reached for subjects with ≥3 CVD risks and was 292 days for subjects with <3 CVD risk factors. P value was determined by log–rank test ($\chi 2$=0.1, at 1 degree of freedom). Abbreviations: CVD, cardiovascular disease

3.5 Adherence and persistence comparison by the prescriber specialty

There were six categories of prescriber specialty in the study subjects: 1) endocrinology, 2) family medicine, 3) internal medicine, 4) nephrology, 5) neurology, and 6) unknown. Most of the study subjects (n=182, or 77.1%) were prescribed with dulaglutide by endocrinologists at index date (Figure 7).

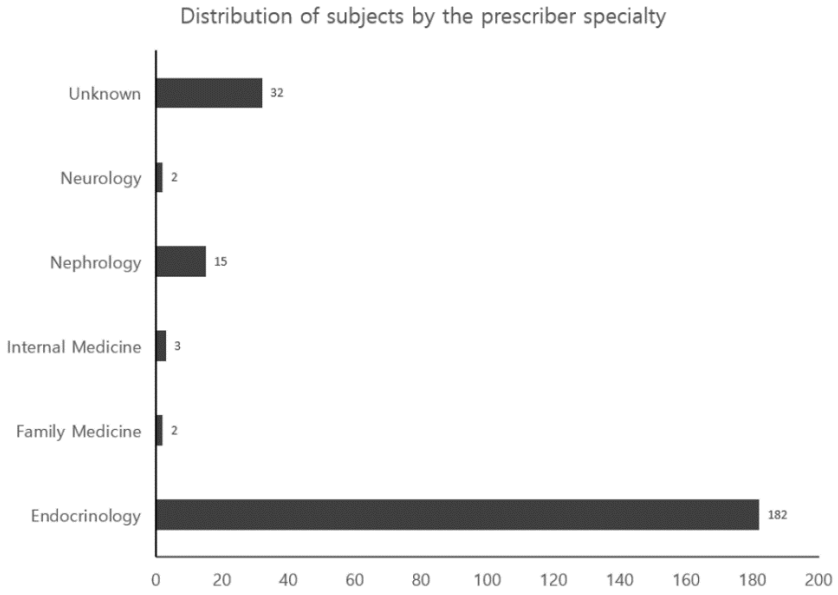

Figure 7 Distribution of the number of subjects based on the specialty of the prescriber from whom they received prescriptions for dulaglutide at index date

The one-way ANOVA test results showed that there was no statistically significant difference among patients treated with 6 different categories of prescriber specialty with respect to PDC and treatment duration (Table 10, Figure 8).

Table 10 Dulaglutide adherence and persistence of subjects based on prescriber specialty

specialty	PDC, mean (SD)	Treatment duration, mean (SD)	Adherence, n (%)	Continuation, n (%)
Endocrinologist (n=182)	0.66 (0.35)	240.9 (126.9)	92 (51.6)	96 (52.7)
Family Medicine (n=2)	0.135 (0.08)	49 (29.7)	0 (0)	0 (0)
Internal Medicine (n=3)	0.77 (0.32)	281.3 (116.4)	2 (66.7)	2 (66.7)
Nephrology (n=15)	0.58 (0.30)	210.8 (109.2)	4 (26.7)	6 (40)
Neurology (n=2)	0.27 (0.14)	99 (50.9)	0 (0)	0 (0)
Unknown (n=32)	0.66 (0.32)	241.2 (116.4)	15 (46.8)	15 (46.8)
p value	0.143	0.143	0.169	0.348

SD, standard deviation; PDC, proportion of days covered; P value determined by one-way ANOVA tests for PDC and treatment duration and by χ^2 tests for adherence and continuation

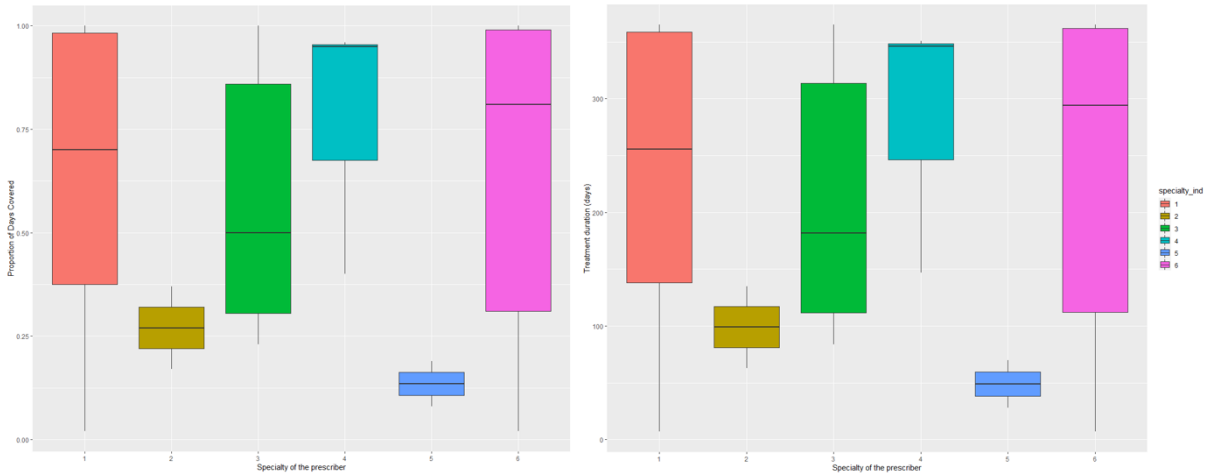

Figure 8 Box plots for PDC (left) and treatment duration (right) of subjects prescribed with dulaglutide at index date by six categories of prescriber specialty (specialty indicators 1 to 6 represent unknown, neurology, nephrology, internal medicine, family medicine, and endocrinology, respectively). One-way ANOVA test results for the comparison of PDC and treatment duration were F statistics=1.668 (p=0.143, degrees of freedom=5), and 1.67 (p=0.143, degrees of freedom=5), respectively.

Likewise, there was no statistically significant difference among patients treated with 6 different categories of prescriber specialty with respect to the proportion of adherent subjects and continuers (Table 10, Figure 9).

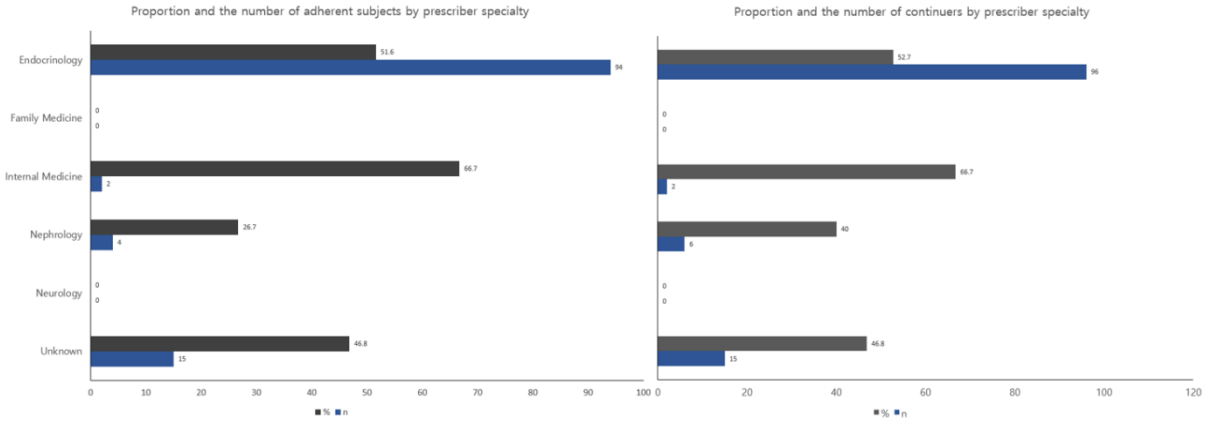

Figure 9 Bar plots for the proportion (grey) and the number (blue) of adherent subjects (left) and continuers (right) based on the specialty of the prescribers of dulaglutide at index date. The χ^2 test results for the comparison of the proportion of adherent subjects and continuers were χ^2= 7.775 (p=0.1691, degrees of freedom=5) and χ^2= 5.5912 (p=0.348, degrees of freedom=5), respectively.

Chapter 4. Discussion

This study found the clinical characteristics that are associated with the adherence and persistence to the treatment with dulaglutide. Most notably, this study found that a year increase in age significantly improved PDC, treatment duration, and the likelihood of adherence and continuation. The results were consistent with previous studies, which have identified older age as a significant predictor of adherence and persistence in T2DM patients treated with antidiabetic medications[48-51]. To the best of our knowledge, reports on the association between age and the adherence and persistence particularly in dulaglutide users have been lacking. Older age is known to be associated with increasing severity of illness and greater awareness of health status[52], which can lead to higher adherence and persistence rates. Given that polypharmacy and increasing susceptibility to AEs and complications in older populations may undermine treatment adherence and persistence[53], this finding is reassuring.

In addition, this study found that changing the treatment dose of dulaglutide significantly improves PDC and treatment duration. Previous studies have found that patients who initiated the low dose (0.75 mg) dulaglutide and then switched to the high dose (1.5 mg) were significantly more likely to be adherent and persistent[30, 54]. Of note, dose switching in this study considered both escalation and de-escalation of dulaglutide dose. Nevertheless, over 90% of the subjects who had switched dose underwent dose escalation. In this sense, the finding of this study was consistent with the previous findings. A clinical study of dulaglutide found that the frequency of gastrointestinal AEs in dulaglutide-treated patients increased in dose-dependent manner, which could potentially undermine adherence and persistence[55]. However, the results of this study showed that dulaglutide was well tolerated overall. Thus, it may be suggested that dose escalation may improve rather than undermine the adherence and persistence of dulaglutide users despite the potentially higher risk of gastrointestinal AEs.

Moreover, this study found that baseline neuropathy significantly increased both PDC and treatment duration. This finding was consistent with a previous study investigating insulin adherence and persistence in T2DM patients, which found that

patients with neuropathy were more likely to be persistent[56]. As of yet, more real-world evidence has to be established about the efficacy of dulaglutide on managing neuropathic comorbidities and its impact on dulaglutide adherence and persistence. Nevertheless, this finding leads to a speculation that the higher PDC and treatment duration in the subjects with neuropathy can be attributed to the once-weekly dosing interval of dulaglutide, which offers an added benefit of convenience. Neuropathic comorbidities are known to complicate routine tasks of diabetes management (e.g., checking blood glucose level) because of exaggerated pain response[57]. In this sense, the once-weekly dosing of dulaglutide may reduce the frequency of such tasks in T2DM patients with baseline neuropathy[58] and improve adherence and persistence. Moreover, it is possible that patients with baseline neuropathy are more likely to have longer T2DM duration, greater disease severity, and more failed previous treatments. These factors may have heightened their awareness of health status and thus improved their adherence and persistence.

This study also found that higher baseline eGFR was associated with significantly higher likelihood of dulaglutide adherence and continuation. It is unlikely that this association is due to the pharmacokinetic profile of dulaglutide. Dulaglutide is composed of two GLP-1 analogues fused to a modified IgG4 Fc fragment by a small peptide link[55]. Due to the large molecular size, dulaglutide is not cleared by the kidney, and no clinically relevant difference in the pharmacokinetics (e.g., total clearance) of dulaglutide was observed in T2DM patients with impaired kidney function[55]. Instead, it may be suspected that factors external to dulaglutide, such as higher medical cost in T2DM patients with impaired kidney function[59], may have affected dulaglutide adherence and persistence. However, a further investigation is warranted. Renal protective effects of GLP-1RAs including dulaglutide, which are known to reduce protein kinase C, oxidative stress, and inflammatory response, have been well established in preclinical studies[60, 61]. Moreover, in clinical studies, treatment with dulaglutide was associated with a significantly smaller decline in eGFR or reduced composite renal outcomes than comparators and placebo[62, 63]. An analysis of integrated data from 9 phase II and III trials of dulaglutide has also found that treatment with dulaglutide decreased albuminuria and was not associated with an increase in AEs reflecting potential acute renal failure[64]. Considering T2DM is the

leading cause of chronic kidney disease[65] and eGFR typically declines approximately 2 to 4 mL/min/year in T2DM patients[64, 66], the renal protective effect of dulaglutide can greatly benefit the patients with low kidney function. Therefore, attention must be paid to such patients to improve treatment adherence and persistence and eventually treatment outcome.

This study found that the presence of obesity at baseline significantly reduced the likelihood of dulaglutide continuation. The weight benefit of GLP-1 RAs including dulaglutide have been demonstrated by randomized clinical trials (RCTs)[67, 68]. For example, a phase 3 clinical of dulaglutide has found a clinically meaningful weight loss (mean bodyweight change from baseline: -2.9 kg) in patients treated with 1.5 mg dulaglutide over 26 weeks[69]. However, previous real-world studies have reported a significant heterogeneity in the magnitude of weight loss in GLP-1 RA users, a substantial proportion of whom underwent no significant change in bodyweight[70, 71]. Treatment effect observed in RCTs often exceeds the real-world effectiveness due in part to insufficient representativeness of clinical trial participants[72] or greater accessibility to resources and support systems that help comply with treatment regimen during RCTs[54]. Considering that clinical improvement may improve treatment persistence[73], the efficacy-effectiveness gap pertaining to the weight benefit of dulaglutide may have led to the significantly lower likelihood of continuing dulaglutide in subjects with baseline, despite the purported weight benefit of dulaglutide.

In the subgroup analysis involving patients at higher risk of CVD (i.e., with 2 or more identifiable CVD risk factors), this study found that the dulaglutide adherence and persistence in those with high CVD risk and those with low CVD risk were not significantly different. This result may be attributed to the large portion of the study subjects having high CVD risk (n=169, or 71.6%). Furthermore, it may be speculated that the comparable adherence and persistence rates in dulaglutide users at high CVD risk may be due to the potential delay of the CVD preventive effect of dulaglutide. Cardiovascular benefits of dulaglutide and their durability, particularly in middle-aged or older T2DM patients, are well-established[74]. However, underlying metabolic abnormalities that eventually lead to CVDs may remain asymptomatic for years before clinical manifestation[75, 76]. Similarly, the CVD preventive effect of a

medication may become apparent over an extended period of time. Considering that perceived or objective clinical improvement may improve treatment adherence and persistence[73], such delay may have prevented the CVD benefits of dulaglutide from improving dulaglutide adherence and persistence, at least within a year. On the other hand, the set of clinical factors associated with the adherence and persistence of dulaglutide users with high CVD risk was comparable to those of all subjects. Of note, this study found that in subjects with high CVD risk, the presence of baseline hypertension and the higher baseline LDL-C level significantly increased the likelihood of adherence. These results may be an indication that in T2DM patients with high CVD risk, the CV benefit of dulaglutide may lead to better dulaglutide adherence. However, a further investigation is warranted whether such phenomenon is due to the experience of clinical improvement or an expectation for it.

Previous studies have found that one of the reasons for discontinuing dulaglutide is experiencing AEs like gastrointestinal symptoms[30, 36]. The results of this study showed that AEs known to be associated with dulaglutide were relatively rare in the study subjects. <1% of the study subjects experienced an AE except abdominal pain (1.3%). These results may suggest that dulaglutide was generally well tolerated, and the experience of AEs at least within a year may not significantly interfere with medication-taking behaviors in dulaglutide users. Of note, the incidence rates of AEs as reported by a meta-analysis of RCTs of dulaglutide were higher, with 7.8%, 11.2%, 7.3%, and 5% of RCT participants treated with dulaglutide reporting to have experienced hypoglycemia, nausea, vomiting, and diarrhea, respectively[77]. Thus, the results of this study pertaining to AEs should be taken with caution due to potential underreporting of the symptoms that were transient or non-emergent. Moreover, a previous study reported that experiencing early response (defined as improvements in HbA1c within three to six months after treatment initiation) was associated with significantly higher adherence and persistence in GLP-1RA users including those treated with dulaglutide[29]. However, in the post hoc analysis of this study involving the subjects with ≥90 days of treatment duration, there was no significant difference in the magnitude of early response (i.e., net or percent changes in HbA1c level within 3 months) between adherent patients (or continuers) and non-adherent patients (or discontinuers) after propensity score

matching on baseline characteristics (Figure 10).

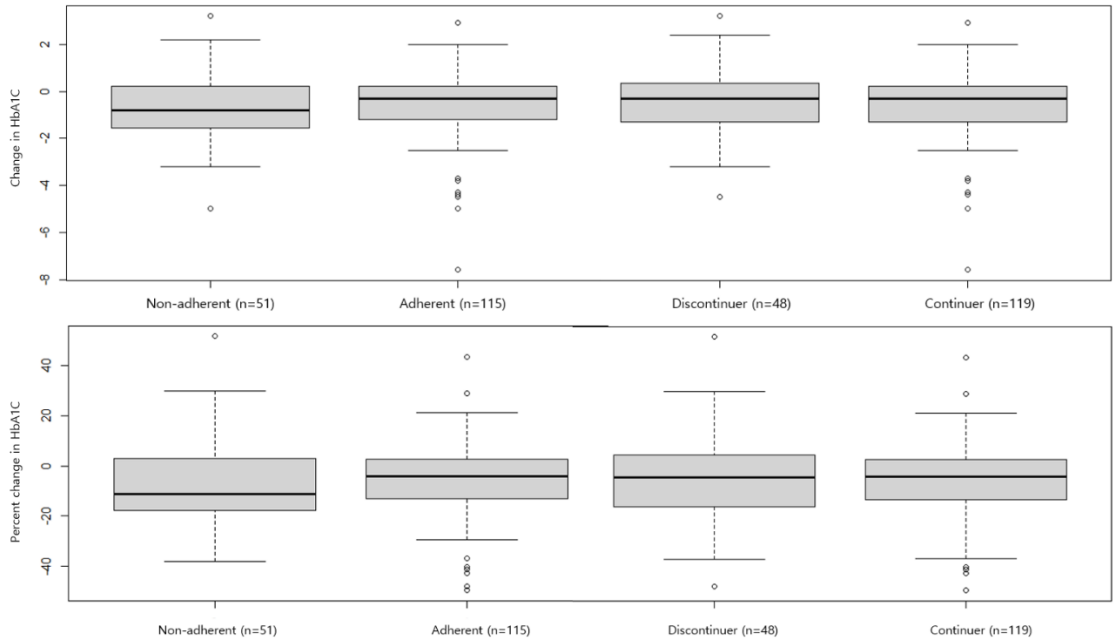

Figure 10 Between group comparison of net change in HbA1c level (top) and percent change in HbA1c level (bottom) at 3 months after dulaglutide initiation

This study found that the dulaglutide adherence in the study subject was not optimal. Moreover, only one half of the subjects (50.4%) continued treatment with dulaglutide for one year. These results are consistent with the findings of previous studies[28, 29, 31, 34], which reported the adherence and persistence rates of injectable antidiabetic medications including dulaglutide were suboptimal. Notably, the subjects of this study demonstrated a congruity in treatment adherence and treatment continuation (Figure 11). Most subjects either 1) adherently continued treatment with dulaglutide or 2) were non-adherent discontinuers. Only few subjects were adherent discontinuers or non-adherent continuers. These results suggest that the subjects who adhered to dulaglutide treatment tended to take the medication without substantial missed doses. Moreover, these results may account for the clinical factors that affect both adherence and persistence in a congruent manner.

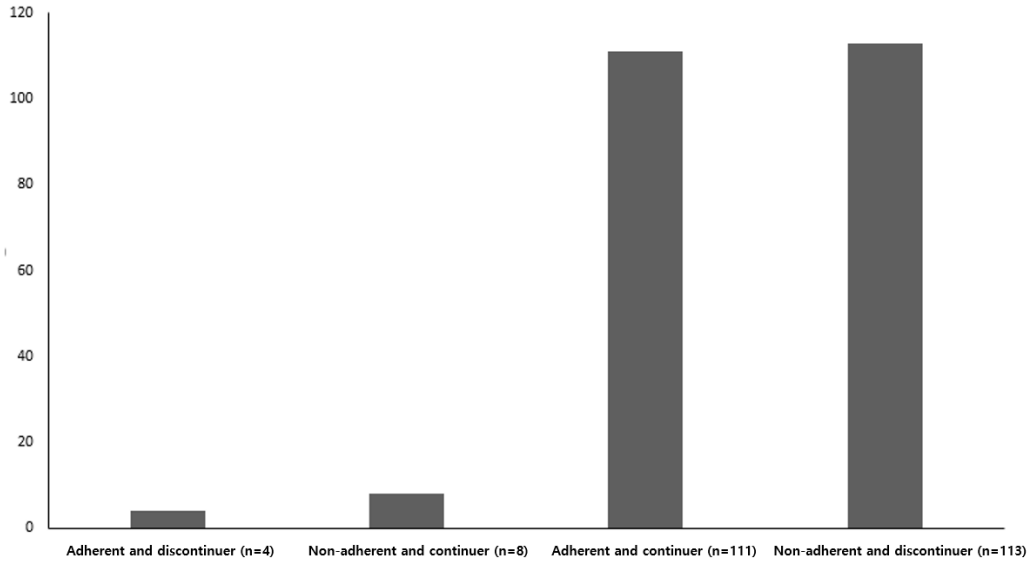

Figure 11 Distribution of subjects based on adherence status and continuation status; Adherence and non-adherence status was discriminated at the cutoff value of PDC=0.8; Continuation and discontinuation status was determined based on the absence and presence of >60 days prescription gap between two consecutive prescription records.

This study had a few strengths. First, this study used electronic medical records stored in a tertiary university hospital. Previous studies have utilized administrative claims data to analyze dulaglutide adherence and persistence and demonstrate higher adherence and persistence in dulaglutide users than other GLP-1RA users[31, 32, 78]. The longitudinal records contained in claims data are known for relatively low risk of selection bias and high external validity [38]. However, claims data lack information about procedures and prescriptions outside insurance coverage. Moreover, claims data do not contain patient-level laboratory test results, which could contain as much if not more clinically meaningful information as the records of medical activities. By using electronic medical records of a tertiary university hospital, this study was able to provide a higher granularity information on the factors for dulaglutide adherence and persistence, including CVD risks. Second, this study analyzed dulaglutide adherence and persistence by using four outcome variables. By doing so, this study was able to identify the clinical characteristics that affect dulaglutide adherence and persistence congruently or distinctly. Assessing dulaglutide adherence and persistence using four outcome variables enabled the observation of the pattern in medication taking behavior in dulaglutide users. Third, the follow-up period of this study was one year, which was relatively longer than

the previous studies. Previous studies measured dulaglutide adherence and persistence over a six-month period[28, 30, 31]. Although the study subjects' adherence and persistence rates were comparable to the studies, the longer follow-up period may have provided a more accurate assessment of dulaglutide adherence and persistence.

This study had a few limitations. First, the results of this study could not be corroborated by causal explanations. Of note, there were unmeasured confounders that could have affected the medication behavior in dulaglutide users. It is well-established that there are multiple dimensions of factors for treatment adherence and persistence: health care-related factors (e.g., access to health care), condition-related factors (e.g., the alleviation of symptom), therapy-related factors (e.g., ease of taking medication), but also social factors (e.g., social support, economic factors), patient-related factors (e.g., demographics, health beliefs), and social factors (e.g., social support, economic factors)[73]. Specifically, the data source of this study did not contain data on social factors and health care-related factors. Moreover, condition-related factors, patient-related factors, or therapy-related factors that are not routinely captured by EMR may not have been included in the analysis. Despite the unmeasured potential confounders, the results of this study were consistent with those of the previous studies. A further investigation using more comprehensive data from multiple data sources may be warranted to provide a more holistic description of characteristics associated with dulaglutide adherence and persistence. Second, this was a single center study with a small sample size. This study used EMR from a tertiary university hospital, in which patients with greater disease severity are more likely to be treated, leading to a potential risk of selection bias. However, the results of this study on dulaglutide adherence and persistence were similar to those of the previous studies which used national claims data. Third, this study was conducted by assuming that the decision to adhere to and continue the treatment with dulaglutide is largely patient-oriented. In the analysis, it was not possible to ascertain the extent to which the decision to continue (or discontinue) dulaglutide was driven by physicians or patients. However, by employing four distinct outcome measures, the impact of such uncertainty may have been mitigated. On the one hand, persistence, as measured by treatment duration and continuation status, can be more

prone to the uncertainty in understanding the driver of clinical decisions. On the other hand, adherence as measured by PDC and adherence status describes the density or sparseness of prescription filling records while on treatment. In this sense, it may be reasonable that adherence rather than persistence may be more appropriate for evaluating the medication taking behavior in T2DM patients treated with dulaglutide.

Chapter 5. Conclusion

Clinical characteristics of dulaglutide users that could have affected their adherence and persistence were identified, which were generally comparable to the reports of the previous studies. Physicians treating T2DM patients with dulaglutide can refer to those clinical characteristics identified in this study to finetune their approaches to optimize the adherence and persistence to dulaglutide, and possibly to other anti-diabetic medications, not only before, but during the treatment.

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국문 초록

Dulaglutide는 Glucagon-like Peptide 1 수용체 작용체(GLP-1RA) 계열의 제2형 당뇨병(T2DM) 치료제다. 그러나 Dulaglutide는 주사제로 사용되기 때문에 치료 순응도와 지속도가 낮다. 본 연구는 대한민국에서 Dulaglutide로 치료받는 제2형 당뇨병 환자의 순응도 및 지속도에 영향을 미치는 임상적 특징을 분석했다. 본 연구는 후향적 코호트 연구로 서울대학교병원(SNUH)의 Observational Medical Outcomes Partnership Common Data Model(OMOP CDM, 버전 5.3.1)로 변환된 전자 의무 기록을 사용했다. 2018년 1월 1일부터 2019년 12월 31일 사이에 Dulaglutide(0.75mg 또는 1.5mg)로 치료를 시작한 제2형 당뇨병 환자의 치료 시작 후 1년간 기록된 정보를 분석에 사용했다. 순응도는 proportion of days covered(PDC)와 adherence status(PDC≥0.8 또는 PDC<0.8)를 사용해 평가했다. 지속도는 60일을 초과하는 처방 공백 없이 지속적으로 치료받은 기간과 치료 중단 여부로 평가했다. 다변량 선형 회귀 및 다변량 로지스틱 회귀 분석을 사용해 연속 및 범주형 결과변수에 영향을 주는 요인을 분석했다. 또한 2 가지 이상의 심혈관질환(Cardiovascular disease, CVD) 위험 인자를 가진 환자를 대상으로 하위집단 분석을 수행했다. 마지막으로 민감도분석을 통해 결과의 강건성(robustness)을 평가했다. 총 236명의 환자가 분석에 포함됐다. 다변량 로지스틱 회귀분석 결과 연령 및 사구체 여과율이 높을수록 순응도 및 치료 지속도가 유의하게 증가했다. 반면 비만이 있거나 설포닐유레아 및 인슐린을 사용하는 환자는 치료 지속 가능성이 낮았다. 다변량 선형 회귀분석 결과, 연령 및 용량 변경, 신경병증이 PDC와 치료 기간을 유의하게 증가시켰다. 심혈관질환 고위험군을 대상으로 실시한 하위집단 분석 결과 심혈관질환 위험도는 Dulaglutide 순응도와 지속도에 통계적으로 유의한 영향을 주지 않았다. 본 연구 결과가 Dulaglutide로 치료받는 제2형 당뇨병 환자의 순응도 및 지속도를 향상시키고 궁극적으로 치료효과를 높이는데 활용되길 기대한다.

주요어 : type 2 diabetes mellitus, medication adherence, medication persistence, dulaglutide

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