Medication Adherence in the First Year of Treatment and Cardiovascular Events in Young Adults With Diabetes

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Medication Adherence in the First Year of Treatment and Cardiovascular Events in Young Adults With Diabetes

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ABSTRACT

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Introduction: The prevalence of type 2 diabetes mellitus (T2DM) in young adults is increasing considerably worldwide. Developing diabetes at a younger age results in prolonged disease exposure, heightening the risk of chronic complications that significantly affect individuals of working age and exacerbate the societal and personal burdens burden. Although adherence to treatment regimens and persistence with medication are crucial to achieving optimal health outcomes in patients with diabetes patients, those who appear healthy, such as younger or recently diagnosed individuals, may have a higher risk of non-adherence to treatment regimens. This study explores the relationship between medication adherence and cardiovascular disease (CVD) in young adults with diabetes.

Methods: From the Korean National Health Insurance Service database, we identified 233,241 young patients with T2DM aged 20–44 years who had newly started medications. After applying inclusion and exclusion criteria, a total of 76,867 participants were included in the main analysis. The exposure of interest, medication adherence, was measured based on the proportion of days

covered (PDC) in the first year of treatment. The primary outcome was a composite CVD event including hospitalization for myocardial infarction, stroke, or heart failure, and cardiovascular death. We constructed Cox proportional hazard models adjusting for demographic, socioeconomic, clinical and lifestyle-related variables.

Results: The mean age of the participants was 39.2 ± 4.3 years and 76.9% were male. Of them, 44.1% of participants adhered to their medication regimen, i..e, PDC ≥ 80%, in the first year from medication initiation. During a median (inter quartile range) follow-up of 8.1 [6.1–10.7] years, 4,302 new CVD events were recorded. Non-adherence to antihyperglycemic medication was associated with a higher risk of CVD events, with an adjusted hazard ratio (95% confidence interval) for composite CVD events of 1.45 (1.36–1.54) for the non-adherent group compared with the adherent group. Suboptimal medication adherence was associated with a higher risk of CVD with a dose-response relationship.

Conclusion: Suboptimal medication adherence is associated with a higher risk of CVD events, which could affect individuals of working age. Comprehensive management may help minimize individual and societal burdens.

Key words: **type 2 diabetes mellitus (T2DM), medication adherence, cardiovascular events, young adults**

1. INTRODUCTION

1.1 Background

1.1.1 Disease burden of diabetes

The incidence of type 2 diabetes mellitus (T2DM) is increasing worldwide[1–3], including in Korea[4,5]. In 2021, the International Diabetes Federation reported that 537 million adults had been diagnosed with diabetes globally, with a projected increase to 643 million by 2030 and a significant increase among younger people[2]. The World Health Organization (WHO) also reports a four-fold rise in global diabetes cases over recent decades, underscoring the urgent need for preventative and therapeutic measures[6]. The WHO emphasizes the importance of policies that promote healthy living and establish strong healthcare systems capable of providing prevention, early detection, and treatment to effectively manage this epidemic.

The Korean Diabetes Association estimated that over 5.3 million individuals had diabetes, and 14 million people aged over 30 years were prediabetic in Korea[4] in 2021–2022. The prevalence of diabetes among males aged over 30 years increased from 12.4% in 2012 to 16.9% in 2022. In contrast, the prevalence among females over the same period rose from 11.1% to 12.6%, displaying a fluctuating trend.

In addition to these concerning trends, there has been a corresponding rise in diabetes-related complications, such as cardiovascular diseases (CVDs) and microvascular conditions. These complications worsen patient outcomes, increase healthcare costs[1], and reduce quality of life[8]. Hence, the costs of diabetes include direct medical care costs and indirect costs associated with the loss of productivity or income[1,8–10], highlighting the importance of comprehensive healthcare strategies.

1.1.2 Diabetes in young adults

The global increase in T2DM among young adults is alarming, particularly given the serious risk factors, such as obesity, family history, and a lack of physical activity[11]. In Korea, the prevalence of diabetes and prediabetes among individuals aged 19–39 years were 2.2% and 21.8% in 2019–2022, estimated to affect 0.3 and 3 million individuals, respectively[4]. When it comes to the long-term trend, another evidence suggested that the incidence rate for T2DM diagnoses increased slightly among individuals aged 20–39 years, from 0.5 to 0.7 for diabetes and 2.0 to 2.6 for pre-diabetes from 2006 to 2015 per 1,000 individuals in Korea[12,13].

Developing diabetes at a younger age leads to prolonged disease exposure, increasing the risk of chronic complications, impacting those of working age, and intensifying the societal burden. Early-onset diabetes, sometimes referred to as young-onset diabetes, generally defined as diabetes diagnosed between the ages of 20 and 39[14], often manifests as a more aggressive form of the disease[15]. Compared to type 1 diabetes mellitus[16] or late-onset T2DM[17], early-onset diabetes is associated with a markedly higher incidence of diabetic complications and a more rapid progression of these complications[15].

1.1.3 Challenges regarding medication adherence in young adults with diabetes and remaining knowledge gaps

CVD in diabetes is multifactorial; regulating the associated risk factors substantially reduces cardiovascular events[18,19]. Higher glycemia increases the risk of CVD in T2DM[20,21]; thus, effective management of blood glucose levels is crucial for preventing CVD in individuals with T2DM[18]. Healthy lifestyle behaviors, diabetes self-management education and support, avoidance of

therapeutic inertia, and social determinants of health should be considered in the glucose-lowering management of T2DM[19]. Indeed, treatment efficacy is often dependent on patients' lifestyles, risk factors, and treatment goals. Hence, personalized treatment plans tailored to the unique needs and circumstances of each individual are critical[18,19].

Adherence to treatment regimens and persistence with medication—taking drugs according to the prescribed schedule, dosage, and designated period—are crucial for achieving optimal health outcomes in patients with diabetes[22]. This challenge is particularly pronounced due to the complex nature of managing diabetes, requiring significant lifestyle modification and diligent medication treatment[23]. It has been generally acknowledged that non-adherence rates for chronic disease regimens and lifestyle modifications reach 50%[24]. Many factors potentially influence these challenges, including demographic-, psychological-, social-, medical system-, disease-, and treatment-related factors[22].

Patients who appear healthy—such as younger individuals, those recently diagnosed with diabetes, or those on minimal medication—may have a higher risk of non-adherence to treatment protocols[25]. This is often attributed to a perception of lower immediate health risks, which can reduce the urgency and perceived necessity of strict adherence to treatment regimens. In particular, younger patients with T2DM but without complications often underestimate the severity of their condition, leading to a greater likelihood of engaging in unhealthy behaviors[25].

Supporting evidence from the Australian National Diabetes Audit—a large-scale, national cross-sectional study—indicates that younger patients with T2DM (average age: 53) are twice as likely to neglect self-care recommendations than their older counterparts (average age: 73)[26]. These recommendations include adhering to dietary advice, taking prescribed medications consistently, and regularly monitoring blood glucose levels. Another study from the United States utilizing a large pharmacy claims database suggested that patients 25–44 years of age were 49% less likely to adhere

to medication regimens than those aged 45–64 years[25]. Furthermore, a study utilizing healthcare claim data from Japan—a universal health insurance system similar to Korea—reported that lower age is associated with non-persistence and non-adherence to antidiabetic regimens in patients with diabetes who newly started medication[27]. Specifically, patients aged 35–44, 45–54, and 55–64 years showed significantly higher odds of medication adherence compared to those aged 18–34 years, with odds ratios of 1.23 (95% confidence interval [CI]: 0.97–1.57), 1.54 (1.22–1.94), and 2.05 (1.61–2.61), respectively.

However, most research on medication adherence has primarily incorporated middle-aged and older adults, leaving a notable gap in our understanding of how younger adults manage their diabetes treatments and the potential consequences related to their risk for major vascular complications.

1.2 Study aim

The present study investigates the relationship between medication adherence and CVD in young adults with diabetes utilizing national health claim data from Korea.

2. METHODS

2.1 Study population

We used claim data from the Korean National Health Insurance Service (NHIS), which generally reflects the entire Korean population. This database incorporates mortality and sociodemographic information, reimbursement claims coded based on the International Classification of Disease (ICD-10), prescription data, and general health check-up information. The list of ICD-10 codes used for eligibility check, outcome ascertainments, and covariate is provided in Appendix 1. We identified 1,407,305 individuals who were diagnosed with T2DM (ICD-10: E11) at the age of 20–44 years, between January 1, 2002 and December 31, 2015 (Figure 1). We defined young adults as individuals aged 20–44 years. This age range encompasses a life stage characterized by significant social transitions, potentially influencing diabetes management behaviors including medication adherence.

The eligibility regarding medication initiation was assessed based on the prescription of oral antihyperglycemic agents. The list of antihyperglycemic agents included in this study is provided in Appendix 2–4. Among the individuals prescribed these drugs between January 1, 2003 and December 31, 2022, the following eligibility criteria were applied:

(1) Not prescribed medication before January 1, 2003
(2) First antihyperglycemic agent prescription was obtained on and after the day of first T2DM diagnosis
(3) Aged 20–44 years at the time of the first prescription
(4) Received at least three prescriptions between 2003 and 2022

Among the 233,241 individuals deemed eligible as young T2DM patients with newly initiated medications, the following exclusion criteria were applied:

(1) History of myocardial infarction (MI; ICD-10: I21–23), stroke (I60–64), or heart failure (HF; I50).
(2) CVD incident and death from non-cardiovascular causes within 365 days after the index date. CVD incidents were identified as cardiovascular death or hospitalization due to MI, stroke, or HF. Cardiovascular death was defined as hospitalization within 30 days of death due to CVD (I00–99). The index date refers to the date of the first prescription of antihyperglycemic agents.
(3) Not having at least 90 days of total medication supply during the first 365 days from the index date.
(4) First prescription on or after January 1, 2022.
(5) Missing information on socioeconomic status.
(6) Missing record of general health check-ups within past two years from the index date or incomplete data for clinical or lifestyle-related variables listed as covariates.
(7) Diagnosed with T1DM (E10) and/or gestational diabetes mellitus (GDM; O24.4) and taking insulin therapy within six months before the index date.

To eliminate the possibility of reverse causality, we excluded individuals who had CVD incidents or all-cause death within 365 days after the index date, as these incidents or preceding symptoms may have influenced their medication adherence, either by improving it or hindering their ability to follow the prescribed treatments.

Ultimately, 74,867 individuals were included in the main analysis. Follow-up began on the 366th day post-index date and continued to death or end of follow-up (Figure 2). Since 90% of participants had a follow-up period of less than 5,113 days (14 years), the maximum follow-up duration was set to 5,113 days. Accordingly, the end of follow-up was set to 5,113 days after the day-366 post index date or December 31, 2022, whichever came first.

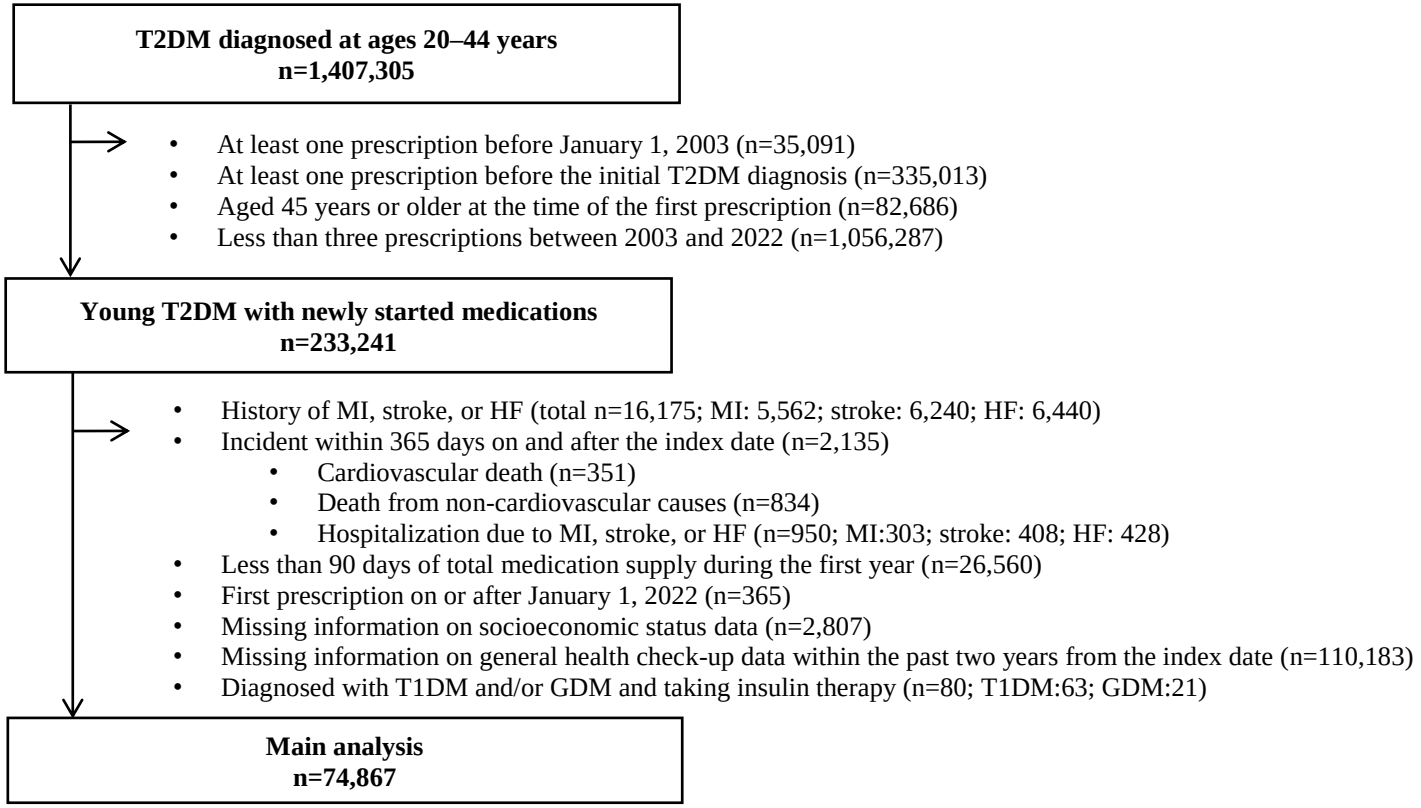

Figure 1. Participant flow chart.
T2DM: type 2 diabetes mellitus, MI: myocardial infarction, HF: heart failure, T1DM: type 1 diabetes mellitus, GDM: Gestational diabetes mellitus.

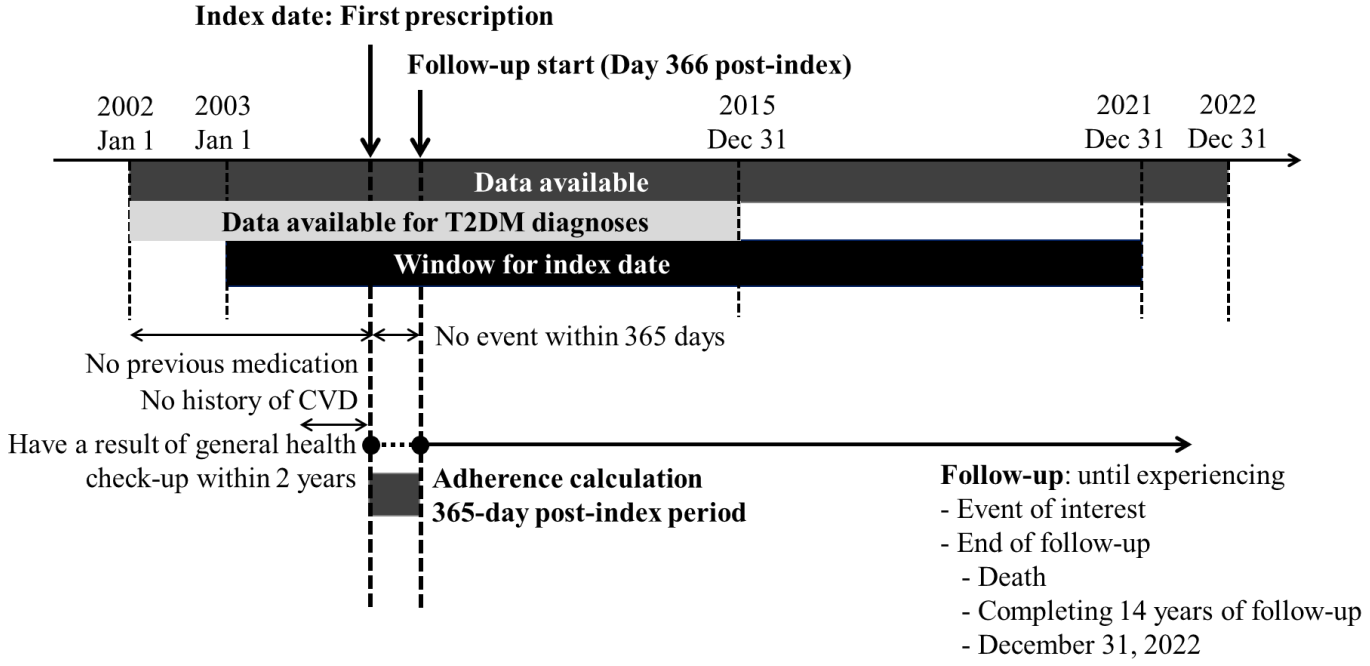

Figure 2. Schedule overview

2.2 Variables

2.2.1 Medication adherence

The exposure of interest, adherence to oral antihyperglycemic medication, was measured using the proportion of days covered (PDC) in the first year from treatment initiation. To calculate PDC, the total number of days that antihyperglycemic medications were provided—accounting for prescription refills and excluding any overlapping days of supply—was divided by the total number of days in the observation period, i.e., 365 days. If a participant used multiple medications or switched drug classes, all days covered by any medication were included in the numerator. A sample prescription pattern for identifying the proportion of days covered is presented in Figure 3.

The analysis period for calculating the PDC was 365 days for the post-index date. Based on a PDC threshold of 80%, sourced from an existing studies[28,29], participants were classified into adherent (PDC≥80%) and non-adherent (PDC<80%) categories. Additionally, we confirmed the results with two additional methods of adherence categorization: (1) dividing PDC into three categories, good (PDC: 80–100%), moderate (50–79%), and poor adherence (0–49%); and (2) quartiles.

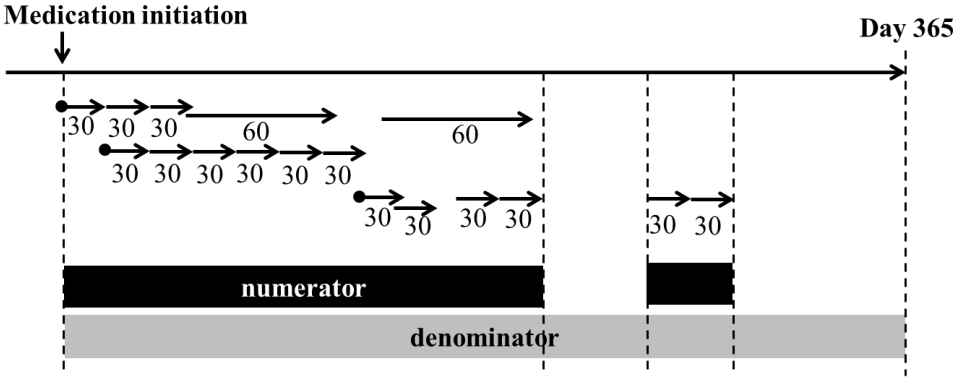

Figure 3. Sample prescription pattern for identifying the proportion of days covered

2.2.2 Outcome measurements

The primary outcome was a composite CVD event, defined as the first hospitalization for MI, stroke, or HF, or cardiovascular death. If a participant experienced one or more events during the follow-up, only the first event was considered the event of interest. In the end point-specific analyses, each type of event, specifically MI, stroke, HF, or cardiovascular death, was evaluated separately. For participants who had multiple events, the first occurrence of each type was recorded as an outcome. Additionally, the all-cause death was assessed to confirm the overall risk of premature death.

2.2.3 Covariates

Information on sex, age at index, duration from the first diagnosis to index, and socioeconomic status (as indicated by monthly health insurance premiums) was retrieved from the NHIS database. Socioeconomic status was classified into quartiles. Information on initial treatment regimens was identified utilizing the prescription data of the index date. Clinical information including Charlson comorbidity index, concurrent medication for hypertension (Appendix 3, 5, 7) or dyslipidemia (Appendix 4, 6, 7), prescription of insulin or Glucagon-like peptide-1 (GLP-1) receptor agonist (Appendix 8) were confirmed based on claims within six months before the index date. Further clinical and lifestyle-related variables were sourced from the database of general health check-ups on or nearest to the index date within past two years. The information on body mass index (BMI; kg/m^2), fasting glucose, systolic blood pressure, and total cholesterol were retrieved from the result of general health check-ups. The lifestyle-related information included self-reported smoking status (never, past, or current), frequency of alcohol consumption (none, 1–2 times per week, or ≥3 times per week), physical activity levels (none, 1–2 times per week, or ≥3 times per week).

2.3 Statistical analysis

Baseline characteristics were described as mean and standard deviation (SD), median and interquartile range [IQR], or frequency and percentage. The incidence rate of CVD events was calculated as the number of events per 10,000 person-years of follow-up. The cumulative incidence of CVD events was assessed using the Kaplan–Meier method. The hazard ratios (HRs) and 95% CIs of CVD events associated with medication adherence were computed utilizing Cox proportional hazard models. The proportional hazard assumption was confirmed using log-minus-log plots and was not violated. We constructed four models to adjust the covariates: Model 1 was the unadjusted model; Model 2 adjusted for sex, age at index, duration from diagnosis to index, index year, and socioeconomic status; Model 3 adjusted further for clinical measures; and Model 4 adjusted further for lifestyle-related variables. Covariates were selected based on previous studies and their potential associations with medication adherence and CVD. In addition, we calculated absolute number of preventable events by calculating population attributable risk percentage (PAR%).

$$\mathrm{PAR\%} = \frac{\mathrm{p(adjusted\ HR\ -\ 1)}}{1\ +\ \mathrm{p(adjusted\ HR\ -\ 1)}}$$

$$\mathrm{Number\ of\ preventable\ events} = \mathrm{I} \times \mathrm{N} \times \frac{\mathrm{PAR\%}}{100}$$

I: incidence rate, N: total population size.

Additionally, we conducted sex-stratified analyses given the potential associations of sex with medication adherence or CVD. The p-value for interaction between sex and adherence with CVD was assessed using the interaction term with Model 4 adjusting for all covariates. Furthermore, we performed a stratified analysis by index period (i.e., the year of the index date). Participants were divided into two groups: those who initiated medication between 2003 and 2013, and those who

initiated it between 2014 and 2021.The interaction between index period and adherence with CVD was also confirmed.

A two-sided $p<0.05$ was considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria).

2.4 Analyses incorporating individuals aged 20–39 years

Early-onset diabetes may exhibit distinct pathophysiological characteristics compared to late-onset diabetes and require unique clinical considerations[13]. Therefore, we conducted a separate analysis focusing on individuals aged 20–39 years. By restricting to this narrow age range, we sought to further explore the relationship between medication adherence and cardiovascular events among young adults.

Similar to the analysis of individuals aged 20–44 years, inclusion and exclusion criteria were applied to individuals with T2DM who began new medication regimens (Figure 4). All methods used in the former analyses were similarly applied to this restricted group. Furthermore, the results of younger (i.e., 20–39 years) and older (i.e., 40–44 years) subgroups were compared, and the interaction between age group and adherence with CVD was assessed.

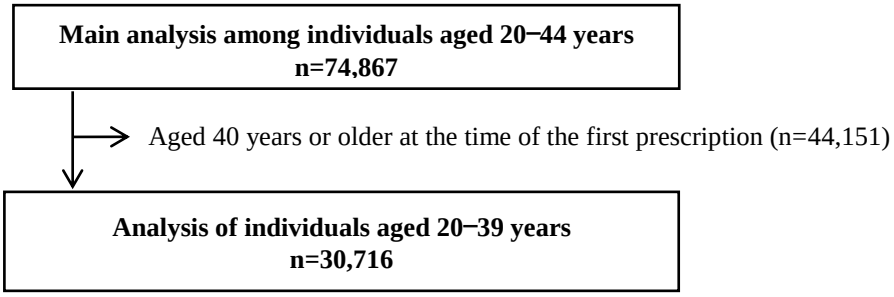

Figure 4. Participant flow chart for the analysis of individuals aged 20-39 years.

2.5 Factors associated with good adherence

To investigate the factors associated with good adherence during the first year from medication initiation, we performed univariate and multivariable analyses using logistic regression models. The dependent variable in this model was medication adherence, defined as a dichotomous variable with a cut-off of PDC 80%, categorized as below 80% and 80% or above. The method for calculating PDC was applied in the same manner as in previous analyses. The independent variables, representing potential factors associated with adherence, were listed as covariates in the previous model that evaluated the association between adherence and CVD events. The continuous variables, including age at index and duration from diagnosis to index, were categorized into five-year age groups and quartiles, respectively. Due to the very small number of participants in the 20–24 and 25–29 age groups, these groups were combined into a single 20–29 age group. The following factors were categorized as dichotomous: index year (2003–2013 or 2014–2021); Charlson Comorbidity Index (0 or $\geq$1, indicating the presence or absence of comorbidities); alcohol consumption (drinker or non-drinker); and physical activity (inactive, defined as regular activity less than 2 times/week, or active). Since a small number of participants had been taking insulin or GLP-1 RA therapies, these two factors were not included in this analysis. In addition, combination therapy is a possible factor affecting adherence positively and negatively, we further categorized the initial treatment regimen into monotherapy, the combination therapy of two, or three or more in this analysis.

2.6 Ethical consideration

The study protocol was approved by the Institutional Review Board of Severance Hospital at the Yonsei University College of Medicine (Approval No. 4-2023-1357). Informed consent was waived, as this is a retrospective study using de-identified administrative data.

3. RESULTS

3.1 Analyses of individuals aged 20–44 years

3.1.1 General characteristics

The mean age of the participants was 39.2 ± 4.3 years, and 76.9% were male (Table 1). Mean age at diagnosis was 36.8 ± 4.9 years, and median [IQR] duration from diagnosis to index was 409 [37–1,313] days. The median [IQR] BMI was 26.7 [24.2–29.6], and 68.1% of the participants had obesity (BMI ≥25). Moreover, 1,631 (1,196 males and 435 females) were also diagnosed with T1DM, and 216 females had been diagnosed with GDM. Most participants did not have severe comorbidities, as evidenced by Charlson comorbidity index scores=0.

Overall, the median [IQR] PDC was 75.1% [49.3–91.0%], and 44.1% of participants adhered to the medication in the first year from medication initiation. Participants who adhered to the medication were likely to be female, to be of higher socioeconomic status, to take medication for hypertension or dyslipidemia, not to be a current smoker, and to engage in regular physical activity.

Of all participants, 34.0% of participants started their medication with monotherapy, whereas 66.0% started with a combinatorial regimen of two or more drugs (Table 2). Most participants started their regimen with Biguanides; 86.2% of participants had prescribed Biguanides as the first regimen.

Table 1. Baseline characteristics

Characteristics	Total		Adherent		Non-adherent	
Total	**74,867**		**33,049**	**(44.1)**	**41,818**	**(55.9)**
Proportion of days covered, %	75.1	[49.3–91.0]	92.1	[86.8–96.2]	52.9	[34.8–67.7]
Sex						
Male	57,561	(76.9)	24,719	(74.8)	32,842	(78.5)
Female	17,306	(23.1)	8,330	(25.2)	8,976	(21.5)
Age at index, years	39.2	± 4.3	39.9	± 3.84	38.7	± 4.5
Age at diagnosis, years	36.8	± 4.9	37.2	± 4.7	36.4	± 5.0
Duration from diagnosis to index, days	409	[37–1,313]	485	[62–1,428]	354	[28–1,212]
Socioeconomic status, quartile						
Q4, highest	18,720	(25.0)	9,155	(27.7)	9,565	(22.9)
Q3	18,715	(25.0)	8,550	(25.9)	10,165	(24.3)
Q2	18,720	(25.0)	7,718	(23.4)	11,002	(26.3)
Q1, lowest	18,712	(25.0)	7,626	(23.1)	11,086	(26.5)
Diagnosed with T1DM	1,631	(2.2)	660	(2.0)	971	(2.3)
Diagnosed with gestational diabetes	216	(0.3)	88	(0.3)	128	(0.3)
Taking insulin therapy	296	(0.4)	141	(0.4)	155	(0.4)
Taking GLP-1 receptor agonist therapy	22	(0.03)	11	(0.03)	11	(0.03)
Charlson comorbidity index≥1	18,991	(25.4)	8,428	(25.5)	10,513	(25.1)
Taking medication for hypertension	20,529	(27.4)	11,310	(34.2)	9,219	(22.0)
Taking medication for dyslipidemia	27,529	(36.8)	13,356	(40.4)	14,173	(33.9)
Body mass index	26.7	[24.2–29.6]	26.8	[24.3–29.7]	26.6	[24.1–29.4]
Obesity (body mass index≥25)	51,008	(68.1)	22,867	(69.2)	28,141	(67.3)

Table 1. Baseline characteristics (Continued)

Characteristics	Total		Adherent		Non-adherent	
Total	**74,867**		**33,049**	**(44.1)**	**41,818**	**(55.9)**
Fasting blood glucose, mg/dL	147	[120–203]	145	[120–195]	149	[120–209]
Systolic blood pressure, mmHg	128	[119–136]	129	[120–137]	127	[119–135]
Total cholesterol, mg/dL	207	[180–239]	204	[176–234]	210	[183–239]
Smoking						
Never	28,788	(38.5)	13,269	(40.1)	15,519	(37.1)
Past	12,674	(16.9)	6,269	(19.0)	6,405	(15.3)
Current	33,405	(44.6)	13,511	(40.9)	19,894	(47.6)
Alcohol consumption						
None	26,855	(35.9)	12,352	(37.4)	14,503	(34.7)
1–2 times/week	35,242	(47.1)	15,344	(46.4)	19,898	(47.6)
3 times or more/week	12,770	(17.1)	5,353	(16.2)	7,417	(17.7)
Physical activity						
None	22,033	(29.4)	9,142	(27.7)	12,891	(30.8)
1–2 times/week	22,160	(29.6)	9,736	(29.5)	12,424	(29.7)
3 times or more/week	30,674	(41.0)	14,171	(42.9)	16,503	(39.5)

Numbers represent mean ± standard deviation, median [interquartile range], or frequency (%).

GLP: Glucagon-like peptide-1, T1DM: type 1 diabetes mellitus,

Table 2. Initial treatment regimens

Initial treatment regimen	Number	(%)
Total number of participants	74,867	
Drug class		
Alpha-glucosidase inhibitors	3,176	(4.2)
DPP-4 inhibitors	28,538	(38.1)
Meglitinides	893	(1.2)
Biguanides	64,567	(86.2)
Thiazolidinediones	4,639	(6.2)
SGLT-2 inhibitors	2,826	(3.8)
Sulfonylureas	29,052	(38.8)
Therapy type		
Monotherapy	25,437	(34.0)
Combination of two or more drugs	49,430	(66.0)

DPP-4: Dipeptidyl Peptidase-4; SGLT-2: Sodium-Glucose Cotransporter-2.

3.1.2 Medication adherence and composite cardiovascular events

From 2003 through 2021, a significant improvement in medication adherence was observed (Table 3). Among participants who began their initial regimen in 2003, only 20.7% adhered to their medication during the first year. In contrast, 53.1% of participants who started their medication in 2021 adhered. This upward trend in medication adherence remained steep until approximately 2010, after which it shifted to a more gradual increase.

During a median [IQR] follow-up of 8.1 [6.1–10.7] years (adherent group: 7.9 [6.0–10.3] years, non-adherent group: 8.3 [6.2–11.0] years), 4,302 new CVD events were recorded. Incidence rates per 10,000 person-years were 26.6 in the adherent group and 35.8 in the non-adherent group. The cumulative incidence of composite CVD events was higher in the non-adherent group (Figure 5). After adjusting the set of covariates, non-adherence to antihyperglycemic medication was associated with a higher risk of CVD events. With Model 4 adjusting all potential covariates, the adjusted HR (95% CI) for composite CVD events was 1.45 (1.36–1.54) among the non-adherent group comparing to adherent group (Table 4).

The reduced CVD risk according to higher adherence was robust across different categorizations; suboptimal medication adherence was associated with a higher risk of CVD; a dose-response relationship was observed (Figure 6 and Table 5). Participants in the lowest PDC quartiles had a 69% higher risk of CVD than those in the highest quartile group after adjusting for all covariates.

Utilizing these results, the PAR% was calculated as 20.1%. Given the incidence rate of 68.9 per 10,000 person-years, the number of preventable events was estimated to be approximately 104 for this study population. According to the most recent data published in 2024 by the Korean Diabetes Association, approximately 300 thousand individuals aged 19–39 years and 659 thousand

individuals aged 40–49 years were estimated to have diabetes in Korea. Thus, on the higher side, approximately 630 thousand young adults aged 20–44 years (i.e., the sum of 300 thousand and 330 thousand, half of 660 thousand) in Korea may have diabetes. We further assumed that 352 thousand individuals (55.9%) would be non-adherent to medication during the first year of treatment. Applying the estimated PAR% and incidence rate observed in this study, 4,874 CVD events among individuals with diabetes aged 20–44 years could be preventable if all were adherent to their medication during the first year of treatment.

Table 3. Index year and medication adherence

		Adherent		Non-adherent	
Year	**Participants**	**Number**	**(%)**	**Number**	**(%)**
Total	**74,867**	**33,049**	**(44.1)**	**41,818**	**(55.9)**
2003	540	112	(20.7)	428	(79.3)
2004	1,270	285	(22.4)	985	(77.6)
2005	1,885	429	(22.8)	1,456	(77.2)
2006	2,335	656	(28.1)	1,679	(71.9)
2007	2,624	1,004	(38.3)	1,620	(61.7)
2008	2,382	946	(39.7)	1,436	(60.3)
2009	2,365	1,030	(43.6)	1,335	(56.4)
2010	4,825	2,123	(44.0)	2,702	(56.0)
2011	6,892	3,118	(45.2)	3,774	(54.8)
2012	7,527	3,430	(45.6)	4,097	(54.4)
2013	7,937	3,548	(44.7)	4,389	(55.3)
2014	6,867	4,003	(58.3)	2,864	(41.7)
2015	10,394	4,842	(46.6)	5,552	(53.4)
2016	6,074	2,965	(48.8)	3,109	(51.2)
2017	3,820	1,904	(49.8)	1,916	(50.2)
2018	2,529	1,336	(52.8)	1,193	(47.2)
2019	1,323	667	(50.4)	656	(49.6)
2020	677	332	(49.0)	345	(51.0)
2021	601	319	(53.1)	282	(46.9)

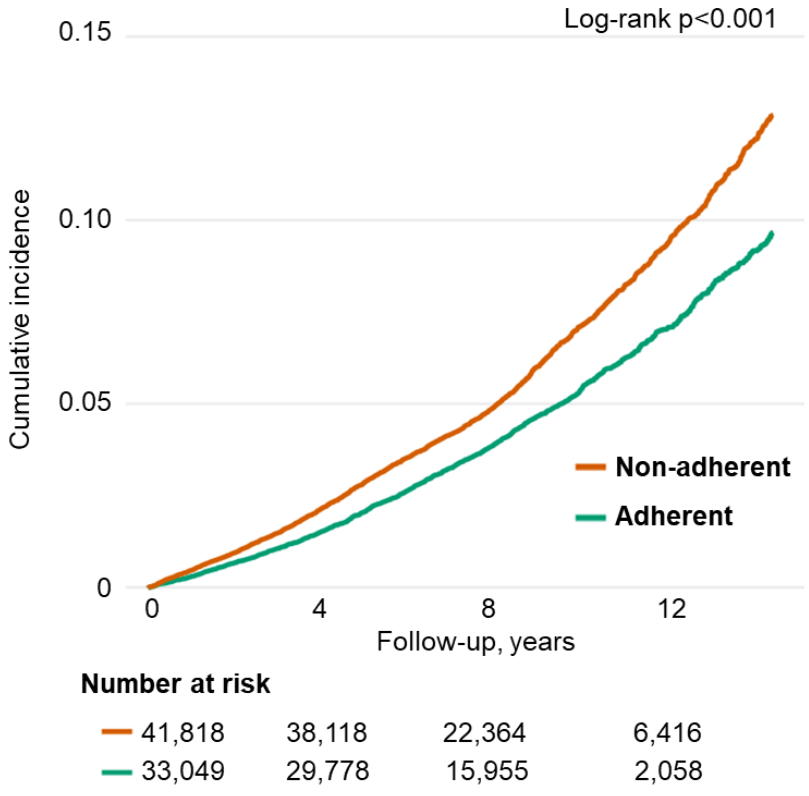

Figure 5. Cumulative incidence of composite cardiovascular events according to medication adherence

Table 4. Medication adherence and composite cardiovascular events

Adherence	Events	P-Y[a]	Rate[b]	Model 1		Model 2		Model 3		Model 4	
				HR	(95%CI)	HR	(95%CI)	HR	(95%CI)	HR	(95%CI)
Adherent	1,510	26.6	56.7	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)
Non-adherent	2,792	35.8	78.1	1.33	(1.25–1.42)	1.40	(1.32–1.50)	1.46	(1.37–1.56)	1.45	(1.36–1.54)

[a]Person-years (×10,000), [b]incidence rate per 10,000 person-years

Model 1: Unadjusted.

Model 2: Adjusted for sex, age at index, duration from diagnosis to index, index year, and socioeconomic status.

Model 3: Model 2 + initial treatment regimen, drug class, taking insulin therapy, taking GLP-1 RA therapy, Charlson comorbidity index, taking medication for hypertension, taking medication for dyslipidemia, body mass index, fasting blood glucose, systolic blood pressure, and total cholesterol.

Model 4: Model 3 + smoking status, alcohol consumption, and physical activities.

HR: hazard ratio, CI: confidence interval, GLP-1 RA: Glucagon-like peptide-1 receptor agonist.

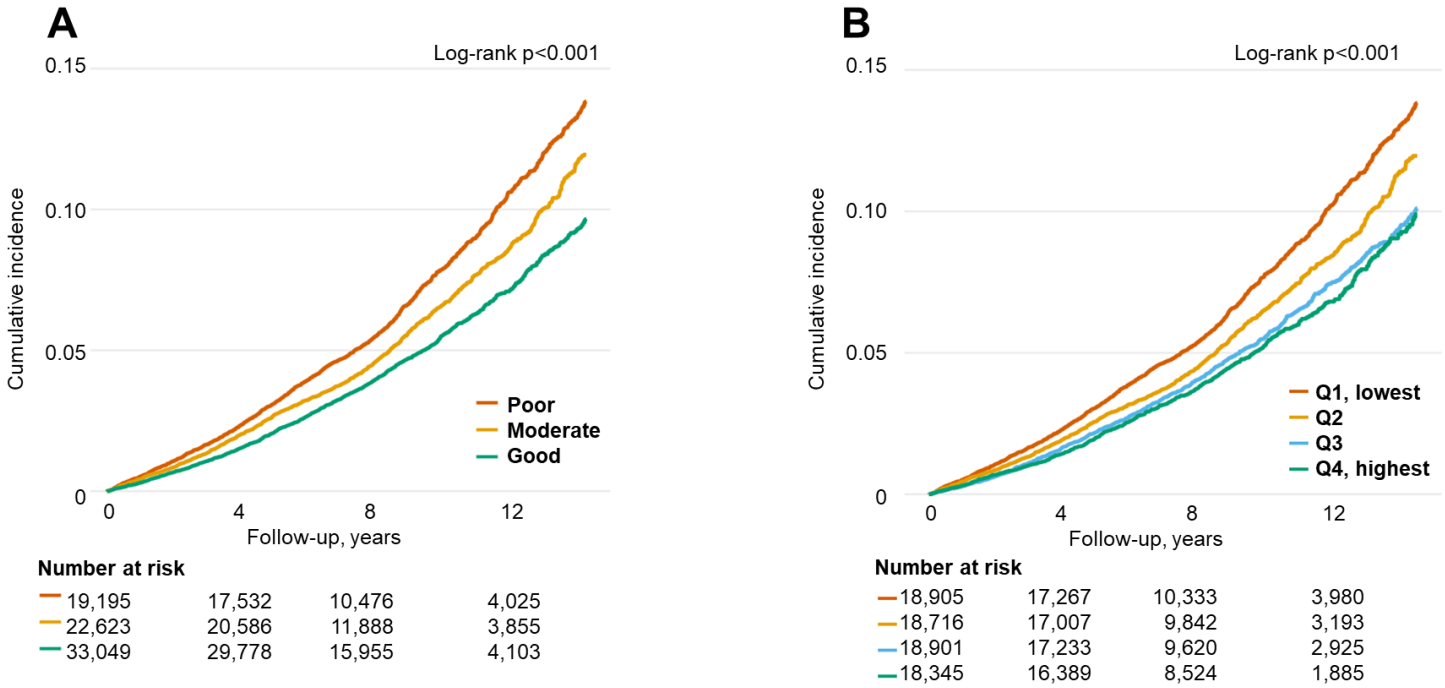

Figure 6. Cumulative incidence of composite cardiovascular events according to medication adherence.
(A) By adherence group, (B) by PDC quartile. PDC: proportion of days covered.

Table 5. Medication adherence and composite cardiovascular events across different categorizations

Adherence	Events	P-Y[a]	Rate[b]	Model 1		Model 2		Model 3		Model 4	
				HR	(95%CI)	HR	(95%CI)	HR	(95%CI)	HR	(95%CI)
By adherence group											
Good	1,510	26.6	56.7	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)
Moderate	1,351	19.1	70.8	1.22	(1.13–1.31)	1.27	(1.18–1.36)	1.30	(1.21–1.41)	1.29	(1.20–1.39)
Poor	1,441	16.7	86.4	1.46	(1.35–1.57)	1.57	(1.46–1.69)	1.67	(1.55–1.80)	1.64	(1.53–1.77)
By PDC quartiles											
Q4, highest	798	14.4	55.4	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)
Q3	957	15.8	60.7	1.06	(0.97–1.17)	1.09	(0.99–1.20)	1.12	(1.02–1.23)	1.11	(1.01–1.22)
Q2	1,124	15.8	71.2	1.23	(1.13–1.35)	1.31	(1.19–1.43)	1.36	(1.24–1.49)	1.34	(1.22–1.47)
Q1, lowest	1,423	16.5	86.2	1.49	(1.35–1.61)	1.60	(1.47–1.75)	1.73	(1.58–1.89)	1.69	(1.55–1.85)
Continuous PDC											
Per 10% decrease	4,302	62.4	68.9	1.06	(1.05–1.07)	1.08	(1.06–1.09)	1.09	(1.07–1.10)	1.08	(1.07–1.10)

[a]Person-years (×10,000), [b]incidence rate per 10,000 person-years

Model 1: Unadjusted.

Model 2: Adjusted for sex, age at index, duration from diagnosis to index, index year, and socioeconomic status.

Model 3: Model 2 + initial treatment regimen, drug class, taking insulin therapy, taking GLP-1 RA therapy, Charlson comorbidity index, taking medication for hypertension, taking medication for dyslipidemia, body mass index, fasting blood glucose, systolic blood pressure, and total cholesterol.

Model 4: Model 3 + smoking status, alcohol consumption, and physical activities.

HR: hazard ratio, CI: confidence interval, PDC: proportion of days covered, GLP-1 RA: Glucagon-like peptide-1 receptor agonist.

3.1.3 Endpoint-specific analyses including all-cause death

Based on the endpoint-specific analyses, there were 1,106 MIs, 1,173 strokes, 2,386 cases of HF, 646 cardiovascular-related deaths, and 2,034 all-cause deaths recorded (Table 6, 7, and Figure 7). Among all types of events, including all-cause deaths, individuals in the non-adherent group consistently demonstrated an elevated risk compared to the adherent group. Notably, the disparity in cumulative incidence between the adherent and non-adherent groups for all-cause death was particularly prominent from the early phase of follow-up (Figure 7). A 53% higher risk of all-cause death was observed in the non-adherent group and the median ages at death were 47 [45–50] years for cardiovascular-related and 47 [44–49] years for all causes, with the highest recorded age being 57 years.

Table 6. Medication adherence and each cardiovascular event

Adherence	Events	P-Y[a]	Rate[b]	Unadjusted		Adjusted[c]	
				HR	(95%CI)	HR	(95%CI)
Myocardial infarction							
Adherent	375	26.9	13.9	1.00	(Reference)	1.00	(Reference)
Non-adherent	731	36.4	20.1	1.26	(1.11–1.42)	1.32	(1.06–1.79)
Stroke							
Adherent	389	27.0	14.4	1.00	(Reference)	1.00	(Reference)
Non-adherent	784	36.3	21.6	1.31	(1.17–1.48)	1.46	(1.29–1.65)
Heart failure							
Adherent	874	26.9	32.5	1.00	(Reference)	1.00	(Reference)
Non-adherent	1,512	36.2	41.8	1.14	(1.05–1.24)	1.32	(1.21–1.44)
Cardiovascular death							
Adherent	182	27.1	6.7	1.00	(Reference)	1.00	(Reference)
Non-adherent	464	36.6	12.7	1.43	(1.23–1.66)	1.47	(1.26–1.71)

[a]Person-years (×10,000), [b]incidence rate per 10,000 person-years

[c]Adjusted for sex, age at index, duration from diagnosis to index, index year, socioeconomic status, initial treatment regimen, drug class, taking insulin therapy, taking GLP-1 RA therapy, Charlson comorbidity index, taking medication for hypertension, taking medication for dyslipidemia, body mass index, fasting blood glucose, systolic blood pressure, total cholesterol, smoking status, alcohol consumption, and physical activities.

HR: hazard ratio, CI: confidence interval, GLP-1 RA: Glucagon-like peptide-1 receptor agonist.

Table 7. Medication adherence and all-cause death

Adherence	Events	P-Y[a]	Rate[b]	Unadjusted		Adjusted[c]	
				HR	(95%CI)	HR	(95%CI)
All-cause death							
Adherent	631	27.1	23.3	1.00	(Reference)	1.00	(Reference)
Non-adherent	1,403	36.6	38.3	1.60	(1.46–1.76)	1.53	(1.39–1.69)

[a]Person-years (×10,000), [b]incidence rate per 10,000 person-years

[c]Adjusted for sex, age at index, duration from diagnosis to index, index year, socioeconomic status, initial treatment regimen, drug class, taking insulin therapy, taking GLP-1 RA therapy, Charlson comorbidity index, taking medication for hypertension, taking medication for dyslipidemia, body mass index, fasting blood glucose, systolic blood pressure, total cholesterol, smoking status, alcohol consumption, and physical activities.

HR: hazard ratio, CI: confidence interval, GLP-1 RA: Glucagon-like peptide-1 receptor agonist.

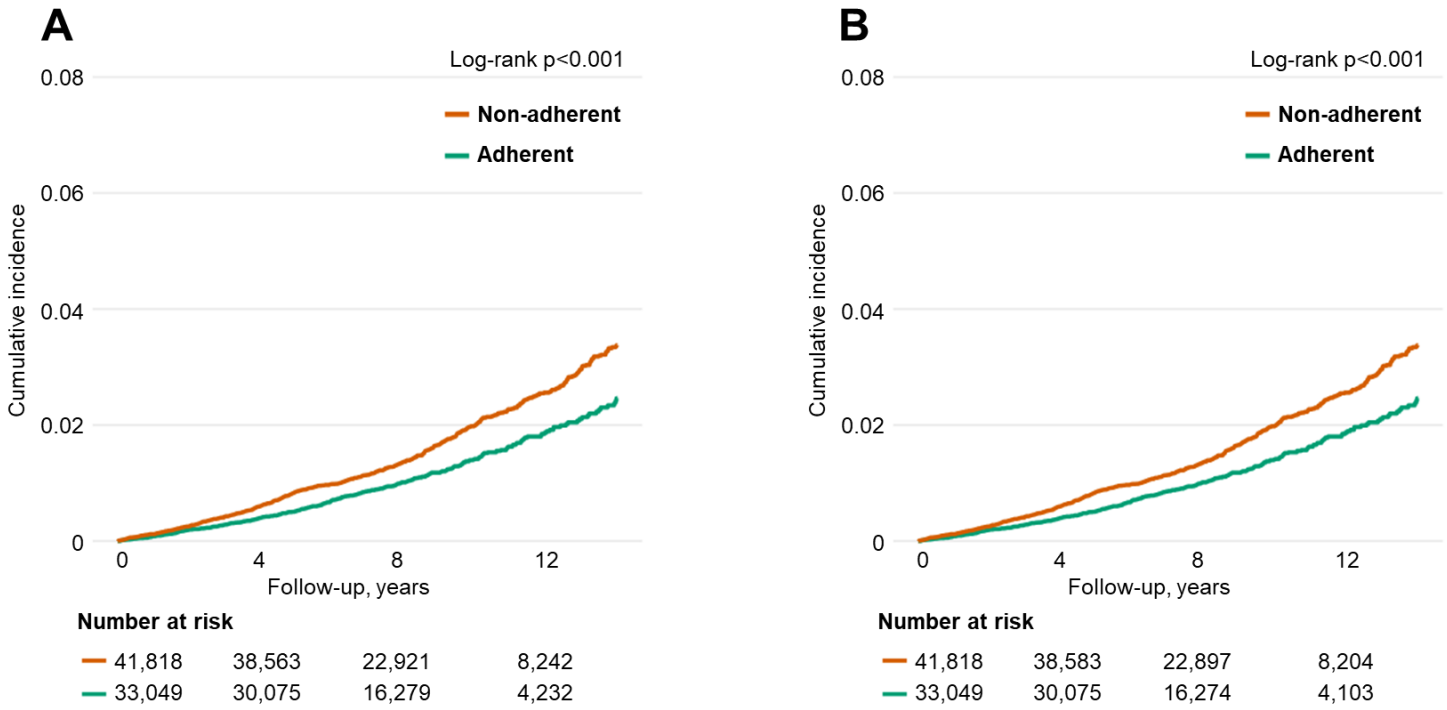

Figure 7. Cumulative incidence of each cardiovascular event by medication adherence.
(A) Myocardial infarction, (B) Stroke, (C) heart failure, (D) cardiovascular death, (E) all-cause death.

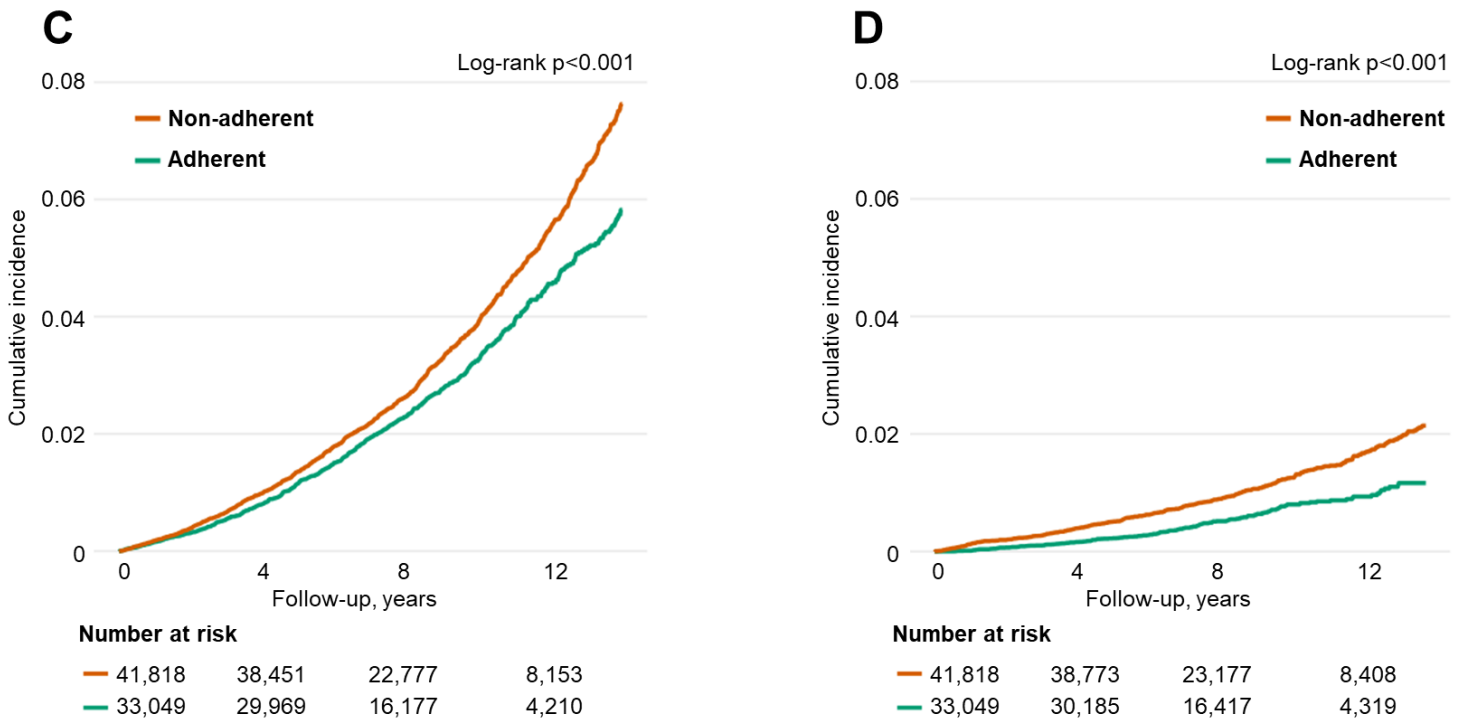

Figure 7. Cumulative incidence of each cardiovascular event by medication adherence (Continued).
(A) Myocardial infarction, (B) Stroke, (C) heart failure, (D) cardiovascular death, (E) all-cause death.

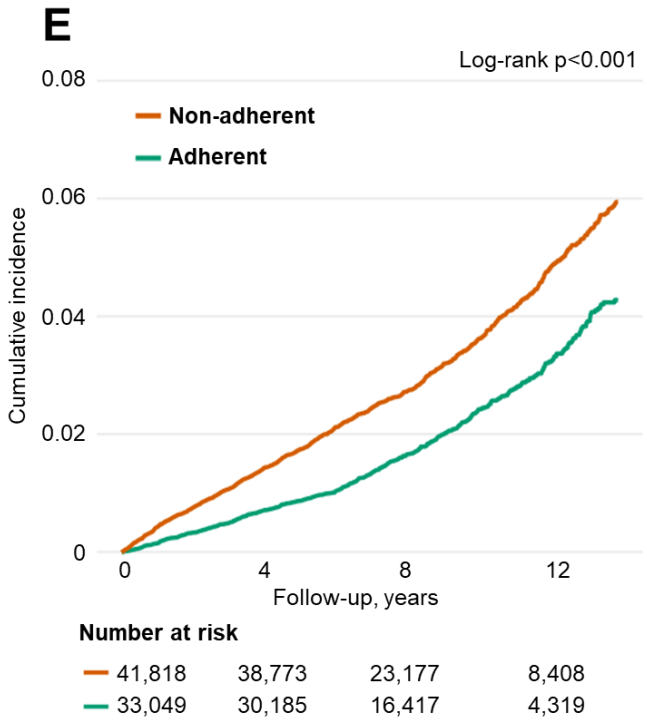

Figure 7. Cumulative incidence of each cardiovascular event by medication adherence (Continued).
(A)Myocardial infarction, (B) Stroke, (C) heart failure, (D) cardiovascular death, (E) all-cause death.

3.1.4 Sex-stratified analyses

Comparing the general characteristics between male and female participants revealed overall better adherence in females, with median [IQR] PDCs of 74.0% [49.3–90.4%] in males and 78.4% [52.1–92.6%] in females (Table 8). Female participants were more likely to have longer duration from diagnosis to index, belonged to lower socioeconomic groups, exhibited fewer comorbidities, were less likely to have obesity, and were more likely to be non-smokers and non-alcohol consumers than their male counterparts.

The median follow-ups were 8.2 [6.1–10.9] years for males and 7.8 [6.0–10.2] years for females. During follow-up, 3,379 and 923 composite CVD events were confirmed for males and females, respectively (Figure 8, Table 9). Higher risks for composite CVD events in the non-adherent group were consistent between sexes: unadjusted and adjusted HRs (95% CIs) were 1.32 (1.23–1.42) and 1.43 (1.33–1.54) in males, and 1.37 (1.20–1.56) and 1.48 (1.29–1.70) in females. Suboptimal medication adherence was associated with a higher risk of composite CVD events; a dose-response relationship was observed for both sexes after adjusting for a set of covariate (Table 10), although Kaplan-Meier curve was not distinct in female. Notably, male participants in the lowest PDC quartiles showed 71% increased risk of composite CVD compared to the participants in the highest PDC quartiles. The interaction between adherence and sex was not statistically significant; when applying the interaction term with Model 4 of the Cox proportional hazards model, p-values for interaction were p=0.28 with categorization based on adherent/non-adherent and p=0.19 with categorization by PDC quartiles.

Table 8. Baseline characteristics by sex

Characteristics	Total		Male		Female	
Total	**74,867**		**57,561**	**(76.9)**	**17,306**	**(23.1)**
Proportion days covered, %	75.1	[49.3–91.0]	74.0	[49.3–90.4]	78.4	[52.1–92.6]
Age at index, years	39.2	± 4.3	39.1	± 4.1	39.6	± 4.7
Age at diagnosis, years	36.8	± 4.9	36.8	± 4.7	36.6	± 5.5
Duration from diagnosis to index, days	409	[37–1,313]	386	[35–1,208]	509	[49–1,717]
Socioeconomic status, quartile						
Q4, highest	18,720	(25.0)	15,499	(26.9)	3,221	(18.6)
Q3	18,715	(25.0)	15,795	(27.4)	2,920	(16.9)
Q2	18,720	(25.0)	14,619	(25.4)	4,101	(23.7)
Q1, lowest	18,712	(25.0)	11,648	(20.2)	7,064	(40.8)
Diagnosed with T1DM	1,631	(2.2)	1,196	(2.1)	435	(2.5)
Diagnosed with GDM	216	(0.3)	0	(0)	216	(1.3)
Taking insulin therapy	296	(0.4)	202	(0.4)	94	(0.5)
Taking GLP-1 RA therapy	22	(0.03)	11	(0.02)	11	(0.06)
Charlson comorbidity index≥1	18,991	(25.4)	14,795	(25.7)	4,196	(24.3)
Taking medication for hypertension	20,529	(27.4)	16,700	(29.0)	3,829	(22.1)
Taking medication for dyslipidemia	27,529	(36.8)	21,674	(37.7)	5,855	(33.8)
Body mass index	26.7	[24.2–29.6]	26.8	[24.5–29.4]	26.4	[23.4–29.9]
Obesity (BMI≥25)	51,008	(68.1)	40,223	(69.9)	10,785	(62.3)
Fasting blood glucose, mg/dL	147	[120–203]	147	[120–203]	148	[120–202]
Systolic blood pressure, mmHg	128	[119–136]	130	[120–137]	121	[112–132]

Table 8. Baseline characteristics by sex (Continued)

Characteristics	Total		Male		Female	
Total	**74,867**		**57,561**	**(76.9)**	**17,306**	**(23.1)**
Total cholesterol, mg/dL	207	[180–239]	208	[181–238]	205	[178–234]
Smoking						
Never	28,788	(38.5)	13,454	(23.4)	15,334	(88.6)
Past	12,674	(16.9)	11,924	(20.7)	750	(4.3)
Current	33,405	(44.6)	32,183	(55.9)	1,222	(7.1)
Alcohol consumption						
None	26,855	(35.9)	15,607	(27.1)	11,248	(65.0)
1–2 times/week	35,242	(47.1)	30,176	(52.4)	5,066	(29.3)
3 times or more/week	12,770	(17.1)	11,778	(20.5)	992	(5.7)
Physical activity						
None	22,033	(29.4)	16,726	(29.1)	5,307	(30.7)
1–2 times/week	22,160	(29.6)	17,753	(30.8)	4,407	(25.5)
3 times or more/week	30,674	(41.0)	23,082	(40.1)	7,592	(43.9)

Numbers represent mean ± standard deviation, median [interquartile range], or frequency (%).

T1DM: type 1 diabetes mellitus, GDM: gestational diabetes mellitus, BMI: body mass index, GLP: Glucagon-like peptide-1.

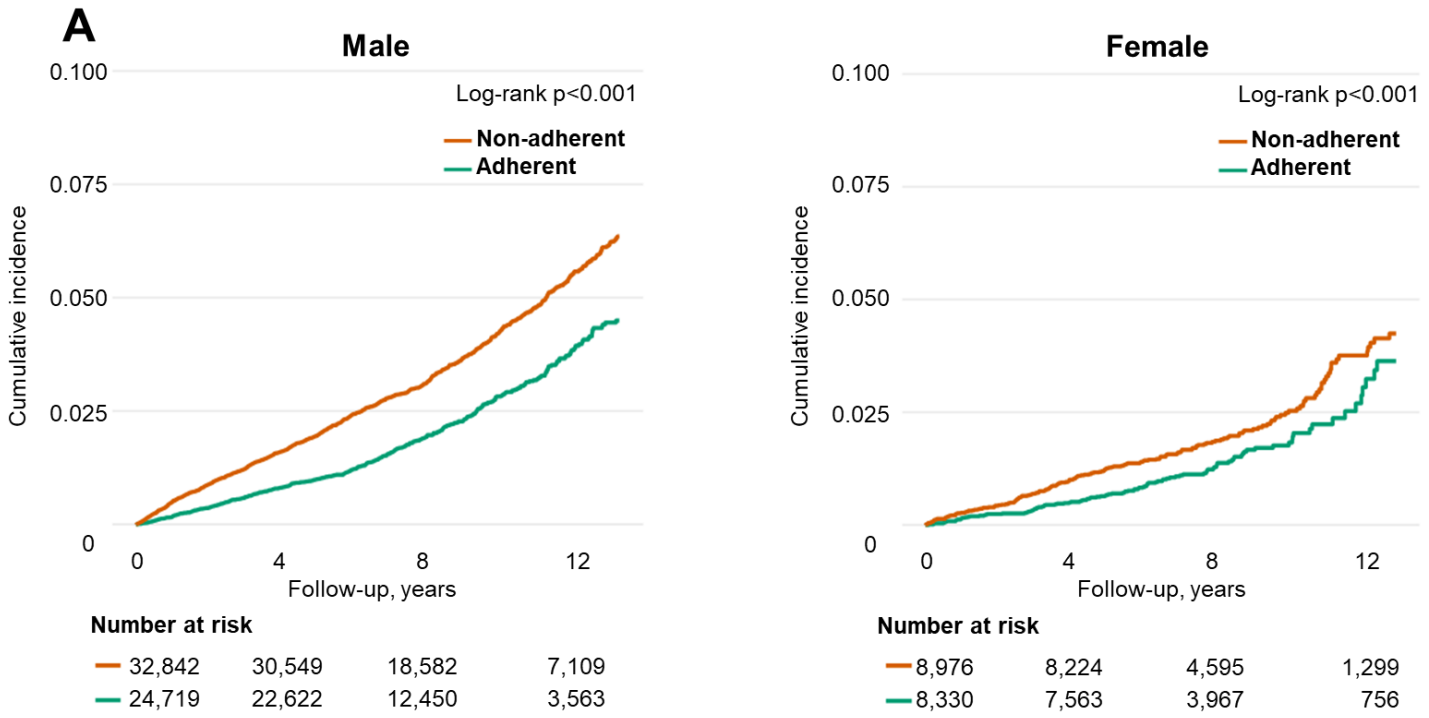

Figure 8. Cumulative incidence of composite cardiovascular events according to medication adherence by sex.
(A) Adherent vs. non-adherent, (B) by adherence group, (C) by PDC quartile. PDC: proportion of days covered.

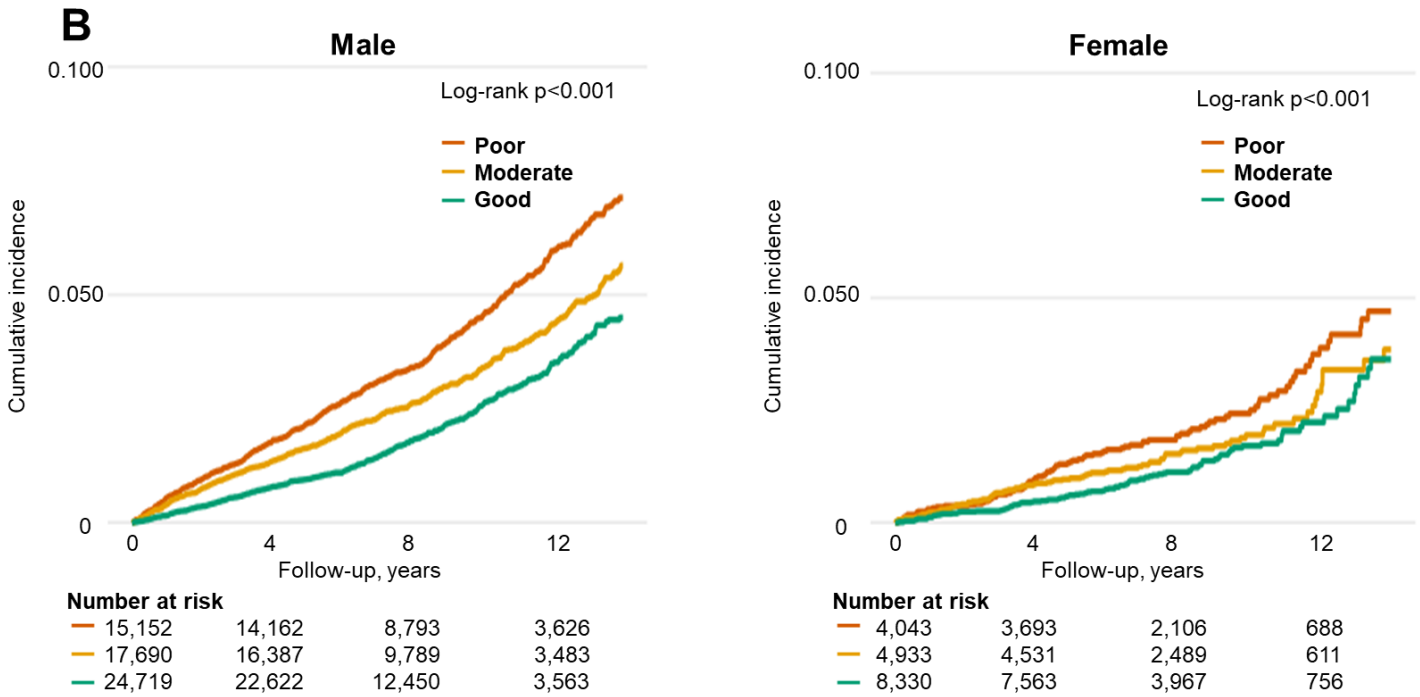

Figure 8. Cumulative incidence of composite cardiovascular events according to medication adherence by sex. (Continued)
(A) Adherent vs. non-adherent, (B) by adherence group, (C) by PDC quartile. PDC: proportion of days covered.

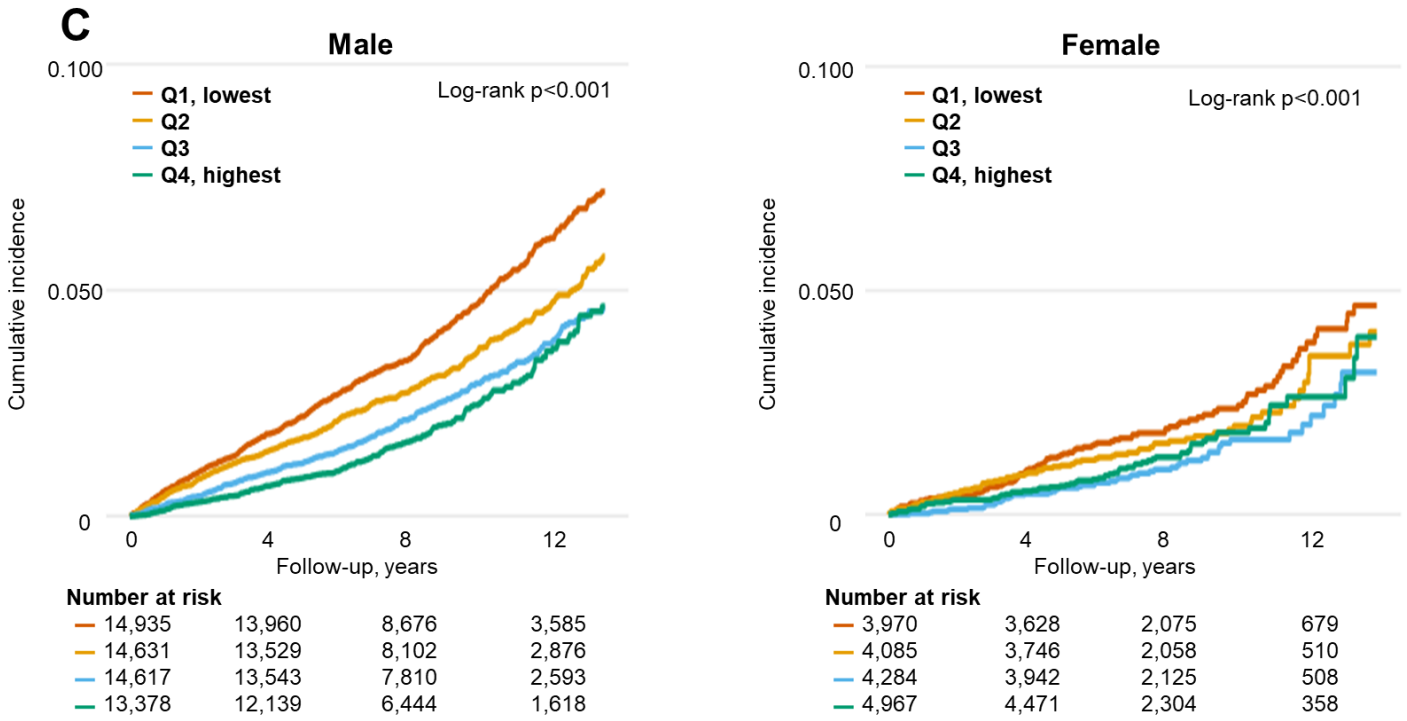

Figure 8. Cumulative incidence of composite cardiovascular events according to medication adherence by sex. (Continued)
(A) Adherent vs. non-adherent, (B) by adherence group, (C) by PDC quartile. PDC: proportion of days covered.

Table 9. Association between medication adherence and composite cardiovascular events by sex

Adherence	Events	P-Y[a]	Rate[b]	Model 1		Model 2		Model 3		Model 4	
				HR	(95%CI)	HR	(95%CI)	HR	(95%CI)	HR	(95%CI)
Male											
Adherent	1,152	20.1	57.3	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)
Non-adherent	2,227	28.5	78.1	1.32	(1.23–1.42)	1.39	(1.29–1.49)	1.45	(1.35–1.56)	1.43	(1.33–1.54)
Female											
Adherent	358	6.5	55.1	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)
Non-adherent	565	7.3	77.4	1.37	(1.20–1.56)	1.44	(1.26–1.65)	1.49	(1.30–1.70)	1.48	(1.29–1.70)

[a]Person-years (×10,000), [b]incidence rate per 10,000 person-years

Model 1: Unadjusted.

Model 2: Adjusted for age at index, duration from diagnosis to index, index year, and socioeconomic status.

Model 3: Model 2 + initial treatment regimen, drug class, taking insulin therapy, taking GLP-1 RA therapy, Charlson comorbidity index, taking medication for hypertension, taking medication for dyslipidemia, body mass index, fasting blood glucose, systolic blood pressure, and total cholesterol.

Model 4: Model 3 + smoking status, alcohol consumption, and physical activities.

HR: hazard ratio; CI: confidence interval, GLP-1 RA: Glucagon-like peptide-1 receptor agonist.

Table 10. Association between medication adherence and composite cardiovascular events by sex across different categorizations

Adherence	Events	P-Y[a]	Rate[b]	Unadjusted		Adjusted[c]	
				HR	(95%CI)	HR	(95%CI)
By adherence group							
Male							
Good	1,152	20.1	57.3	1.00	(Reference)	1.00	(Reference)
Moderate	1,052	15.1	69.7	1.18	(1.09–1.29)	1.25	(1.15–1.37)
Poor	1,175	13.3	88.3	1.47	(1.36–1.60)	1.65	(1.52–1.80)
Female							
Good	358	6.5	55.1	1.00	(Reference)	1.00	(Reference)
Moderate	299	4.0	74.8	1.35	(1.16–1.57)	1.43	(1.22–1.67)
Poor	266	3.3	90.6	1.39	(1.19–1.63)	1.56	(1.32–1.83)
By PDC quartiles							
Male							
Q4, highest	590	10.6	55.7	1.00	(Reference)	1.00	(Reference)
Q3	757	12.3	61.5	1.07	(0.96–1.19)	1.12	(1.00–1.25)
Q2	870	12.5	69.6	1.20	(1.08–1.33)	1.30	(1.17–1.45)
Q1, lowest	1,162	13.2	88.0	1.50	(1.36–1.65)	1.71	(1.54–1.90)
Female							
Q4, highest	208	3.8	54.7	1.00	(Reference)	1.00	(Reference)
Q3	200	3.5	57.1	1.03	(0.85–1.25)	1.07	(0.88–1.30)
Q2	254	3.3	77.0	1.37	(1.14–1.65)	1.47	(1.22–1.77)
Q1, lowest	261	3.3	79.1	1.38	(1.15–1.65)	1.55	(1.28–1.88)

[a]Person-years (×10,000), [b]incidence rate per 10,000 person-years

Model 1: Unadjusted.

Model 2: Adjusted for sex, age at index, duration from diagnosis to index, index year, and socioeconomic status.

Model 3: Model 2 + initial treatment regimen, drug class, taking insulin therapy, taking GLP-1 RA therapy, Charlson comorbidity index, taking medication for hypertension, taking medication for dyslipidemia, body mass index, fasting blood glucose, systolic blood pressure, and total cholesterol.

Model 4: Model 3 + smoking status, alcohol consumption, and physical activities.

HR: hazard ratio, CI: confidence interval, PDC: proportion of days covered, GLP-1 RA: Glucagon-like peptide-1 receptor agonist.

3.1.5 Stratified analyses by index period

Comparing the overall characteristics of participants who started their medication in the periods 2003–2013 and 2014–2021, those who initiated medication during the latter period (i.e., between 2014–2021) showed a better medication adherence. Median [IQR] PDCs were 72.9% [47.7–89.6%] and 78.1% [52.6–92.3%] among participants initiated medication in 2003–2013 and 2014–2021, respectively (Table 11). Participants started their medication in the latter period were more likely to have longer duration from diagnosis to index, exhibited more comorbidities, were more likely to have obesity, and were less likely to be current-smokers than those who started their medication in the earlier period.

The median [IQR] follow-up was 10.4 [9.0–12.8] years among participants initiated their medication in 2003–2013, whereas it was 6.7 [4.7–7.0] years among those initiated in 2014–2021. The increased risk of composite CVD events in participants with suboptimal medication adherence were consistent across both index periods (Table 12 and 13). The increased hazard was prominent among those initiated their medication in the earlier period, between 2003–2013; the adjusted HR (95% CI) of lowest PDC quartile group was 1.86 (1.66–2.08) compared to the highest quartile group. The interaction between the index period and adherence with CVD was not statistically significant: p-values for interaction were p=0.21 for categorization of adherent/non-adherent and p=0.068 for PDC by quartile.

Table 11. Baseline characteristics by index period

Characteristics	Total		2003–2013		2014–2021	
Total	**74,867**		**40,582**	**(54.2)**	**34,285**	**(45.8)**
Proportion days covered, %	75.1	[49.3–91.0]	72.9	[47.7–89.6]	78.1	[52.6–92.3]
Sex						
Male	57,561	(76.9)	31,893	(78.6)	25,668	(74.9)
Female	17,306	(23.1)	8,686	(21.4)	8,617	(25.1)
Age at index, years	39.2	± 4.3	38.7	± 4.4	39.9	± 4.0
Age at diagnosis, years	36.8	± 4.9	37.0	± 4.6	36.6	± 5.2
Duration from diagnosis to index, days	409	[37–1,313]	272	[25–926]	670	[88–1,815]
Socioeconomic status, quartile						
Q4, highest	18,720	(25.0)	7,693	(19.0)	11,027	(32.2)
Q3	18,715	(25.0)	9,568	(23.6)	9,147	(26.7)
Q2	18,720	(25.0)	11,025	(17.2)	7,695	(22.4)
Q1, lowest	18,712	(25.0)	12,296	(30.3)	6,416	(18.7)
Diagnosed with T1DM	1,631	(2.2)	1,036	(2.6)	595	(1.7)
Diagnosed with GDM	216	(0.3)	115	(0.3)	101	(0.3)
Charlson comorbidity index≥1	18,991	(25.4)	10,370	(22.6)	8,621	(25.2)
Taking medication for hypertension	20,529	(27.4)	10,323	(25.4)	10,206	(29.8)
Taking medication for dyslipidemia	27,529	(36.8)	12,130	(29.9)	15,399	(44.9)
Body mass index	26.7	[24.2–29.6]	26.3	[24.0–29.0]	27.2	[24.6–30.2]
Obesity (BMI≥25)	51,008	(68.1)	26,318	(64.9)	24,690	(72.0)
Fasting blood glucose, mg/dL	147	[120–203]	149	[119–207]	146	[120–198]
Systolic blood pressure, mmHg	128	[119–136]	128	[119–135]	128	[119–136]
Total cholesterol, mg/dL	207	[180–239]	208	[182–237]	206	[178–237]

Table 11. Baseline characteristics by index period (Continued)

Characteristics	Total		2003–2013		2014–2021	
Total	**74,867**		**40,582**	**(54.2)**	**34,285**	**(45.8)**
Smoking						
Never	28,788	(38.5)	15,733	(38.8)	13,055	(38.1)
Past	12,674	(16.9)	6,087	(15.0)	6,587	(19.2)
Current	33,405	(44.6)	18,762	(46.2)	14,643	(42.7)
Alcohol consumption						
None	26,855	(35.9)	14,908	(36.7)	11,947	(34.9)
1–2 times/week	35,242	(47.1)	19,264	(47.5)	15,978	(46.6)
3 times or more/week	12,770	(17.1)	6,410	(15.8)	6,360	(18.6)
Physical activity						
None	22,033	(29.4)	13,683	(33.7)	8,350	(24.4)
1–2 times/week	22,160	(29.6)	12,625	(31.1)	9,535	(28.7)
3 times or more/week	30,674	(41.0)	14,274	(35.2)	16,400	(47.8)

Numbers represent mean ± standard deviation, median [interquartile range], or frequency (%).

T1DM: type 1 diabetes mellitus, GDM: gestational diabetes mellitus, BMI: body mass index, GLP: Glucagon-like peptide-1.

Table 12. Association between medication adherence and composite cardiovascular events by index period

Adherence	Events	P-Y[a]	Rate[b]	Model 1		Model 2		Model 3		Model 4	
				HR	(95%CI)	HR	(95%CI)	HR	(95%CI)	HR	(95%CI)
Medication initiation during 2003–2013											
Adherent	965	17.5	55.1	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)
Non-adherent	2,016	25.6	78.8	1.39	(1.28–1.50)	1.45	(1.34–1.57)	1.52	(1.40–1.64)	1.50	(1.39–1.62)
Medication initiation during 2014–2021											
Adherent	545	9.2	59.2	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)
Non-adherent	776	10.2	76.1	1.27	(1.14–1.42)	1.30	(1.17–1.46)	1.36	(1.22–1.53)	1.35	(1.21–1.51)

[a]Person-years (×10,000), [b]incidence rate per 10,000 person-years

Model 1: Unadjusted.

Model 2: Adjusted for sex, age at index, duration from diagnosis to index, index year, and socioeconomic status.

Model 3: Model 2 + initial treatment regimen, drug class, taking insulin therapy, taking GLP-1 RA therapy, Charlson comorbidity index, taking medication for hypertension, taking medication for dyslipidemia, body mass index, fasting blood glucose, systolic blood pressure, and total cholesterol.

Model 4: Model 3 + smoking status, alcohol consumption, and physical activities.

HR: hazard ratio; CI: confidence interval, GLP-1 RA: Glucagon-like peptide-1 receptor agonist.

Table 13. Association between medication adherence and composite cardiovascular events by index period

Adherence	Events	P-Y[a]	Rate[b]	Unadjusted		Adjusted[c]	
				HR	(95%CI)	HR	(95%CI)
By adherence group							
Medication initiation during 2003–2013							
Good	965	17.5	55.1	1.00	(Reference)	1.00	(Reference)
Moderate	947	13.4	70.7	1.25	(1.14–1.37)	1.32	(1.21–1.50)
Poor	1,069	12.1	88.3	1.53	(1.41–1.67)	1.72	(1.57–1.89)
Medication initiation during 2014–2021							
Good	545	9.2	59.2	1.00	(Reference)	1.00	(Reference)
Moderate	404	5.7	70.9	1.19	(1.05–1.36)	1.25	(1.10–1.42)
Poor	372	4.5	82.7	1.37	(1.20–1.57)	1.49	(1.30–1.70)
By PDC quartile							
Medication initiation during 2003–2013							
Q4, highest	471	9.2	51.2	1.00	(Reference)	1.00	(Reference)
Q3	674	10.8	62.4	1.18	(1.05–1.33)	1.23	(1.09–1.38)
Q2	779	11.1	70.2	1.32	(1.18–1.48)	1.42	(1.27–1.60)
Q1, lowest	1,057	12.0	88.1	1.63	(1.46–1.82)	1.86	(1.66–2.08)
Medication initiation during 2014–2021							
Q4, highest	327	5.2	62.9	1.00	(Reference)	1.00	(Reference)
Q3	283	5.0	56.6	0.90	(0.77–1.06)	0.93	(0.80–1.10)
Q2	345	4.7	73.4	1.17	(1.01–1.37)	1.24	(1.07–1.45)
Q1, lowest	366	4.5	81.3	1.31	(1.13–1.52)	1.43	(1.22–1.67)

[a]Person-years (×10,000), [b]incidence rate per 10,000 person-years

[c]Adjusted for sex, age at index, duration from diagnosis to index, index year, socioeconomic status, initial treatment regimen, drug class, taking insulin therapy, taking GLP-1 RA therapy, Charlson comorbidity index, taking medication for hypertension, taking medication for dyslipidemia, body mass index, fasting blood glucose, systolic blood pressure, total cholesterol, smoking status, alcohol consumption, and physical activities.

HR: hazard ratio, CI: confidence interval, PDC: proportion of days covered, GLP-1 RA: Glucagon-like peptide-1 receptor agonist.

3.2 Analyses of individuals aged 20–39 years

3.2.1 General characteristics

The mean age at index was 35.1 ± 3.5 years and 82.5% were male (Table 14). The mean age at diagnosis was 33.2 ± 4.1 years and the median time [IQR] from the first diagnosis to the index was 277 [24–916] days. Among all participants, 71.3% had obesity (BMI≥25), while the median BMI was 27.2 [24.5–30.3]. Of total, 905 (3.0%; 331 males and 574 females) were diagnosed with T1DM and 147 (0.5%) females were diagnosed with GDM.

Overall, the median PDC was 68.8% [43.3–87.9], and 37.1% of the participants adhered to the medication in the first year from medication initiation. Participants who adhered were more likely to be female, be of higher socioeconomic status, to take medication for hypertension or dyslipidemia, not to be a current smoker, and to engage in regular physical activity. Furthermore, approximately two-thirds of the participants initiated their treatment with a regimen combining two or more drugs. Over 80% of the participants' initial regimens included Biguanides (Table 15).

Table 14. Baseline characteristics of participants aged 20–39 years

Characteristics	Total		Adherent		Non-adherent	
Total	**30,716**		**11,391**	**(37.1)**	**19,325**	**(62.9)**
Proportion days covered, %	68.8	[43.3–87.9]	91.2	[86.0–95.9]	49.6	[32.6–65.8]
Sex						
Male	25,337	(82.5)	9,322	(81.8)	16,015	(82.9)
Female	5,379	(17.5)	2,069	(18.2)	3,310	(17.1)
Age at index, years	35.1	± 3.5	35.6	± 3.2	34.8	± 3.6
Age at diagnosis, years	33.2	± 4.1	33.6	± 4.0	33.1	± 4.2
Duration from diagnosis to index, days	277	[24–916]	344	[35–1,021]	243	[18–855]
Socioeconomic status, quartile						
Q4, highest	7,684	(25.0)	3,226	(28.3)	4,458	(23.1)
Q3	7,675	(25.0)	2,961	(26.0)	4,714	(24.4)
Q2	7,681	(25.0)	2,681	(23.5)	5,000	(25.9)
Q1, lowest	7,676	(25.0)	2,523	(22.2)	5,153	(26.7)
Diagnosed with T1DM	905	(3.0)	331	(2.9)	574	(3.0)
Diagnosed with GDM	147	(0.5)	52	(0.5)	95	(0.5)
Taking insulin therapy	125	(0.4)	53	(0.5)	72	(0.4)
Taking GLP-1 RA therapy	11	(0.04)	7	(0.1)	4	(0.02)
Charlson comorbidity index≥1	6,975	(22.7)	2,624	(23.0)	4,351	(22.5)
Taking medication for hypertension	7,115	(23.2)	3,493	(30.7)	3,622	(18.7)
Taking medication for dyslipidemia	9,813	(32.0)	4,129	(36.3)	5,684	(29.4)
Body mass index	27.2	[24.5–30.3]	27.4	[24.7–30.4]	27.1	[24.5–30.1]
Obesity (BMI≥25)	21,899	(71.3)	8,275	(72.7)	13,624	(70.5)
Fasting blood glucose, mg/dL	147	[116–212]	145	[117–204]	148	[116–217]

Table 14. Baseline characteristics of participants aged 20–39 years (Continued)

Characteristics	Total		Adherent		Non-adherent	
Total	**30,716**		**11,391**	**(37.1)**	**19,325**	**(62.9)**
Systolic blood pressure, mmHg	129	[120–136]	130	[120–138]	128	[120–135]
Total cholesterol, mg/dL	208	[182–238]	206	[178–235]	210	[183–239]
Smoking						
Never	11,434	(37.2)	4,388	(38.5)	7,046	(36.5)
Past	4,293	(14.0)	1,824	(16.0)	2,469	(12.8)
Current	14,989	(48.8)	5,179	(45.5)	9,810	(50.8)
Alcohol consumption						
None	10,677	(34.8)	4,176	(36.7)	6,501	(33.6)
1–2 times/week	15,965	(52.0)	5,801	(50.9)	10,164	(52.6)
3 times or more/week	4,074	(13.3)	1,414	(12.4)	2,660	(13.8)
Physical activity						
None	9,670	(31.5)	3,275	(28.8)	6,365	(33.1)
1–2 times/week	9,493	(30.9)	3,545	(31.1)	5,948	(30.8)
3 times or more/week	11,553	(37.6)	4,571	(40.1)	6,982	(36.1)

Numbers represent mean ± standard deviation, median [interquartile range], or frequency (%).

T1DM: type 1 diabetes mellitus, GDM: gestational diabetes mellitus, BMI: body mass index, GLP: Glucagon-like peptide-1.

Table 15. Initial treatment regimens among participants aged 20–39 years

Initial treatment regimen	Number	(%)
Total number of participants	**30,176**	
Drug class		
Alpha-glucosidase inhibitors	1,922	(6.3)
DPP-4 inhibitors	9,902	(32.2)
Meglitinides	555	(1.8)
Biguanides	25,389	(82.7)
Thiazolidinediones	1,972	(6.4)
SGLT-2 inhibitors	980	(3.2)
Sulfonylureas	14,028	(45.7)
Therapy type		
Monotherapy	10,463	(34.1)
Combination of two or more drugs	20,253	(65.9)

DPP-4: Dipeptidyl Peptidase-4; SGLT-2: Sodium-Glucose Cotransporter-2.

3.2.2 Medication adherence and composite cardiovascular events

From 2003 through 2021, a significant improvement in medication adherence was observed among participants aged 20–39 years as well (Table 16). Among participants who began their initial medication regimen in 2003, only 21.7% adhered their medication during the first year. In contrast, 45.1% of participants who started their medication in 2021 adhered. Within the overall upward trend in medication adherence, there were years with little change and others with sharp increases.

During a median [IQR] follow-up of 9.1 [6.6–13.1] years (adherent group: 8.7 [6.4–11.9] years, non-adherent group: 9.5 [6.8–13.7] years), 1,732 new CVD events were recorded. Incidence rates per 10,000 person-years were 10.2 in the adherent group and 18.5 in the non-adherent group. The cumulative incidence of CVD events was higher in the non-adherent group than in the adherent group (Figure 9). After adjusting the set of covariates, non-adherence to antihyperglycemic medication was associated with a higher risk of CVD events. Under Model 4, which adjusted for all potential covariates, the adjusted HR and 95% CI for composite CVD events was 1.42 (1.27–1.57) for the non-adherent group compared with the adherent group (Table 17).

The reduced CVD risk according to higher adherence was robust across different categorizations; suboptimal medication adherence was associated with a higher risk of CVD with a dose-response relationship observed (Figure 10, Table 18). Of note, participants in the lowest PDC quartiles had a 75% higher risk of CVD compared with the highest quartile group after adjusting for all covariates.

Table 16. Index year and medication adherence among participants aged 20–39 years

		Adherent		Non-adherent	
Index year	**Participants**	**Number**	**(%)**	**Number**	**(%)**
Total	**30,716**	**11,391**	**(37.1)**	**19,325**	**(62.9)**
2003	508	110	(21.7)	398	(78.3)
2004	1,216	277	(22.8)	939	(77.2)
2005	1,807	411	(22.7)	1,396	(77.3)
2006	1,872	509	(27.2)	1,363	(72.8)
2007	1,803	669	(37.1)	1,134	(62.9)
2008	1,494	550	(36.8)	944	(63.2)
2009	1,188	476	(40.1)	712	(59.9)
2010	1,768	682	(38.6)	1,086	(61.4)
2011	2,399	912	(38.0)	1,487	(62.0)
2012	2,558	985	(38.5)	1,573	(61.5)
2013	2,768	1,046	(37.8)	1,722	(62.2)
2014	3,109	1,279	(41.1)	1,830	(58.9)
2015	3,773	1,527	(40.5)	2,246	(59.5)
2016	1,968	844	(42.9)	1,124	(57.1)
2017	1,137	523	(46.0)	614	(54.0)
2018	770	347	(45.1)	423	(54.9)
2019	322	137	(42.5)	185	(57.5)
2020	143	56	(39.2)	87	(60.8)
2021	113	51	(45.1)	62	(54.9)

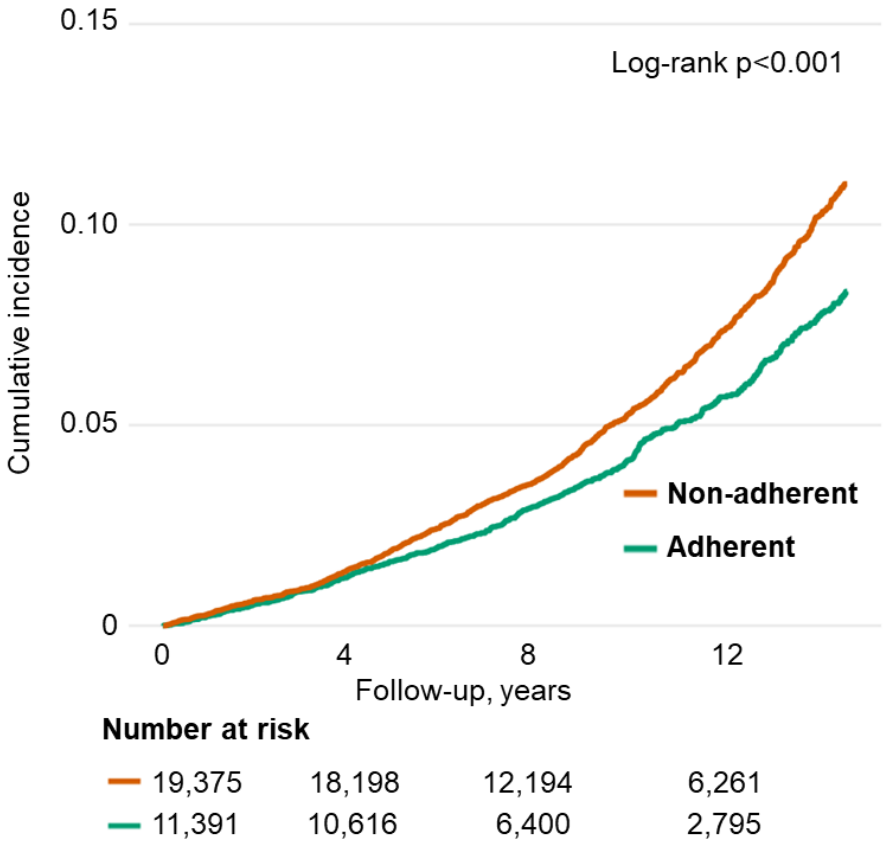

Figure 9. Cumulative incidence of composite cardiovascular events by medication adherence among individuals aged 20–39 years

Table 17. Medication adherence and composite cardiovascular events among individuals aged 20–39 years

Adherence	Events	P-Y[a]	Rate[b]	Model 1		Model 2		Model 3		Model 4	
				HR	(95%CI)	HR	(95%CI)	HR	(95%CI)	HR	(95%CI)
Adherent	500	10.2	49.1	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)
Non-adherent	1,232	18.5	66.6	1.30	(1.17–1.44)	1.34	(1.21–1.50)	1.42	(1.28–1.58)	1.42	(1.27–1.57)

[a]Person-years (×10,000), [b]incidence rate per 10,000 person-years

Model 1: Unadjusted.

Model 2: Adjusted for sex, age at index, duration from diagnosis to index, index year, and socioeconomic status.

Model 3: Model 2 + initial treatment regimen, drug class, taking insulin therapy, taking GLP-1 RA therapy, Charlson comorbidity index, taking medication for hypertension, taking medication for dyslipidemia, body mass index, fasting blood glucose, systolic blood pressure, and total cholesterol.

Model 4: Model 3 + smoking status, alcohol consumption, and physical activities.

HR: hazard ratio; CI: confidence interval, GLP-1 RA: Glucagon-like peptide-1 receptor agonist.

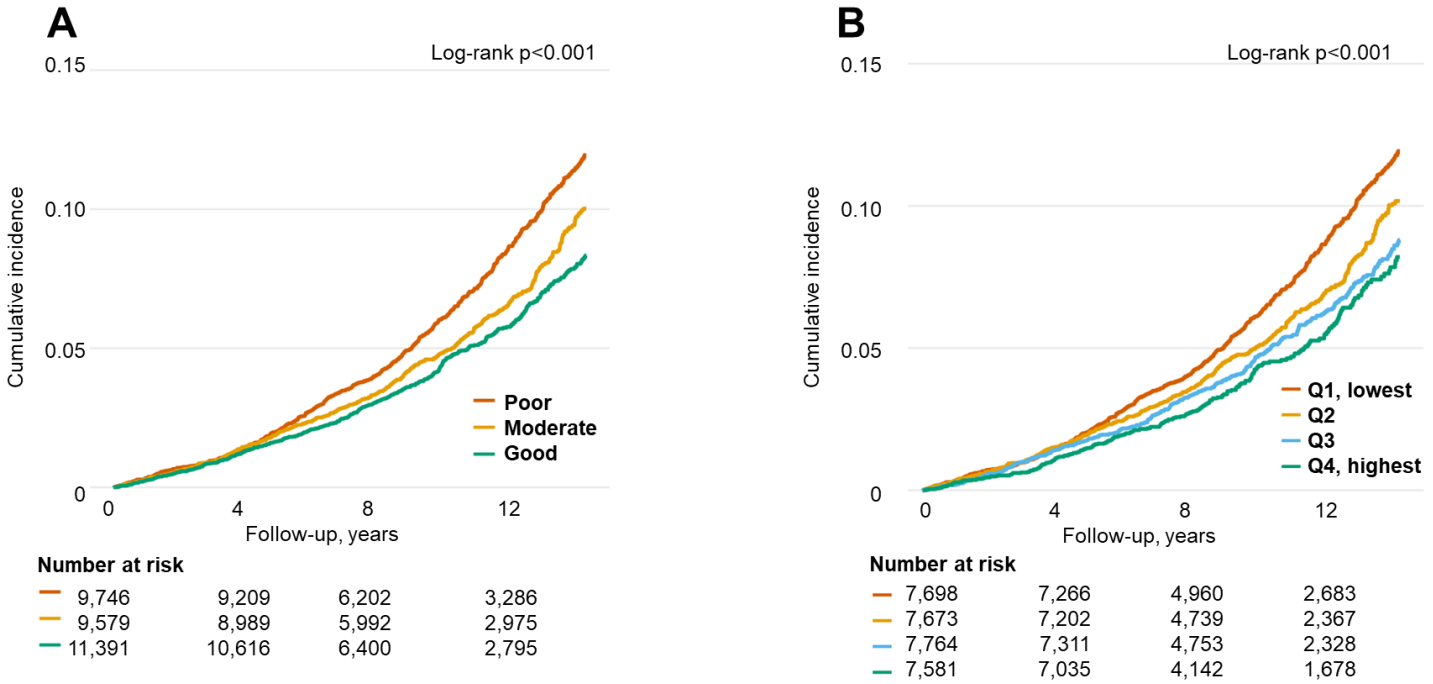

Figure 10. Cumulative incidence of composite cardiovascular events among individuals aged 20–39 years across different adherence categorizations.

(A) By adherence group, (B) by PDC quartile. PDC: proportion of days covered.

Table 18. Medication adherence and composite cardiovascular events across different adherence categorizations among individuals aged 20–39 years

Adherence	Events	P-Y[a]	Rate[b]	Unadjusted		Adjusted[c]	
				HR	(95%CI)	HR	(95%CI)
By adherence group							
Good	500	10.2	49.0	1.00	(Reference)	1.00	(Reference)
Moderate	540	9.1	59.3	1.16	(1.03–1.32)	1.25	(1.11–1.42)
Poor	692	9.4	73.6	1.42	(1.27–1.60)	1.59	(1.41–1.79)
By PDC quartiles							
Q4, highest	303	6.7	45.2	1.00	(Reference)	1.00	(Reference)
Q3	401	7.3	54.9	1.15	(0.99–1.33)	1.22	(1.05–1.42)
Q2	468	7.3	64.1	1.34	(1.16–1.55)	1.49	(1.29–1.73)
Q1, lowest	560	7.5	74.7	1.53	(1.33–1.75)	1.75	(1.52–2.02)

[a]Person-years (×10,000), [b]incidence rate per 10,000 person-years

[c]Adjusted for sex, age at index, duration from diagnosis to index, index year, socioeconomic status initial treatment regimen, drug class, taking insulin therapy, taking GLP-1 RA therapy, Charlson comorbidity index, taking medication for hypertension, taking medication for dyslipidemia, body mass index, fasting blood glucose, systolic blood pressure, total cholesterol, smoking status, alcohol consumption, and physical activities.

HR: hazard ratio, CI: confidence interval, PDC: proportion of days covered, GLP-1 RA: Glucagon-like peptide-1 receptor agonist.

3.2.3 Endpoint-specific analyses including all-cause death

Throughout the follow-up period, there were 441 MIs, 471 strokes, 967 cases of HF, and 223 cardiovascular-related deaths recorded (Figure 11, Table 19). Across all event types, a consistently higher risk was observed in the non-adherent group compared to the adherent group (Table 19), with a particularly higher risk noted for cardiovascular deaths. The survival curves displayed distinct patterns across different event types (Figure 11). Regarding all-cause death, 712 deaths were recorded with median [IQR] ages at death of 43 [40–47] years.

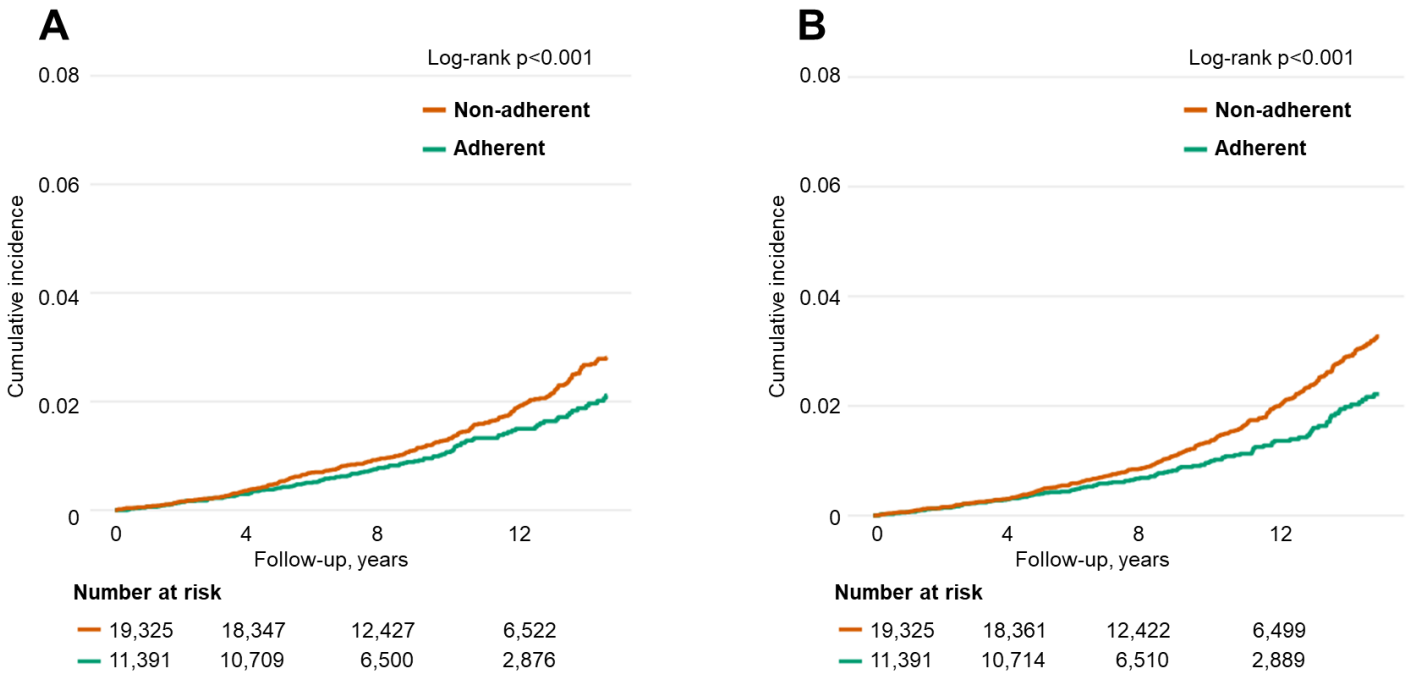

Figure 11. Cumulative incidence of each cardiovascular event by medication adherence among individuals aged 20–39 years.
(A) Myocardial infarction, (B) stroke, (C) heart failure, (D) cardiovascular death, (E) all-cause death.

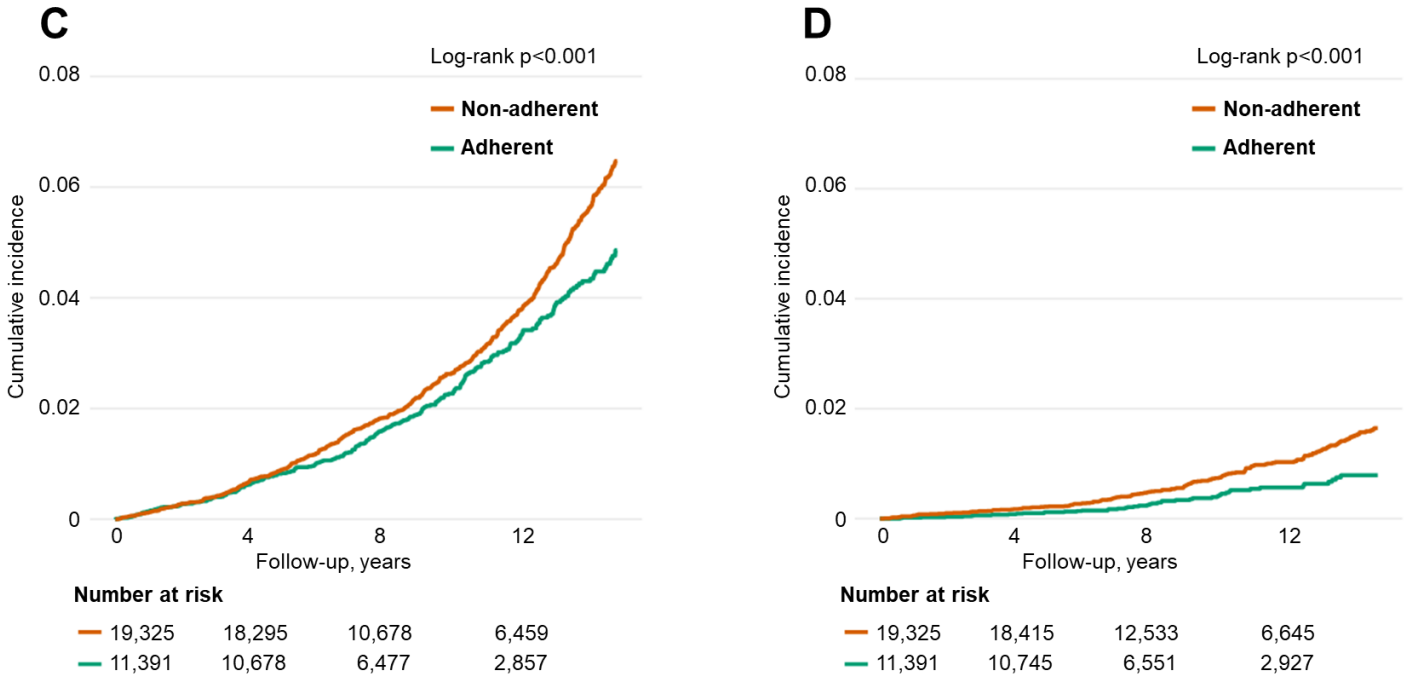

Figure 11. Cumulative incidence of each cardiovascular event by medication adherence among individuals aged 20–39 years. (Continued)

(A) Myocardial infarction, (B) stroke, (C) heart failure, (D) cardiovascular death, (E) all-cause death.

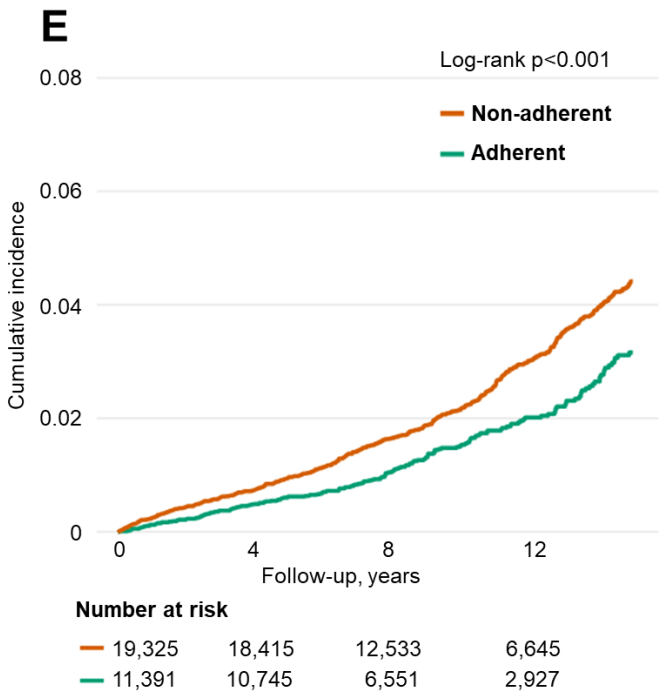

Figure 11. Cumulative incidence of each cardiovascular event by medication adherence among individuals aged 20–39 years. (Continued).
(A) Myocardial infarction, (B) stroke, (C) heart failure, (D) cardiovascular death, (E) all-cause death.

Table 19. Association between medication adherence and each cardiovascular event including all-cause death among individuals aged 20–39 years

Adherence	Events	P-Y[a]	Rate[b]	Unadjusted		Adjusted[c]	
				HR	(95%CI)	HR	(95%CI)
Myocardial infarction							
Adherent	128	10.3	12.4	1.00	(Reference)	1.00	(Reference)
Non-adherent	313	18.8	16.1	1.29	(1.05–1.58)	1.33	(1.07–1.64)
Stroke							
Adherent	126	10.3	12.2	1.00	(Reference)	1.00	(Reference)
Non-adherent	345	18.8	18.4	1.42	(1.16–1.75)	1.53	(1.24–1.89)
Heart failure							
Adherent	285	10.3	27.7	1.00	(Reference)	1.00	(Reference)
Non-adherent	682	18.7	36.5	1.24	(1.08–1.43)	1.42	(1.23–1.63)
Cardiovascular death							
Adherent	47	10.4	4.5	1.00	(Reference)	1.00	(Reference)
Non-adherent	176	18.9	9.3	1.94	(1.41–2.68)	1.97	(1.42–2.74)
All-cause death							
Adherent	188	10.4	18.1	1.00	(Reference)	1.00	(Reference)
Non-adherent	524	18.9	27.8	1.48	(1.25–1.74)	1.49	(1.26–1.77)

[a]Person-years (×10,000), [b]incidence rate per 10,000 person-years

[c]Adjusted for sex, age at index, duration from diagnosis to index, index year, socioeconomic status, initial treatment regimen, drug class, taking insulin therapy, taking GLP-1 RA therapy, Charlson comorbidity index, taking medication for hypertension, taking medication for dyslipidemia, body mass index, fasting blood glucose, systolic blood pressure, total cholesterol, smoking status, alcohol consumption, and physical activities.

HR: hazard ratio, CI: confidence interval, GLP-1 RA: Glucagon-like peptide-1 receptor agonist.

3.2.4 Sex-stratified analyses

The median PDC was comparable between sexes, at approximately 69% (Table 20). Female participants generally appeared younger at both diagnosis and index, were more likely to have longer duration from diagnosis to index, belonged to lower socioeconomic groups, exhibited fewer comorbidities, were less likely to have obesity, and were more likely to be non-smokers and non-alcohol consumers than their male counterparts.

The median follow-ups were 9.3 [6.7–13.3] years for males and 8.5 [6.2–11.8] years for females. During follow-up, 1,425 and 307 composite CVD events were confirmed for males and females, respectively. The higher risks for composite CVD events in the non-adherent group were consistent across both sexes: adjusted HRs (95% CIs) were 1.41 (1.25–1.59) in males and 1.46 (1.14–1.87) in females (Figures 12, Tables 21).

Suboptimal medication adherence was associated with a higher risk of composite CVD events in both sexes (Tables 22). The interaction between sex and adherence was not statistically significant: p-values for interaction were P=0.84 for the categorization as adherent/non-adherent and p=0.65 for the categorization by PDC quartile.

Table 20. Baseline characteristics of participants aged 20–39 years by sex

Characteristics	Total		Male		Female	
Total	**30,716**		**25,337**	**(82.5)**	**5,379**	**(17.5)**
Proportion days covered, %	68.8	[43.3–87.9]	68.7	[43.6–87.7]	69.6	[42.2–89.3]
Age at index, years	35.1	± 3.5	35.4	± 3.2	33.9	± 4.4
Age at diagnosis, years	33.2	± 4.1	33.6	± 3.9	31.7	± 4.8
Duration from diagnosis to index, days	277	[24–916]	267	[22–875]	338	[32–1,165]
Socioeconomic status, quartile						
Q4, highest	7,684	(25.0)	7,006	(27.6)	678	(12.6)
Q3	7,675	(25.0)	6,857	(27.1)	818	(15.2)
Q2	7,681	(25.0)	6,291	(24.8)	1,390	(25.8)
Q1, lowest	7,676	(25.0)	5,183	(20.5)	2,493	(46.4)
Diagnosed with T1DM	905	(3.0)	685	(2.7)	220	(4.1)
Diagnosed with GDM	147	(0.5)	0	(0.0)	147	(2.7)
Taking insulin therapy	125	(0.4)	88	(0.4)	37	(0.7)
Taking GLP-1 RA therapy	11	(0.04)	5	(0.0)	6	(0.1)
Charlson comorbidity index≥1	6,975	(22.7)	5,898	(23.3)	1,077	(20.0)
Taking medication for hypertension	7,115	(23.2)	6,219	(24.6)	896	(16.7)
Taking medication for dyslipidemia	9,813	(32.0)	8,360	(33.0)	1,453	(27.0)
Body mass index	27.2	[24.5–30.3]	27.3	[24.7–30.2]	26.9	[23.4–30.8]
Obesity (BMI≥25)	21,899	(71.3)	18,420	(72.7)	3,479	(64.7)
Fasting blood glucose, mg/dL	147	[116–212]	147	[117–212]	147	[113–212]
Systolic blood pressure, mmHg	129	[120–136]	130	[120–138]	120	[110–130]
Total cholesterol, mg/dL	208	[182–238]	210	[183–239]	204	[177–232]

Table 20. Baseline characteristics of participants aged 20–39 years by sex (Continued)

Characteristics	Total		Male		Female	
Total	**30,716**		**25,337**	**(82.5)**	**5,379**	**(17.5)**
Smoking						
Never	11,434	(37.2)	6,785	(26.8)	4,649	(86.4)
Past	4,293	(14.0)	4,021	(15.9)	272	(6.1)
Current	14,989	(48.8)	14,531	(57.4)	458	(8.5)
Alcohol consumption						
None	10,677	(34.8)	7,348	(29.0)	3,329	(61.9)
1–2 times/week	15,965	(52.0)	14,133	(55.8)	1,832	(34.1)
3 times or more/week	4,074	(13.3)	3,856	(15.2)	218	(4.1)
Physical activity						
None	9,670	(31.5)	7,891	(31.1)	1,779	(33.1)
1–2 times/week	9,493	(30.9)	8,050	(31.8)	1,443	(26.8)
3 times or more/week	11,553	(37.6)	9,396	(37.1)	2,157	(40.1)

Numbers represent mean ± standard deviation, median [interquartile range], or frequency (%).

T1DM: type 1 diabetes mellitus, GDM: gestational diabetes mellitus, BMI: body mass index, GLP: Glucagon-like peptide-1.

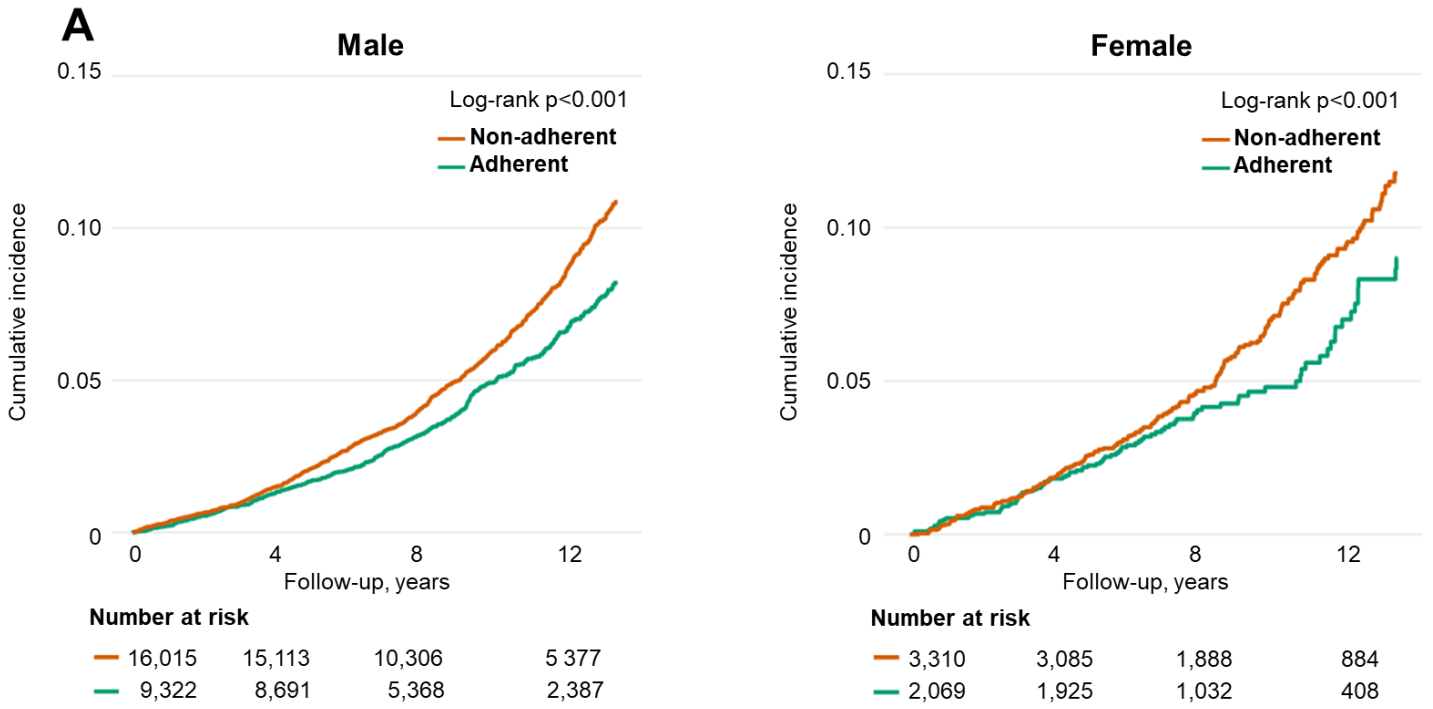

Figure 12. Cumulative incidence of composite cardiovascular events by medication adherence among individuals aged 20–39 years stratified by sex.

(A) Adherent vs. non-adherent, (B) by adherence group, (C) by PDC quartile. PDC: proportion of days covered.

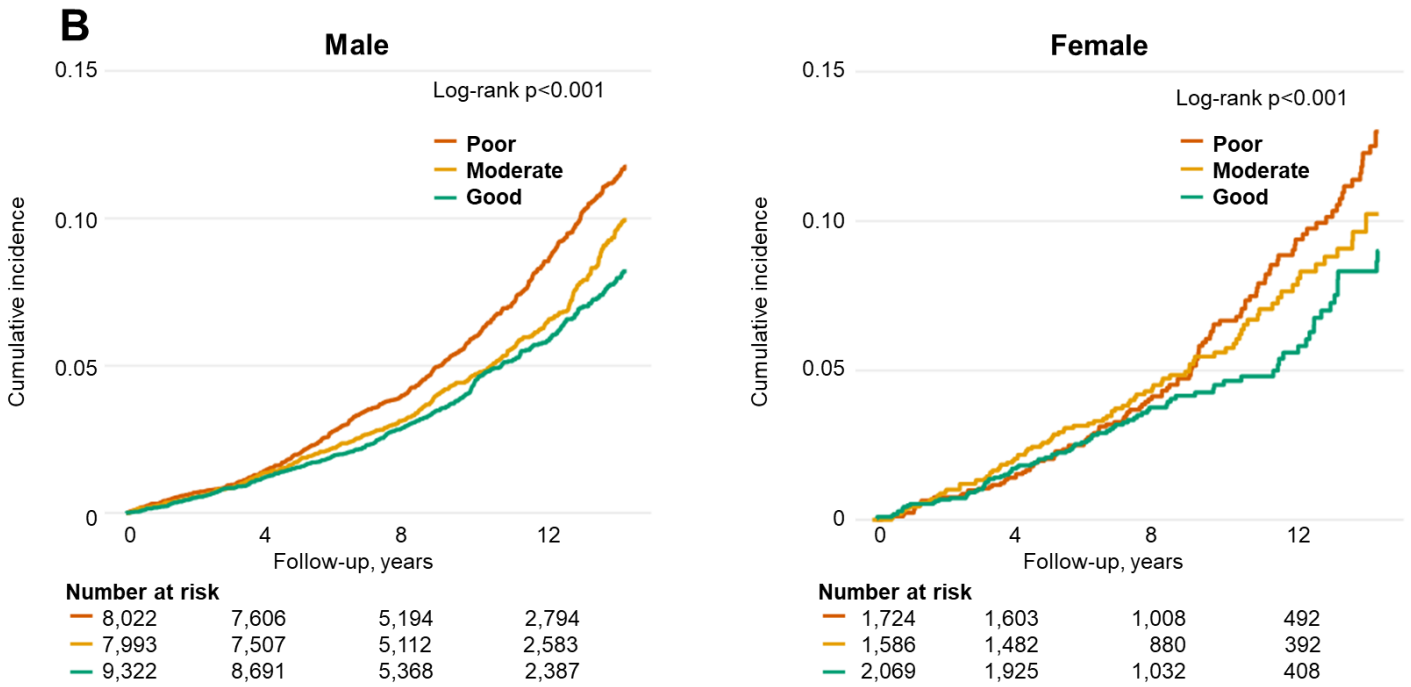

Figure 12. Cumulative incidence of composite cardiovascular events by medication adherence among individuals aged 20–39 years stratified by sex. (Continued)

(A) Adherent vs. non-adherent, (B) by adherence group, (C) by PDC quartile. PDC: proportion of days covered.

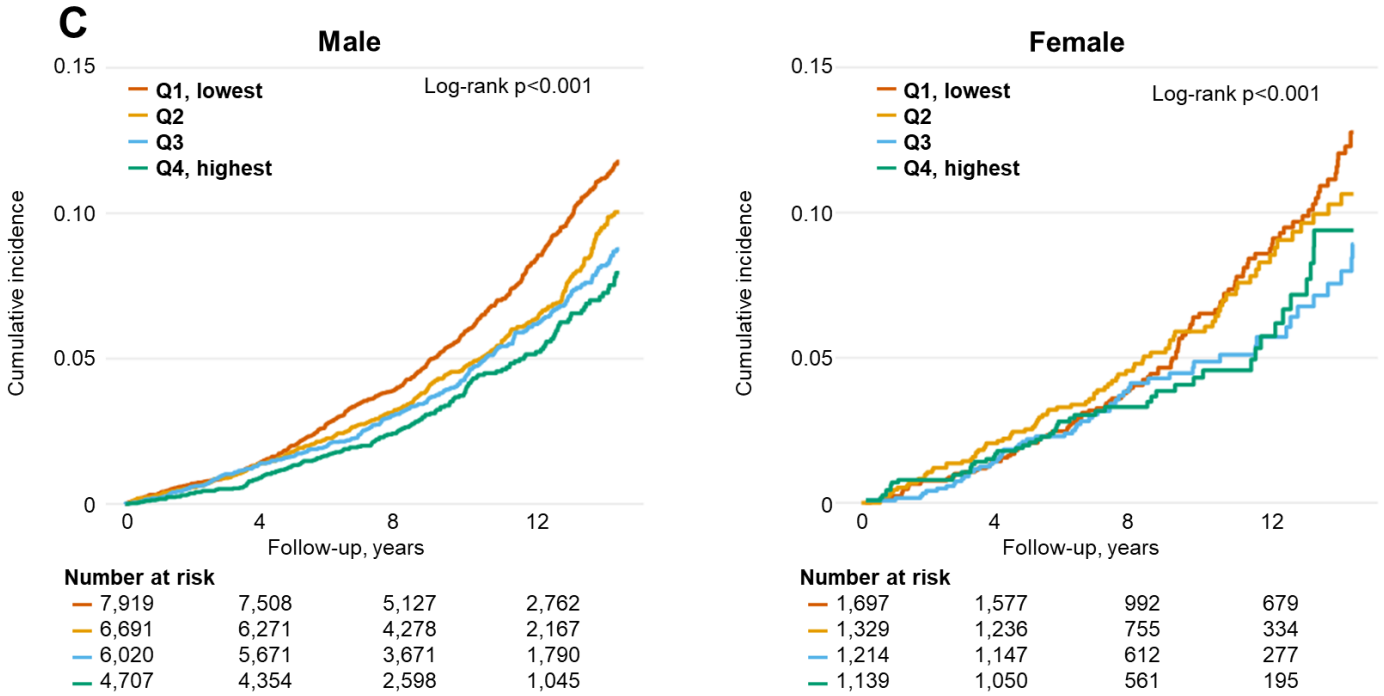

Figure 12. Cumulative incidence of composite cardiovascular events by medication adherence among individuals aged 20–39 years stratified by sex. (Continued)

(A) Adherent vs. non-adherent, (B) by adherence group, (C) by PDC quartile. PDC: proportion of days covered.

Table 21. Medication adherence and composite cardiovascular events among individuals aged 20–39 years stratified by sex

Adherence	Events	P-Y[a]	Rate[b]	Model 1		Model 2		Model 3		Model 4	
				HR	(95%CI)	HR	(95%CI)	HR	(95%CI)	HR	(95%CI)
Male											
Adherent	407	8.5	47.9	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)
Non-adherent	1,018	15.5	65.7	1.30	(1.16–1.46)	1.34	(1.19–1.50)	1.42	(1.26–1.60)	1.41	(1.25–1.59)
Female											
Adherent	93	1.8	51.7	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)
Non-adherent	214	3.0	71.3	1.29	(1.01–1.65)	1.29	(1.08–1.78)	1.44	(1.12–1.85)	1.46	(1.14–1.87)

[a]Person-years (×10,000), [b]incidence rate per 10,000 person-years

Model 1: Unadjusted.

Model 2: Adjusted for age at index, duration from diagnosis to index, index year, and socioeconomic status.

Model 3: Model 2 + initial treatment regimen, drug class, taking insulin therapy, taking GLP-1 RA therapy, Charlson comorbidity index, taking medication for hypertension, taking medication for dyslipidemia, body mass index, fasting blood glucose, systolic blood pressure, and total cholesterol.

Model 4: Model 3 + smoking status, alcohol consumption, and physical activities

HR: hazard ratio; CI: confidence interval, GLP-1 RA: Glucagon-like peptide-1 receptor agonist.

Table 22. Medication adherence and composite cardiovascular events stratified by sex among individuals aged 20–39 years

Adherence	Events	P-Y[a]	Rate[b]	Unadjusted		Adjusted[c]	
				HR	(95%CI)	HR	(95%CI)
By adherence group							
Male							
Good	407	8.5	47.9	1.00	(Reference)	1.00	(Reference)
Moderate	446	7.7	57.9	1.16	(1.01–1.33)	1.24	(1.08–1.42)
Poor	572	7.8	73.3	1.44	(1.27–1.63)	1.60	(1.40–1.82)
Female							
Good	93	1.8	51.7	1.00	(Reference)	1.00	(Reference)
Moderate	94	1.4	67.1	1.21	(0.91–1.62)	1.33	(0.99–1.78)
Poor	120	1.6	75.0	1.36	(1.04–1.78)	1.60	(1.21–2.11)
By PDC quartiles							
Male							
Q4, highest	240	5.4	44.4	1.00	(Reference)	1.00	(Reference)
Q3	335	6.2	54.0	1.17	(0.99–1.38)	1.25	(1.06–1.48)
Q2	387	6.1	63.4	1.36	(1.16–1.60)	1.51	(1.28–1.78)
Q1, lowest	463	6.2	74.7	1.57	(1.34–1.83)	1.79	(1.53–2.10)
Female							
Q4, highest	63	1.2	52.5	1.00	(Reference)	1.00	(Reference)
Q3	66	1.1	60.0	1.07	(0.76–1.51)	1.12	(0.79–1.59)
Q2	81	1.2	67.5	1.29	(0.93–1.79)	1.46	(1.05–2.05)
Q1, lowest	97	1.3	74.6	1.36	(0.99–1.88)	1.63	(1.17–2.27)

[a]Person-years (×10,000), [b]incidence rate per 10,000 person-years

[c]Adjusted for age at index, duration from diagnosis to index, index year, and socioeconomic status, initial antidiabetic regimen, taking insulin therapy, taking GLP-1 RA therapy, drug class, Charlson comorbidity index, taking medication for hypertension, taking medication for dyslipidemia, body mass index, fasting blood glucose, systolic blood pressure, and total cholesterol, smoking status, alcohol consumption, and physical activities.

HR: hazard ratio; CI: confidence interval, PDC: proportion of days covered, GLP-1 RA: Glucagon-Like Peptide-1 Receptor Agonist.

3.3 Comparisons among younger and older subgroups

Of the 74,867 participants, 30,716 (41.0%) were categorized into the younger subgroup (aged 20–39 years) and 44,151 (59.0%) into the older subgroup (aged 40–44 years; Table 23). The mean ages at index were 35.1 ± 3.5 and 42.1 ± 1.4 years, respectively. The younger subgroup had a higher proportion of males (82.5% vs. 73.0%). The median age at diagnosis were 33.2 ± 4.1 and 39.2 ± 3.7 years, and the duration from diagnosis to index was 277 [24–916] and 549 [60–1,617] days in the younger and older subgroups. Moreover, 3.0% and 1.6% had been diagnosed with T1DM, and 71.3% and 65.9% had obesity, respectively. Medication adherence was considerably higher in the older subgroup: median [IQR] PDC 79.2% [54.8–92.3%] vs. 68.8% [43.3–87.9%]. The proportion of participants taking concurrent medications for hypertension or dyslipidemia was higher in the older group.

Approximately one-third of participants started their medication with monotherapy among both younger and older subgroups. Over 80% of participants started their initial regimen including Biguanides in both subgroups. Initial regimen including Dipeptidyl Peptidase-4 (DPP-4) inhibitor was more utilized in older subgroups, whereas regimen including Sulfonylureas was more common in younger subgroups (Table 24).

The increased risk of composite CVD in suboptimal adherence group was similarly observed in younger and older subgroups with a dose-response manner (Figure 13, Table 25). The interaction between age group (20–39 or 40–44 years) and adherence with composite CVD events was not statistically significant: p=0.14 for categorization as adherent/non-adherent and p=0.61 for PDC quartiles. Similar to the results for composite CVD events, significantly increased risks for each cardiovascular event and all-cause death were commonly observed in both younger and older subgroups (Table 26).

Table 23. Comparison of baseline characteristics between participants aged 20–39 and 40–44 years

Characteristics	Total		Aged 20–39 years		Aged 40–44 years	
Total	**74,867**		**30,716**	**(41.0)**	**44,151**	**(59.0)**
Proportion days covered, %	75.1	[49.3–91.0]	68.8	[43.3–87.9]	79.2	[54.8–92.3]
Sex						
Male	57,561	(76.9)	25,337	(82.5)	32,224	(73.0)
Female	17,306	(23.1)	5,379	(17.5)	11,927	(27.0)
Age at index, years	39.2	± 4.3	35.1	± 3.5	42.1	± 1.4
Age at diagnosis, years	36.8	± 4.9	33.2	± 4.1	39.2	± 3.7
Duration from diagnosis to index, days	409	[37–1,313]	277	[24–916]	549	[60–1,617]
Socioeconomic status, quartile						
Q4, highest	18,720	(25.0)	7,684	(25.0)	14,344	(32.5)
Q3	18,715	(25.0)	7,675	(25.0)	10,724	(24.3)
Q2	18,720	(25.0)	7,681	(25.0)	8,807	(20.0)
Q1, lowest	18,712	(25.0)	7,676	(25.0)	10,276	(23.3)
Diagnosed with T1DM	1,631	(2.2)	905	(3.0)	726	(1.6)
Diagnosed with GDM	216	(0.3)	147	(0.5)	69	(0.2)
Taking insulin therapy	296	(0.4)	125	(0.4)	171	(0.4)
Taking GLP-1 RA therapy	22	(0.03)	11	(0.04)	11	(0.02)
Charlson comorbidity index≥1	18,991	(25.4)	6,975	(22.7)	12,616	(27.2)
Taking medication for hypertension	20,529	(27.4)	7,115	(23.2)	13,414	(30.4)
Taking medication for dyslipidemia	27,529	(36.8)	9,813	(32.0)	17,716	(40.1)
Body mass index	26.7	[24.2–29.6]	27.4	[24.7–30.4]	26.4	[24.1–29.1]
Obesity (BMI≥25)	51,008	(68.1)	21,899	(71.3)	29,109	(65.9)
Fasting blood glucose, mg/dL	147	[120–203]	145	[117–204]	147	[122–197]
Systolic blood pressure, mmHg	128	[119–136]	130	[120–138]	127	[118–135]

Table 23. Comparison of baseline characteristics between participants aged 20–39 and 40–44 years (Continued)

Characteristics	Total		Aged 20–39 years		Aged 40–44 years	
Total	**74,867**		**30,716**	**(41.0)**	**44,151**	**(59.0)**
Total cholesterol, mg/dL	207	[180–239]	206	[178–235]	207	[179–237]
Smoking						
Never	28,788	(13,454)	4,388	(38.5)	17,354	(39.3)
Past	12,674	(44,924)	1,824	(16.0)	8,381	(19.0)
Current	33,405	(32,183)	5,179	(45.5)	18,414	(41.7)
Alcohol consumption						
None	26,855	(15,607)	4,176	(36.7)	16,178	(36.6)
1–2 times/week	35,242	(30,176)	5,801	(50.9)	19,277	(43.7)
3 times or more/week	12,770	(11,778)	1,414	(12.4)	8,696	(19.7)
Physical activity						
None	22,033	(16,726)	3,275	(28.8)	12,363	(28.0)
1–2 times/week	22,160	(17,753)	3,545	(31.1)	12,667	(28.7)
3 times or more/week	30,674	(23,082)	4,571	(40.1)	19,121	(43.3)

Numbers represent mean ± standard deviation, median [interquartile range], or frequency (%).

T1DM: type 1 diabetes mellitus, GDM: gestational diabetes mellitus, BMI: body mass index, GLP: Glucagon-like peptide-1.

Table 24. Comparison of initial treatment regimens between participants aged 20–39 and 40–44 years

Initial treatment regimen	Aged 20–39		Aged 40–44	
	Number	(%)	Number	(%)
Total number of participants	**30,716**		**44,151**	
Drug class				
Alpha-glucosidase inhibitors	1,922	(6.3)	1,254	(2.8)
DPP-4 inhibitors	9,902	(32.2)	18,636	(42.2)
Meglitinides	555	(1.8)	338	(0.8)
Biguanides	25,389	(82.7)	39,178	(88.7)
Thiazolidinediones	1,972	(6.4)	2,667	(6.0)
SGLT-2 inhibitors	980	(3.2)	1,846	(4.2)
Sulfonylureas	14,028	(45.7)	15,024	(34.0)
Therapy type				
Monotherapy	10,463	(34.1)	14,974	(33.9)
Combination of two or more drugs	20,253	(65.9)	29,177	(66.1)

DPP-4: Dipeptidyl Peptidase-4; SGLT-2: Sodium-Glucose Cotransporter-2.

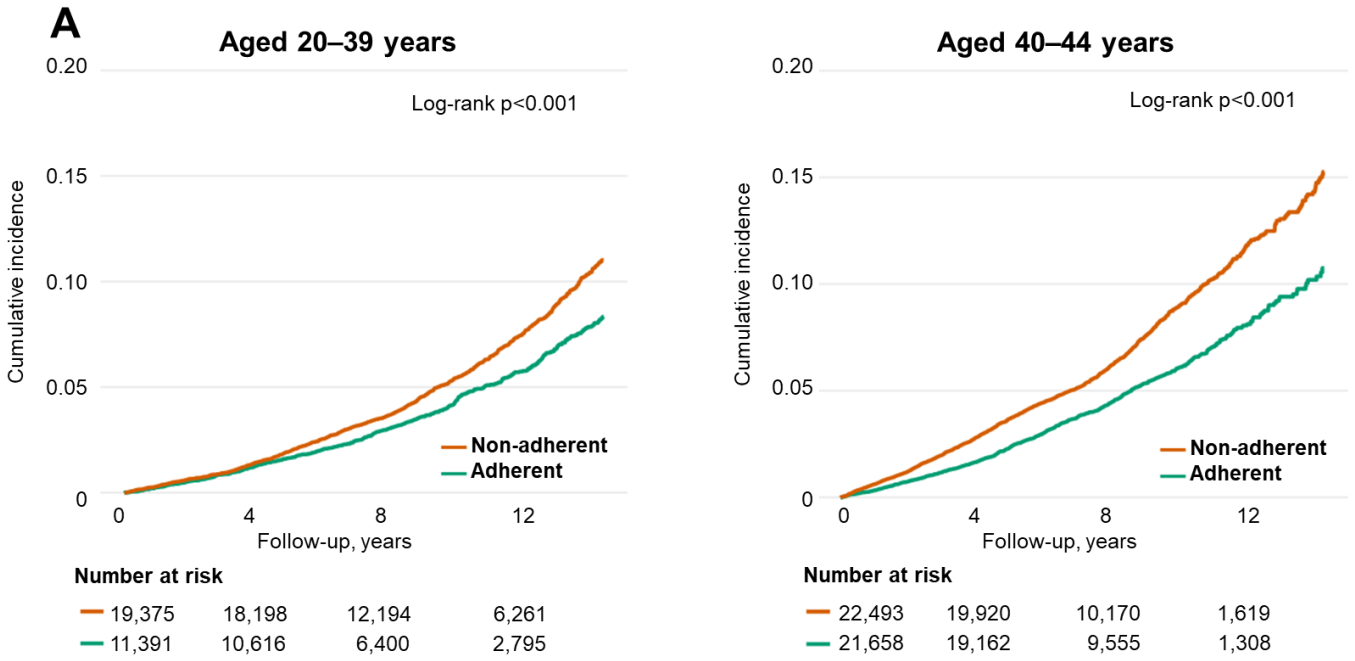

Figure 13. Comparison of the cumulative incidence of composite cardiovascular events between younger and older subgroups.
(A) Adherent vs. non-adherent; (B) by adherence group; (C) by PDC quartile. PDC: proportion of days covered.

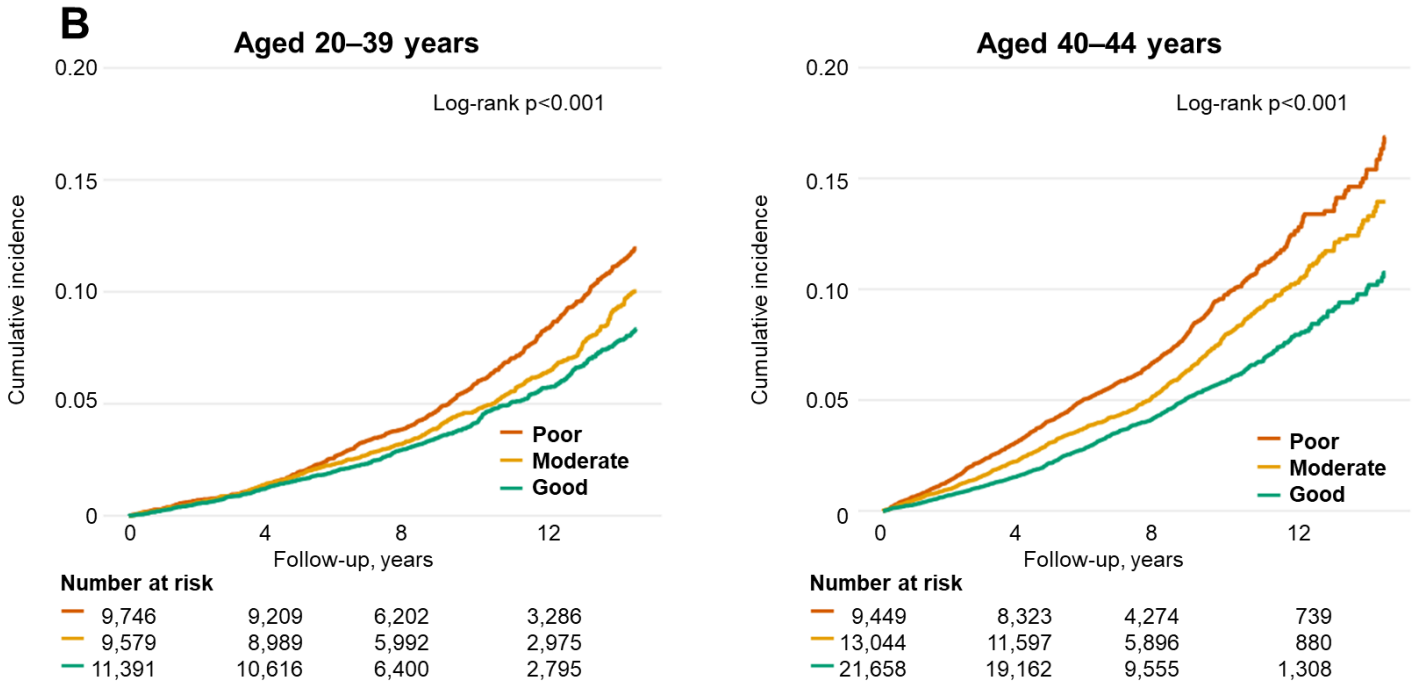

Figure 13. Comparison of the cumulative incidence of composite cardiovascular events between younger and older subgroups. (Continued)

(A) Adherent vs. non-adherent; (B) by adherence group; (C) by PDC quartile. PDC: proportion of days covered.

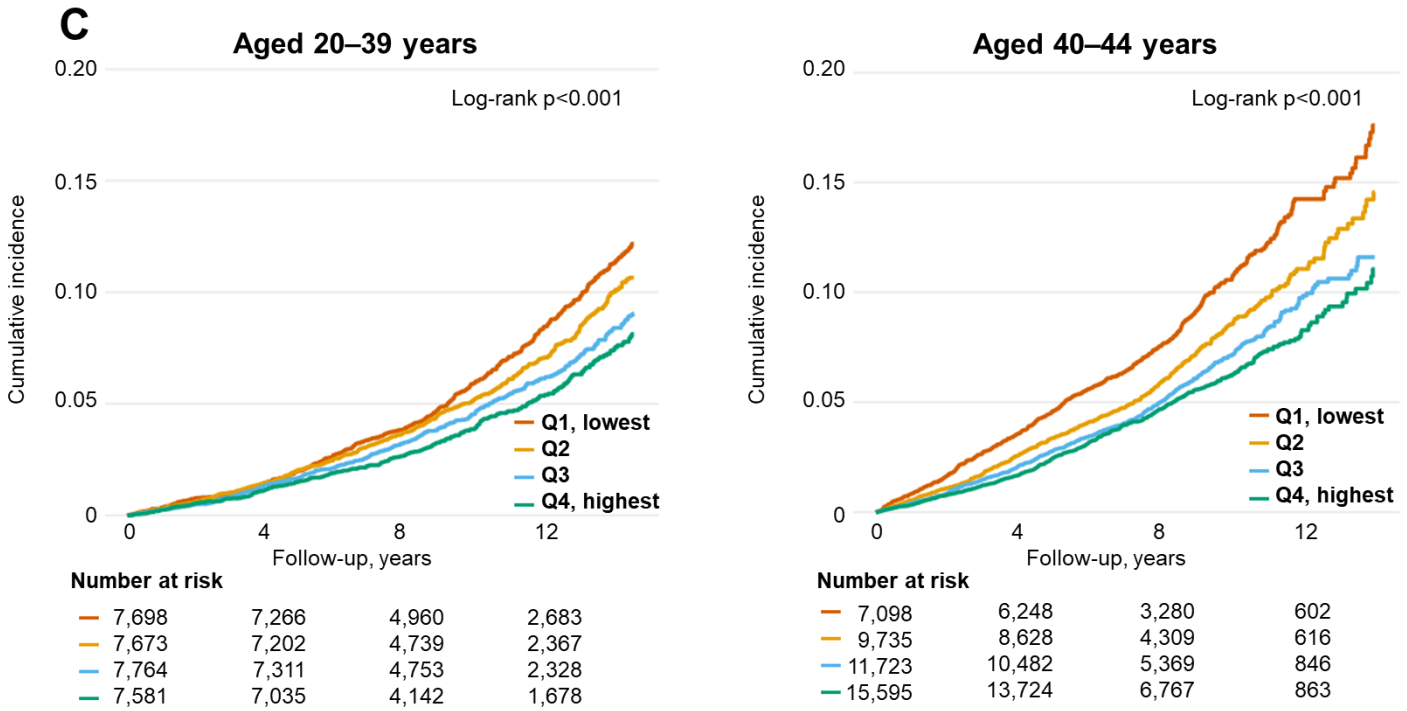

Figure 13. Comparison of the cumulative incidence of composite cardiovascular events between younger and older subgroups. (Continued)

(A) Adherent vs. non-adherent; (B) by adherence group; (C) by PDC quartile. PDC: proportion of days covered.

Table 25. Comparison of the results of composite cardiovascular events between individuals aged 20–39 and 40–44 years

Adherence	Events	P-Y[a]	Rate[b]	Unadjusted		Adjusted[c]	
				HR	(95%CI)	HR	(95%CI)
Adherent vs. non-adherent							
Individuals aged 20–39							
Adherent	500	10.2	49.0	1.00	(Reference)	1.00	(Reference)
Non-adherent	1,232	18.5	66.6	1.30	(1.17–1.44)	1.42	(1.27–1.57)
Individuals aged 40–44							
Adherent	1,010	16.4	61.6	1.00	(Reference)	1.00	(Reference)
Non-adherent	1,560	17.2	90.7	1.46	(1.35–1.58)	1.45	(1.34–1.58)
By adherence group							
Individuals aged 20–39							
Good	500	10.2	49.0	1.00	(Reference)	1.00	(Reference)
Moderate	540	9.1	59.3	1.16	(1.03–1.32)	1.25	(1.11–1.42)
Poor	692	9.4	73.6	1.42	(1.27–1.60)	1.59	(1.41–1.79)
Individuals aged 40–44							
Good	1,010	16.4	61.6	1.00	(Reference)	1.00	(Reference)
Moderate	811	10.0	81.1	1.34	(1.22–1.47)	1.32	(1.20–1.45)
Poor	749	7.3	102.6	1.68	(1.52–1.85)	1.65	(1.49–1.81)
By PDC quartiles							
Individuals aged 20–39							
Q4, highest	303	6.7	45.2	1.00	(Reference)	1.00	(Reference)
Q3	401	7.3	54.9	1.15	(0.99–1.33)	1.22	(1.05–1.42)
Q2	468	7.3	64.1	1.34	(1.16–1.55)	1.49	(1.29–1.73)
Q1, lowest	560	7.5	74.7	1.53	(1.33–1.75)	1.75	(1.52–2.02)
Individuals aged 40–44							
Q4, highest	486	8.1	60.0	1.00	(Reference)	1.00	(Reference)
Q3	540	8.5	63.5	1.04	(0.92–1.18)	1.03	(0.91–1.16)
Q2	693	8.5	81.5	1.36	(1.21–1.52)	1.35	(1.20–1.52)
Q1, lowest	851	8.5	100.1	1.64	(1.47–1.84)	1.62	(1.45–1.82)

[a]Person-years (×10,000), [b]incidence rate per 10,000 person-years

[c]Adjusted for age at index, duration from diagnosis to index, index year, and socioeconomic status, initial antidiabetic regimen, taking insulin therapy, taking GLP-1 RA therapy, drug class, Charlson comorbidity index, taking medication for hypertension, taking medication for dyslipidemia, body mass index, fasting blood glucose, systolic blood pressure, and total cholesterol, smoking status, alcohol consumption, and physical activities.

HR: hazard ratio; CI: confidence interval, PDC: proportion of days covered, GLP-1 RA: Glucagon-Like Peptide-1 Receptor Agonist.

Table 26. Comparison of end-point-specific analyses between individuals aged 20–39 and 40–44 years

Adherence	Events	P-Y[a]	Rate[b]	Unadjusted		Adjusted[c]	
				HR	(95%CI)	HR	(95%CI)
Myocardial infarction							
Individuals aged 20-39							
Adherent	128	10.3	12.4	1.00	(Reference)	1.00	(Reference)
Non-adherent	313	18.8	16.6	1.29	(1.05–1.58)	1.33	(1.07–1.64)
Individuals aged 40-44							
Adherent	247	16.6	14.9	1.00	(Reference)	1.00	(Reference)
Non-adherent	418	17.6	23.7	1.56	(1.36–1.86)	1.55	(1.32–1.82)
Stroke							
Individuals aged 20-39							
Adherent	126	10.3	12.2	1.00	(Reference)	1.00	(Reference)
Non-adherent	345	18.8	18.4	1.42	(1.16–1.75)	1.53	(1.24–1.89)
Individuals aged 40-44							
Adherent	263	16.6	15.8	1.00	(Reference)	1.00	(Reference)
Non-adherent	439	17.6	24.9	1.57	(1.35–1.83)	1.55	(1.33–1.81)
Heart failure							
Individuals aged 20-39							
Adherent	285	10.3	27.7	1.00	(Reference)	1.00	(Reference)
Non-adherent	682	18.7	36.5	1.24	(1.08–1.43)	1.42	(1.23–1.63)
Individuals aged 40-44							
Adherent	589	16.6	35.5	1.00	(Reference)	1.00	(Reference)
Non-adherent	830	17.5	47.4	1.32	(1.19–1.47)	1.37	(1.23–1.52)
Cardiovascular death							
Individuals aged 20-39							
Adherent	47	10.4	4.5	1.00	(Reference)	1.00	(Reference)
Non-adherent	176	18.9	9.3	1.94	(1.41–2.68)	1.97	(1.42–2.74)
Individuals aged 40-44							
Adherent	135	16.7	8.1	1.00	(Reference)	1.00	(Reference)
Non-adherent	288	17.7	16.3	2.00	(1.63–1.45)	1.67	(1.35–2.06)

Table 26. Comparison of end-point-specific analyses between individuals aged 20–39 and 40–44 years (Continued)

Adherence	Events	P-Y[a]	Rate[b]	Unadjusted		Adjusted[c]	
				HR	(95%CI)	HR	(95%CI)
All-cause death							
Individuals aged 20–39							
Adherent	188	10.4	18.1	1.00	(Reference)	1.00	(Reference)
Non-adherent	524	18.9	27.7	1.48	(1.25–1.74)	1.49	(1.26–1.77)
Individuals aged 40–44							
Adherent	443	16.7	26.5	1.00	(Reference)	1.00	(Reference)
Non-adherent	879	17.7	50.0	1.85	(1.65–2.08)	1.52	(1.35–1.71)

[a]Person-years (×10,000), [b]incidence rate per 10,000 person-years

[c]Adjusted for sex, age at index, duration from diagnosis to index, index year, socioeconomic status initial treatment regimen, drug class, taking insulin therapy, taking GLP-1 RA therapy, Charlson comorbidity index, taking medication for hypertension, taking medication for dyslipidemia, body mass index, fasting blood glucose, systolic blood pressure, total cholesterol, smoking status, alcohol consumption, and physical activities.

HR: hazard ratio, CI: confidence interval, GLP-1 RA: Glucagon-like peptide-1 receptor agonist.

3.4 Factors associated with good adherence

In the univariate analysis, being female, being older age at index, having longer duration from diagnosis to index, being indexed in the latter period (i.e., 2014–2021), being of higher socioeconomic status, not having diagnosed with T1DM, taking concurrent medication for hypertension or dyslipidemia, having obesity, being non-smoker (never-smoker or quitter), and being physically active were associated with good medication adherence (Table 27).

After adjusting for all potential factors in the multivariable model, most factors that showed associations in the univariate analysis maintained independent associations with good adherence. Among these, older age at the index, initiating treatment with a combination therapy of three or more drug classes, and taking medication for hypertension were notably associated with a higher likelihood of good adherence. The multivariable-adjusted odds ratios (95% CIs) for good adherence were 2.18 (1.98–2.40) for participants aged 40–44 years compared to those aged 20–29 years, 2.18 (1.19–4.00) for participants whose initial regimen included combination therapy with three or more drug classes compared to those on monotherapy, and 1.75 (1.69–1.80) for participants concurrently taking medication for hypertension compared to those not taking it. Smoking quitters demonstrated better odds of good adherence compared to current smokers, and even in comparison to never-smokers. Non-alcohol drinkers and physically active participants also exhibited a higher odds of good adherence.

In the univariate analyses, all drug classes showed either negative or positive associations with good medication adherence. However, after adjusting for all potential factors simultaneously, most of these associations were no longer significant.

Table 27. Factors associated with good medication adherence

Characteristics	No. of participants	No. (%) of good adherence		Univariate OR (95% CI)		Multivariable OR (95% CI)	
Sex							
Male	57,561	24,719	(42.9)	1.00	(Reference)	1.00	(Reference)
Female	17,306	8,330	(48.1)	1.23	(1.19–1.28)	1.19	(1.13–1.24)
Age at index							
20–29	2,425	650	(26.8)	1.00	(Reference)	1.00	(Reference)
30–34	8,505	1,805	(21.2)	1.34	(1.21–1.49)	1.31	(1.18–1.46)
35–39	19,786	7,936	(40.1)	1.83	(1.66–2.01)	1.70	(1.54–1.87)
40–44	44,151	21,658	(49.1)	2.63	(2.40–2.88)	2.18	(1.98–2.40)
Duration from diagnosis to medication initiation							
Q1, shortest	18,712	7,354	(39.3)	1.00	(Reference)	1.00	(Reference)
Q2	18,720	8,063	(43.1)	1.17	(1.12–1.22)	1.10	(1.06–1.15)
Q3	18,715	8,678	(46.4)	1.34	(1.28–1.39)	1.20	(1.15–1.25)
Q4, longest	18,720	8,954	(47.8)	1.42	(1.66–1.48)	1.17	(1.12–1.22)
Index year							
2003–2013	40,582	16,681	(41.1)	1.00	(Reference)	1.00	(Reference)
2014–2021	34,285	16,368	(47.7)	1.31	(1.27–1.35)	1.03	(1.00–1.07)
Socioeconomic status							
Q1, lowest	18,712	7,626	(40.8)	1.00	(Reference)	1.00	(Reference)
Q2	18,720	7,718	(41.2)	1.02	(0.98–1.06)	1.05	(1.01–1.10)
Q3	18,715	8,550	(45.7)	1.22	(1.17–1.27)	1.16	(1.11–1.21)
Q4, highest	18,720	9,155	(48.9)	1.39	(1.34–1.50)	1.19	(1.14–1.25)
Diagnosed with T1DM							
Yes	1,631	660	(40.5)	1.00	(Reference)	1.00	(Reference)
No	73,236	32,389	(44.2)	1.17	(1.06–1.29)	1.02	(0.92–1.14)

Table 27. Factors associated with good medication adherence (Continued)

Characteristics	No. of participants	No. (%) of good adherence		Univariate OR (95% CI)		Multivariate OR (95% CI)	
Diagnosed with GDM							
Yes	216	88	(40.7)	1.00	(Reference)	1.00	(Reference)
No	74,651	32,961	(44.2)	1.15	(0.88–1.51)	1.05	(0.80–1.39)
Comorbidity							
Present	18,991	8,478	(44.6)	1.00	(Reference)	1.00	(Reference)
Absent	55,876	24,571	(44.0)	1.03	(0.99–1.06)	0.97	(0.94–1.00)
Taking medication for hypertension							
No	54,338	21,739	(40.0)	1.00	(Reference)	1.00	(Reference)
Yes	20,529	11,310	(55.1)	1.84	(1.78–1.90)	1.75	(1.69–1.80)
Taking medication for dyslipidemia							
No	47,338	19,693	(41.6)	1.00	(Reference)	1.00	(Reference)
Yes	27,529	13,356	(48.5)	1.32	(1.28–1.36)	1.09	(1.06–1.13)
Obesity (BMI≥25)							
No	23,859	10,182	(42.7)	1.00	(Reference)	1.00	(Reference)
Yes	51,008	22,867	(44.8)	1.09	(1.06–1.13)	0.98	(0.95–1.01)
Smoking							
Current	33,405	13,511	(40.4)	1.00	(Reference)	1.00	(Reference)
Never	28,788	13,269	(46.1)	1.25	(1.22–1.30)	1.15	(1.11–1.20)
Past	12,674	6,269	(49.5)	1.44	(1.38–1.50)	1.31	(1.26–1.37)
Alcohol consumption							
Drinker	48,012	20,697	(43.1)	1.00	(Reference)	1.00	(Reference)
Non-drinker	26,855	12,352	(46.0)	1.12	(1.09–1.16)	1.10	(1.07–1.14)
Physical activity							
Inactive	44,193	18,878	(42.7)	1.00	(Reference)	1.00	(Reference)
Active	30,674	14,171	(46.2)	1.15	(1.12–1.18)	1.07	(1.04–1.11)

Table 27. Factors associated with good medication adherence (Continued)

Characteristics	No. of participants	No. (%) of good adherence		Univariate OR (95% CI)		Multivariate OR (95% CI)	
Initial treatment regimen							
Mono-therapy	25,437	10,679	(42.0)	1.00	(Reference)	1.00	(Reference)
Combination therapy of two	40,225	17,572	(43.7)	1.07	(1.04–1.11)	1.29	(0.95–1.74)
Combination therapy of three or more	9,205	4,798	(52.1)	1.51	(1.43–1.58)	2.18	(1.19–4.00)
Drag class of initial treatment							
Alpha-glucosidase inhibitors							
Not taking	71,691	31,906	(44.5)	1.00	(Reference)	1.00	(Reference)
Taking	3,176	1,143	(36.0)	0.70	(0.65–0.76)	0.65	(0.48–0.89)
DPP-4 inhibitors							
Not taking	46,329	19,860	(42.9)	1.00	(Reference)	1.00	(Reference)
Taking	28,538	13,189	(46.2)	1.15	(1.11–1.18)	0.80	(0.59–1.08)
Meglitinides							
Not taking	73,974	32,737	(44.3)	1.00	(Reference)	1.00	(Reference)
Taking	893	312	(34.9)	0.67	(0.59–0.78)	0.72	(0.52–1.00)
Biguanides							
Not taking	10,300	3,864	(37.5)	1.00	(Reference)	1.00	(Reference)
Taking	64,567	29,185	(45.2)	1.37	(1.32–1.43)	0.98	(0.72–1.32)
Thiazolidinediones							
Not taking	70,228	30,716	(43.7)	1.00	(Reference)	1.00	(Reference)
Taking	4,639	2,333	(50.3)	1.30	(1.23–1.38)	1.02	(0.74–1.38)
SGLT-2 inhibitors							
Not taking	72,041	31,354	(43.5)	1.00	(Reference)	1.00	(Reference)
Taking	2,826	1,695	(60.0)	1.94	(1.80–2.10)	1.34	(0.98–1.82)
Sulfonylurea							
Not taking	45,815	20,592	(44.9)	1.00	(Reference)	1.00	(Reference)
Taking	29,052	12,457	(42.9)	0.92	(0.89–0.95)	0.82	(0.61–1.11)

OR: odds ratio, CI: confidence interval, T1DM: type 1 diabetes mellitus, GDM: gestational diabetes mellitus, BMI: body mass index, DPP-4: Dipeptidyl Peptidase-4; SGLT-2: Sodium-Glucose Cotransporter-2.

4. DISCUSSION

4.1 Main findings

This retrospective study evaluated Korean national healthcare claims data, focusing on young adults with T2DM who began treatment with oral antidiabetic agents. Non-adherence to medication in the first year was found to be associated with a significantly higher risk of future CVD events. Suboptimal medication adherence was associated with a higher risk of composite CVD events with a dose-response relationship. Among all types of events, including hospitalization due to MI, stroke, or HF, cardiovascular death, and all-cause deaths, individuals in the non-adherence group consistently demonstrated an elevated risk compared to those who adhered to their treatment regimen. All cases of all-cause and cardiovascular deaths occurred by 57 years of age, considered premature death.

When comparing younger (aged 20–39 years) and older (40–44 years) subgroups, Age at diagnosis was younger and the time from first diagnosis to medication initiation was considerably shorter in younger subgroup. Also, medication adherence was higher in the older group. A higher risk of CVD associated with suboptimal medication adherence was more prominent in the older subgroup: individuals with poor adherence (PDC<50) had 65% and 59% increased risks compared to good adherence groups in the older and younger subgroups, respectively. When classified into PDC quartiles, the younger subgroup exhibited a pronounced higher risk of CVD, with a 75% increased risk in the lowest adherence group, while the lowest PDC quartile group in the older subgroup had a 62% higher risk. The interaction between adherence and age group (20–39/40–44 years) was not statistically significant.

Older age at the index date, initiating treatment with a combination therapy of three or more drug classes, and taking medication for hypertension were strongly associated with a higher

likelihood of good adherence. In the univariate analyses, all drug classes showed either negative or positive associations with good medication adherence. However, after adjusting for all potential factors simultaneously, most of these associations were no longer significant.

4.2 Previous studies on medication adherence and cardiovascular events in patients with type 2 diabetes

While many studies have explored the association between medication adherence and cardiovascular events in patients with T2DM, research specifically focusing on younger populations remains limited[30,31].

4.2.1 Studies conducted in Korea

Several studies on the Korean population have attempted to assess the association between medication adherence and cardiovascular events in patients with T2DM patients; however, to our knowledge, none have specifically focused on examining this association in the younger Korean population.

A study utilizing the Korean NHIS database found that non-adherence, measured by the medication possession ratio (MPR), during the first two years after the initial prescription significantly increased the risk of hospitalization and mortality in the third year compared to the adherent group[32]. Hospitalization, the outcome of interest, was defined as hospital admission with a primary diagnosis of diabetes (ICD-10: E10–E14), cardiovascular disease—including ischemic heart disease (I20–I25) and stroke (I60–I64)—or renal disease (N10–N12, N15–N19) during the

third year of the 3-year follow-up period. The adjusted odds ratios were 1.26 (95% CI: 1.08–1.47) for hospitalization and 1.40 (95% CI: 1.01–1.95) for mortality.

Another study using Korean NHIS data involving 65,076 patients with newly diagnosed T2DM aged≥40 years revealed that low medication adherence within the first two years of diagnosis was associated with an elevated risk of long-term all-cause mortality and cardiovascular events, including MI and cerebrovascular disease[33]. Specifically, the lowest medication adherence (PDC ≤20%) was associated with a 45% higher mortality rate and a 41% increased likelihood of developing cerebrovascular disease. However, the higher risk of MI was not statistically significant.

4.2.2 Studies conducted worldwide

Even when expanding the scope of the literature globally, research specifically targeting younger populations remains scarce. A systematic review published in 2016[30] reported that good adherence (≥80% of several indicators) was associated with 28% reduction in all-cause mortality risk (relative risk (RR) [95% CI]: 0.72 [0.62–0.82]; among three studies[32,34,35]) and 10% reduction in hospitalization risk (RR: 0.90 [0.87–0.94]; among seven studies[32,34–39]). Nonetheless, only one study reported outcomes specifically related to CVD and adherence.

Another systematic review conducted in 2021 reported that better adherence/persistence was associated with fewer microvascular and/or macrovascular outcomes[31]. However, the studies showed poor consistency regarding which outcomes were improved.

4.3 Heterogeneity in young adults

Previous studies have reported that a younger age of T2DM diagnosis is associated with higher CVD risks[40–43]. The interaction between age group and adherence with CVD events was not statistically significant in this study. However, an opposite phenomenon between younger (initiated medication between 20–39 years) and older (initiated medication between 40–44 years) subgroups was consistently observed across different adherence categorizations: adjusted HR was higher than unadjusted HR among the younger subgroup, whereas adjusted HR was slightly lower than unadjusted HR among the older subgroup. The crude incidence rate of CVD and medication adherence were both lower among the younger subgroup compared to older subgroup, consistent with previous research[25–27,44]. Age at diagnosis was considerably younger in the younger subgroup at 33.2 ± 4.1 years, compared to 39.2 ± 3.7 years in the older subgroup. Our results might reflect underlying heterogeneity in diabetes among younger patients, possibly due to etiological differences[45–47]. Therefore, further studies exploring the relationship between medication adherence and CVD in young adults could enhance our understanding of these dynamics.

4.4 Factors associated with good medication adherence

In the present study, higher odds of good adherence were particularly prominent among participants who were older at the index date, initiated treatment with a combination therapy of three or more drug classes, or were taking medication for hypertension. Factors attributable to adherence are known to be multifactorial; demographic, socioeconomic, clinical, and lifestyle-related factors may play crucial role in determining medication adherence[22]. Previous studies have identified older age, male sex, higher income, and higher education as potential factors associated with better adherence[22]. This partially agreed with our results, as older age at index and higher income were

associated with higher adherence. However, adherence was higher among females than males in this study. This finding must be interpreted with caution, as a substantial number of female participants were excluded due to missing data from general health check-ups, underscoring the limitations of the database.

It has been reported that patients taking additional medications for conditions such as hypertension or dyslipidemia tend to adhere more consistently to their prescribed treatments[9]. In our study, the use of concurrent medications for hypertension or dyslipidemia was associated with better adherence, particularly in the case of hypertension. This higher adherence is often attributed to increased awareness and motivation due to the heightened risk of cardiovascular events linked to these comorbidities. Additionally, individuals already accustomed to daily medication routines may find it easier to incorporate new treatments, while those not taking other medications might take longer to develop consistent habits. Comprehensive management of blood sugar, blood pressure, and cholesterol, along with personalized therapies to improve cardiovascular outcomes, is essential for reducing overall risk in diabetes management[48]. Encouraging adherence through personalized treatment plans and patient education remains crucial.

The proportion of participants adhering to their medication significantly increased throughout the study period, rising from 20.7% in 2003 to 53.1% in 2021 among young adults aged 20–44 years. One factor contributing to this trend may be the introduction of newly developed drugs, such as DPP-4 inhibitors, Sodium-Glucose Cotransporter-2 (SGLT-2) inhibitors, and fixed-dose combination drugs. Reduced safety concerns, lower physical and mental burdens, and higher treatment satisfaction and motivation are generally recognized as key factors promoting better adherence[22]. In this study, 38.1% of the participants aged 20–44 years initiated treatment with DPP-4 inhibitor monotherapy or combination therapy of DPP-4 inhibitors and Biguanides. Since this study included individuals diagnosed until the end of 2015, fewer patients were initiated on SGLT-

2 inhibitors. This drug class is particularly valued for younger patients with obesity due to its ability to reduce the risk of cardiovascular events and aid weight management. Hence, relatively newly introduced medications, such as DPP-4 and SGLT-2 inhibitors, are expected to provide desirable clinical benefits and reduce the burden on patients[18]. In this study, univariate analysis assessing factors associated with good adherence demonstrated a significant association between these drug classes and good adherence. However, in the multivariable analysis adjusting for all potential factors, the association was no longer significant. This suggests that patients who initiated treatment with these drug classes may have had other factors contributing to better adherence.

Furthermore, it is suggested that single-pill, fixed-dose combination drugs may improve medication adherence by reducing the physical and financial burden of medication[49]. Individuals using concurrent medications may have a higher awareness of the importance of treatment, leading to better adherence. Conversely, those taking a greater number of pills may experience physical difficulty in managing their medications, resulting in lower adherence. Although we did not account for the number of pills taken daily or per administration due to methodological limitations, approximately 30% of participants were observed to initiate treatment with one or more combination drugs. As single-pill fixed-dose combination drugs are now available not only for single diseases but also for multiple diseases, future studies incorporating adherence to combination drugs addressing multiple conditions could offer valuable insights.

4.5. Strengths and limitations

The strength of this study includes its utilization of nationwide claim data from a universal single-payer, allowing the seamless handling of comprehensive information, including mortality, diagnoses, prescriptions, lifestyles, and laboratory data.

However, several limitations must be addressed. First, medication adherence was assessed using PDC, which is based on prescription data and does not fully capture whether medication is taken. While the most accurate method for measuring adherence involves pharmacokinetic modeling, which directly quantifies drug concentrations in a patient's blood or urine[40], this approach is not generally applicable. Hence, indirect measures such as the MPR and PDC are widely used as alternatives for evaluating medication adherence[50]. In this study, most participants were prescribed multiple medications and followed complex prescription patterns. Consequently, PDC was selected as the measure of adherence, as it allows for a more accurate assessment in the context of complex medication regimens. Nonetheless, it is essential to recognize that PDC may overestimate adherence rates[51], and the bias direction caused by adherence measures can vary[52].

Second, many participants were excluded from the analyses due to a lack of data regarding general health check-ups. This could introduce bias, as individuals with easier access to free health check-ups, such as employed and older individuals, may have been more likely to be included in the study. To address this, we performed a sensitivity analysis with participants excluded from the main analysis but had all essential data, excluding general health check-up results (Appendix 9 and 10). The sensitivity analysis showed substantially robust findings.

Third, we did not incorporate information on prescriptions not covered by national health insurance. In Korea, T2DM treatment follows clinical guidelines and standard care protocols, favoring medications that align with evidence-based, cost-effective therapies covered by insurance. Thus, prescriptions for diabetes treatments not covered by insurance are rare and, thus, did not significantly impact the results.

Fourth, although this study includes a relatively long follow-up period of 14 years, it does not provide information on cardiovascular risk beyond that timeframe. Medication adherence is anticipated to affect the risk of CVD and mortality not only in the short term but throughout the

lifespan. Therefore, further studies with extended follow-up periods are warranted to comprehensively assess lifetime cardiovascular risk.

Fifth, our hypothesis emphasizes medication adherence during the first year after treatment initiation, as this period is critical for the long-term success of subsequent treatments. In this study, participants who adhered to their medication regimen during the first year were likelier to maintain good adherence in the following years. However, significant changes in adherence during the second and subsequent years may have occurred, potentially influencing the risk of CVD events. Future research that accounts for transitions in adherence over the follow-up period could offer deeper insights into this relationship.

5. CONCLUSIONS

In this analysis of national healthcare claims data focusing on young adults with T2DM started oral antidiabetic medication, we found that non-adherence to medication in the first year markedly increased the risk of future CVD events. Suboptimal medication adherence was associated with a heightened risk of CVD, displaying a dose-response relationship that suggests more significant non-adherence leads to increased CVD risks. Considering the rising prevalence of T2DM among young adults, which escalates the risk of vascular complications and impacts working-age individuals, comprehensive management may help minimize individual and societal burdens.

APPENDICES

Appendix 1. List of ICD-10 codes used for eligibility check, outcome ascertainments, and covariate

Appendix 2a. List of pharmaceutical code of oral antihyperglycemic agents (Single-agent drugs)

Appendix 2b. List of pharmaceutical code of oral antihyperglycemic agents (Combination drugs)

Appendix 3. List of pharmaceutical code of fixed-dose combination drug for diabetes and hypertension

Appendix 4. List of pharmaceutical code of fixed-dose combination drug for diabetes and dyslipidemia

Appendix 5. List of pharmaceutical code of oral antihypertensive agents

Appendix 6. List of pharmaceutical code of oral lipid-lowering agents

Appendix 7. List of pharmaceutical code of fixed-dose combination drug for hypertension and dyslipidemia

Appendix 8. List of pharmaceutical code of insulin and GLP-1

Appendix 9. Comparison of general characteristics between main and sensitivity analyses

Appendix 10. Comparison of the result between main and sensitivity analyses

Appendix 1. list of ICD-10 codes used for eligibility check, outcome ascertainments, and covariate

ICD-10 codes	Disease entity
Type 2 diabetes mellitus	
E11	Type 2 diabetes mellitus
Type 1 diabetes mellitus	
E10	Type 1 diabetes mellitus
Gestational diabetes	
O24.4	Diabetes mellitus arising in pregnancy
Myocardial infarction	
I21	Acute myocardial infarction
I22	Subsequent myocardial infarction
I23	Certain current complications following acute myocardial infarction
Stroke	
I60	Subarachnoid haemorrhage
I61	Intracerebral haemorrhage
I62	Other nontraumatic intracranial haemorrhage
I63	Cerebral infarction
I64	Stroke, not specified as haemorrhage or infarction
Heart failure	
I50	Heart failure
Cardiovascular disease	
I00-99	Diseases of the circulatory system

Appendix 2a. List of pharmaceutical code of oral antihyperglycemic agents (Single-agent drugs)

Drug class	Code[a]	Active ingredient
Alpha-glucosidase inhibitors	1006	Acarbose
	2490	Voglibose
DPP-4 inhibitors	5008	Vildagliptin
	5011	Sitagliptin Phosphate Hydrate
	6133	Saxagliptin Hydrate
	6164	Linagliptin
	6191	Gemigliptin Tartrate Sesquihydrate
	6242	Alogliptin Benzoate
	6273	Teneligliptin Hydrobromide Hydrate
	6396	Anagliptin
	6453	Evogliptin Tartrate
	6858	Vildagliptin Hydrochloride
	6953	Teneligliptin Hydrochloride Hydrate
	6954	Teneligliptin Ditosylate Dihydrate
	7012	Vildagliptin Nitrate
Meglitinides	3795	Repaglinide
	4302	Nateglinide
	4861	Mitiglinide Calcium Hydrate
Biguanides	1915	Metformin Hydrochloride
SGLT-2 inhibitors	5273	Dapagliflozin Propanediol Hydrate
	6282	Empagliflozin
	6361	Ipragliflozin L-Proline
	6743	Ertugliflozin L-Pyroglutamic Acid
	7129	Dapagliflozin Formate
Thiazolidinediones	4319	Pioglitazone Hydrochloride
	5259	Lobeglitazone Sulfate
Sulfonylureas	1654	Glibenclamide
	1656	Gliclazide
	1657	Glimepiride
	1658	Glipizide

[a]The 4-digit code represents the first four digits of the original active ingredients code indexed in the reimbursable drugs list, available at: https://www.hira.or.kr/bbsDummy.do?pgmid=HIRAA030014050000.
DPP-4: Dipeptidyl Peptidase-4; SGLT-2: Sodium-Glucose Cotransporter-2.

Appendix 2b. List of pharmaceutical code of oral antihyperglycemic agents (Combination drugs)

Drug class	Code[a]	Active ingredient
DPP-4 inhibitor + Biguanides		
	5023	Metformin hydrochloride 1g
	5023	Sitagliptin phosphate hydrate (as sitagliptin 50mg)
	5029	Metformin hydrochloride 0.85g
	5029	Sitagliptin phosphate hydrate (as sitagliptin 50mg)
	5137	Metformin hydrochloride 0.5g
	5137	Sitagliptin phosphate hydrate (as sitagliptin 50mg)
	5247	Metformin hydrochloride 1g
	5247	Sitagliptin phosphate hydrate (as sitagliptin 0.1g)
	5070	Metformin hydrochloride 0.85g
	5070	Vildagliptin 50mg
	5071	Metformin hydrochloride 1g
	5071	Vildagliptin 50mg
	5096	Metformin hydrochloride 0.5g
	5096	Vildagliptin 50mg
	5185	Metformin hydrochloride 0.5g
	5185	Saxagliptin hydrate (as saxagliptin 5mg)
	5086	Metformin hydrochloride 1g
	5086	Saxagliptin hydrate (as saxagliptin 5mg)
	5205	Linagliptin 2.5mg
	5205	Metformin hydrochloride 1g
	5206	Linagliptin 2.5mg
	5206	Metformin hydrochloride 0.85g
	5207	Linagliptin 2.5mg
	5207	Metformin hydrochloride 0.5g
	5238	Gemigliptin tartrate sesquihydrate (as gemigliptin 25mg)
	5238	Metformin hydrochloride 0.5g
	6320	Gemigliptin tartrate sesquihydrate (as gemigliptin 50mg)
	6320	Metformin hydrochloride 1g
	6450	Gemigliptin tartrate sesquihydrate (as gemigliptin 50mg)
	6450	Metformin hydrochloride 0.5g
	6541	Gemigliptin tartrate sesquihydrate (as gemigliptin 25mg)
	6541	Metformin hydrochloride 1g
	6356	Alogliptin Benzoate
	6356	Metformin Hydrochloride
	6357	Alogliptin Benzoate
	6357	Metformin Hydrochloride
	6755	Alogliptin Benzoate
	6755	Metformin Hydrochloride
	6418	Metformin Hydrochloride
	6418	Teneligliptin Hydrobromide Hydrate

Drug class	Code[a]	Active ingredient
DPP-4 inhibitor + Biguanides (Continued)		
	6419	Metformin Hydrochloride
	6419	Teneligliptin Hydrobromide Hydrate
	6420	Metformin Hydrochloride
	6420	Teneligliptin Hydrobromide Hydrate
	6484	Anagliptin
	6484	Metformin Hydrochloride
	6486	Anagliptin
	6486	Metformin Hydrochloride
	6499	Evogliptin Tartrate
	6499	Metformin Hydrochloride
	6500	Evogliptin Tartrate
	6500	Metformin Hydrochloride
	6501	Evogliptin Tartrate
	6501	Metformin Hydrochloride
	7041	Metformin Hydrochloride
	7041	Vildagliptin Nitrate
	7042	Metformin Hydrochloride
	7042	Vildagliptin Nitrate
	7043	Metformin Hydrochloride
	7043	Vildagliptin Nitrate
	7082	Metformin Hydrochloride
	7082	Teneligliptin Hydrochloride Hydrate
	7083	Metformin Hydrochloride
	7083	Teneligliptin Hydrochloride Hydrate
	7084	Metformin Hydrochloride
	7084	Metformin Hydrochloride
	7109	Metformin Hydrochloride
	7109	Teneligliptin Ditosylate Dihydrate
	7110	Metformin Hydrochloride
	7110	Teneligliptin Ditosylate Dihydrate
DPP-4 inhibitor + Thiazolidinediones		
	6305	Alogliptin Benzoate
	6305	Pioglitazone Hydrochloride
	6306	Alogliptin Benzoate
	6306	Pioglitazone Hydrochloride
SGLT-2 inhibitor + Biguanides		
	6398	Dapagliflozin Propanediol Hydrate
	6398	Metformin Hydrochloride
	6414	Dapagliflozin Propanediol Hydrate
	6414	Metformin Hydrochloride
	6490	Empagliflozin
	6490	Metformin Hydrochloride

Drug class	Code[a]	Active ingredient
SGLT-2 inhibitor + Biguanides (Continued)		
	6491	Empagliflozin
	6491	Metformin Hydrochloride
	6492	Empagliflozin
	6492	Metformin Hydrochloride
	6493	Empagliflozin
	6493	Metformin Hydrochloride
	6494	Empagliflozin
	6494	Metformin Hydrochloride
	6495	Empagliflozin
	6495	Metformin Hydrochloride
Thiazolidinediones + Biguanides		
	4981	Metformin Hydrochloride
	4981	Pioglitazone Hydrochloride
	6538	Lobeglitazone Sulfate
	6538	Metformin Hydrochloride
	6539	Lobeglitazone Sulfate
	6539	Metformin Hydrochloride
	6540	Lobeglitazone Sulfate
	6540	Metformin Hydrochloride
	6557	Lobeglitazone Sulfate
	6557	Metformin Hydrochloride

[a]The 4-digit code represents the first four digits of the original active ingredients code indexed in the reimbursable drugs list, available at: https://www.hira.or.kr/bbsDummy.do?pgmid=HIRAA030014050000.
DPP-4: Dipeptidyl Peptidase-4; SGLT-2: Sodium-Glucose Cotransporter-2.

Appendix 3. List of pharmaceutical code of fixed-dose combination drug for diabetes and hypertension

Drug class	Code	Active ingredient

NONE

Appendix 4. List of pharmaceutical code of fixed-dose combination drug for diabetes and dyslipidemia

Drug class	Code[a]	Active ingredient
DPP-4 inhibitor + HMG-CoA reductase inhibitors		
	6646	gemigliptin tartrate sesquihydrate (as gemigliptin 50mg)
	6646	rosuvastatin calcium (as rosuvastatin 5mg)
	6647	gemigliptin tartrate sesquihydrate (as gemigliptin 50mg)
	6647	rosuvastatin calcium (as rosuvastatin 10mg)
	6648	gemigliptin tartrate sesquihydrate (as gemigliptin 50mg)
	6648	rosuvastatin calcium (as rosuvastatin 20mg)
Biguanides + HMG-CoA reductase inhibitors		
	6718	atorvastatin calcium (as atorvastatin 10mg)
	6718	metformin hydrochloride 0.5g
	6738	atorvastatin calcium (as atorvastatin 10mg)
	6738	metformin hydrochloride 1g
	6719	atorvastatin calcium (as atorvastatin 10mg)
	6719	metformin hydrochloride 0.75g
	6720	atorvastatin calcium (as atorvastatin 20mg)
	6720	metformin hydrochloride 0.5g
	6721	atorvastatin calcium (as atorvastatin 20mg)
	6721	metformin hydrochloride 0.75g
	6725	metformin hydrochloride 0.5g
	6725	rosuvastatin calcium (as rosuvastatin 5mg)
	6726	metformin hydrochloride 0.75g
	6726	rosuvastatin calcium (as rosuvastatin 5mg)
	6727	metformin hydrochloride 0.5g
	6727	rosuvastatin calcium (as rosuvastatin 10mg)
	6728	metformin hydrochloride 0.75g
	6728	rosuvastatin calcium (as rosuvastatin 10mg)
	6833	metformin hydrochloride 1g
	6833	rosuvastatin calcium (as rosuvastatin 5mg)
	6834	metformin hydrochloride 1g
	6834	rosuvastatin calcium (as rosuvastatin 10mg)
	7025	metformin hydrochloride 0.5g
	7025	vildagliptin hydrochloride (as vildagliptin 50mg)
	7026	metformin hydrochloride 0.85g
	7026	vildagliptin hydrochloride (as vildagliptin 50mg)
	7027	metformin hydrochloride 1g
	7027	vildagliptin hydrochloride (as vildagliptin 50mg)

[a]The 4-digit code represents the first four digits of the original active ingredients code indexed in the reimbursable drugs list, available at: https://www.hira.or.kr/bbsDummy.do?pgmid=HIRAA030014050000.
DPP-4: Dipeptidyl Peptidase-4.

Appendix 5. List of pharmaceutical code of oral antihypertensive agents

Drug class	Code[a]	Active ingredient
Alpha-1-, beta-blockers		
	1250	carvedilol
ACE inhibitors		
	1042	alacepril
	1229	captopril
	1330	cilazapril
	1516	enalapril maleate
	1845	lisinopril
	2113	perindopril tertbutylamine
	2224	ramipril
	5016	perindopril arginine
Alpha-1 blockers		
	1491	doxazosin mesylate
	4834	Phenoxybenzamine
ARBs		
	1226	candesartan cilexetil
	1773	irbesartan
	1857	losartan potassium
	2471	valsartan
	3788	telmisartan
	4292	eprosartan mesylate
	4685	olmesartan medoxomil
	5152	fimasartan potassium trihydrate
	6514	sacubitril/valsartan sodium hydrate
Beta-blockers		
	1114	atenolol
	1168	betaxolol hydrochloride
	1170	bevantolol hydrochloride
	4831	S-atenolol
	4895	nebivolol hydrochloride
	1179	bisoprolol fumarate
	1291	celiprolol hydrochloride
	1983	nadolol
CCBs		
	1076	amlodipine besylate
	1140	barnidipine hydrochloride
	1151	benidipine hydrochloride
	1331	cilnidipine
	1575	felodipine
	1803	lacidipine

Drug class	Code[a]	Active ingredient
CCBs (Continued)		
	1803	lacidipine
	1820	lercanidipine hydrochloride
	1880	manidipine hydrochloride
	4598	amlodipine maleate
	4599	amlodipine camsylate
	4646	amlodipine adipate
	4708	amlodipine mesylate monohydrate
	4762	amlodipine orotate
	4797	amlodipine nicotinate
	4832	S-amlodipine besylate
	4865	S-amlodipine nicotinate
Diuretics		
	1744	indapamide
ACE inhibitors + CCBs		
	4471	felodipine 2.5mg
	4471	ramipril 2.5mg
	4472	felodipine 5mg
	4472	ramipril 5mg
ACE inhibitors + Diuretics		
	5562	indapamide 1.25mg
	5562	perindopril arginine 5mg
ARBs + CCBs		
	4928	amlodipine besylate (as amlodipine 5mg)
	4928	valsartan 0.16g
	4929	amlodipine besylate (as amlodipine 5mg)
	4929	valsartan 80mg
	4958	amlodipine besylate (as amlodipine 10mg)
	4958	valsartan 0.16g
	5005	amlodipine besylate (as amlodipine 5mg)
	5005	olmesartan medoxomil 20mg
	5822	amlodipine besylate (as amlodipine 5mg)
	5822	olmesartan medoxomil 40mg
	5824	amlodipine besylate (as amlodipine 10mg)
	5824	olmesartan medoxomil 40mg
	5027	amlodipine camsylate (as amlodipine 5mg)
	5027	losartan potassium (as losartan 91.6mg)
	5030	amlodipine camsylate (as amlodipine 5mg)
	5030	losartan potassium (as losartan 45.8mg)
	5139	amlodipine camsylate (as amlodipine 10mg)
	5139	losartan potassium (as losartan 45.8mg)

Drug class	Code[a]	Active ingredient
ARBs + CCBs (Continued)		
	5115	amlodipine besylate (as amlodipine 5mg)
	5115	telmisartan 80mg
	5116	amlodipine besylate (as amlodipine 5mg)
	5116	telmisartan 40mg
	5117	amlodipine besylate (as amlodipine 10mg)
	5117	telmisartan 40mg
	6231	amlodipine besylate (as amlodipine 10mg)
	6231	telmisartan 80mg
	5212	S-amlodipine besylate (as S-amlodipine 2.5mg)
	5212	telmisartan 40mg
	5213	S-amlodipine besylate (as S-amlodipine 5mg)
	5213	telmisartan 40mg
	5214	S-amlodipine besylate (as S-amlodipine 2.5mg)
	5214	telmisartan 80mg
	6448	telmisartan 80mg
	6448	S-amlodipine besylate (as S-amlodipine 5mg)
	5222	lercanidipine hydrochloride 10mg
	5222	valsartan 80mg
	5223	lercanidipine hydrochloride 10mg
	5223	valsartan 0.16g
	5224	lercanidipine hydrochloride 20mg
	5224	valsartan 0.16g
	5226	S-amlodipine besylate (as S-amlodipine 2.5mg)
	5226	valsartan 80mg
	5227	S-amlodipine besylate (as S-amlodipine 2.5mg)
	5227	valsartan 0.16g
	5228	S-amlodipine besylate (as S-amlodipine 5mg)
	5228	valsartan 0.16g
	5229	amlodipine adipate (as amlodipine 5mg)
	5229	valsartan 80mg
	5230	amlodipine adipate (as amlodipine 5mg)
	5230	valsartan 0.16g
	5231	amlodipine adipate (as amlodipine 10mg)
	5231	valsartan 0.16g
	5232	amlodipine orotate (as amlodipine 5mg)
	5232	valsartan 80mg
	5233	amlodipine orotate (as amlodipine 5mg)
	5233	valsartan 0.16g
	5234	amlodipine oratate (as amlodipine 10mg)
	5234	valsartan 0.16g

Drug class	Code[a]	Active ingredient
ARBs + CCBs (Continued)		
	5476	olmesartan medoxomil 40mg
	5476	amlodipine maleate (as amlodipine 5mg)
	5477	olmesartan medoxomil 20mg
	5477	amlodipine maleate (as amlodipine 5mg)
	5478	s-amlodipine nicotinate (as s-amlodipine 2.5mg)
	5478	olmesartan medoxomil 20mg
	5479	s-amlodipine nicotinate (as s-amlodipine 2.5mg)
	5479	olmesartan medoxomil 40mg
	5480	s-amlodipine nicotinate (as s-amlodipine 5mg)
	5480	olmesartan medoxomil 40mg
	6313	s-amlodipine nicotinate (as s-amlodipine 5mg)
	6313	olmesartan medoxomil 20mg
	6294	amlodipine orotate (as amlodipine 10mg)
	6294	olmesartan medoxomil 40mg
	6295	amlodipine orotate (as amlodipine 5mg)
	6295	olmesartan medoxomil 20mg
	6296	amlodipine orotate (as amlodipine 5mg)
	6296	olmesartan medoxomil 40mg
	6328	olmesartan medoxomil 20mg
	6328	S-amlodipine besylate (as S-amlodipine 2.5mg)
	6329	olmesartan medoxomil 40mg
	6329	S-amlodipine besylate (as S-amlodipine 2.5mg)
	6330	olmesartan medoxomil 40mg
	6330	S-amlodipine besylate (as S-amlodipine 5mg)
	6374	amlodipine besylate (as amlodipine 5mg)
	6374	losartan potassium (as losartan 45.8mg)
	6375	amlodipine besylate (as amlodipine 10mg)
	6375	losartan potassium (as losartan 45.8mg)
	6376	amlodipine besylate (as amlodipine 5mg)
	6376	losartan potassium (as losartan 91.6mg)
	6519	amlodipine besylate (as amlodipine 5mg)
	6519	fimasartan potassium trihydrate (as fimasartan potassium 30mg)
	6520	amlodipine besylate (as amlodipine 10mg)
	6520	fimasartan potassium trihydrate (as fimasartan potassium 30mg)
	6521	amlodipine besylate (as amlodipine 10mg)
	6521	fimasartan potassium trihydrate (as fimasartan potassium 60mg)
	6527	amlodipine besylate (as amlodipine 5mg)
	6527	fimasartan potassium trihydrate (as fimasartan potassium 60mg)
	6529	amlodipine besylate (as amlodipine 5mg)
	6529	candesartan cilexetil 8mg

Drug class	Code[a]	Active ingredient
ARBs + CCBs (Continued)		
	6530	amlodipine besylate (as amlodipine 5mg)
	6530	candesartan cilexetil 16mg
	6531	amlodipine besylate (as amlodipine 10mg)
	6531	candesartan cilexetil 16mg
	6624	azilsartan medoxomil potassium (as azilsartan medoxomil 80mg)
	6624	azilsartan medoxomil potassium (as azilsartan medoxomil 40mg)
	6973	S-amlodipine nicotinate (as S-amlodipine 2.5mg)
	6973	telmisartan 80mg
	6974	S-amlodipine nicotinate (as S-amlodipine 2.5mg)
	6974	telmisartan 40mg
	6975	S-amlodipine nicotinate (as S-amlodipine 5mg)
	6975	telmisartan 80mg
	6976	S-amlodipine nicotinate (as S-amlodipine 5mg)
	6976	telmisartan 40mg
ARBs + Diuretics		
	2625	hydrochlorothiazide 12.5mg
	2625	losartan potassium (as losartan 45.8mg)
	3789	hydrochlorothiazide 25mg
	3789	losartan potassium (as losartan 91.6mg)
	4869	hydrochlorothiazide 12.5mg
	4869	losartan potassium (as losartan 91.6mg)
	3564	hydrochlorothiazide 12.5mg
	3564	valsartan 80mg
	4426	hydrochlorothiazide 12.5mg
	4426	valsartan 0.16g
	3857	hydrochlorothiazide 12.5mg
	3857	irbesartan 0.15g
	3858	hydrochlorothiazide 12.5mg
	3858	irbesartan 0.3g
	4237	candesartan cilexetil 16mg
	4237	hydrochlorothiazide 12.5mg
	4432	hydrochlorothiazide 12.5mg
	4432	telmisartan 40mg
	4433	hydrochlorothiazide 12.5mg
	4433	telmisartan 80mg
	5026	hydrochlorothiazide 25mg
	5026	telmisartan 80mg
	4605	eprosartan mesylate (as eprosartan 0.6g)
	4605	hydrochlorothiazide 12.5mg

Drug class	Code[a]	Active ingredient
ARBs + Diuretics (Continued)		
	5136	hydrochlorothiazide 12.5mg
	5136	olmesartan medoxomil 20mg
	5220	fimasartan potassium trihydrate (as fimasartan potassium 60mg)
	5220	hydrochlorothiazide 12.5mg
	5268	fimasartan potassium trihydrate (as fimasartan potassium 0.12g)
	5268	hydrochlorothiazide 12.5mg
	6736	azilsartan medoxomil potassium (as azilsartan medoxomil 40mg)
	6736	chlorthalidone 25mg
	7090	losartan potassium (as losartan 45.8mg)
	7090	chlorthalidone 12.5mg
	7091	losartan potassium (as losartan 91.6mg)
	7091	chlorthalidone 12.5mg
Beta-blockers + Diuretics		
	2621	atenolol 50mg
	2621	chlorthalidone 12.5mg
	4698	bisoprolol fumarate 2.5mg
	4698	hydrochlorothiazide 6.25mg
	4699	bisoprolol fumarate 5mg
	4699	hydrochlorothiazide 6.25mg
	4700	bisoprolol fumarate 10mg
	4700	hydrochlorothiazide 6.25mg
CCBs + Beta-blockers		
	2624	felodipine 5mg
	2624	metoprolol succinate 47.5mg
CCBs + Diuretics		
	6735	azilsartan medoxomil potassium (as azilsartan medoxomil 40mg)
	6735	chlorthalidone 12.5mg
ARBs + CCBs + Diuretics		
	5197	amlodipine besylate (as amlodipine 5mg)
	5197	hydrochlorothiazide 12.5mg
	5197	olmesartan medoxomil 40mg
	5198	amlodipine besylate (as amlodipine 5mg)
	5198	hydrochlorothiazide 12.5mg
	5198	olmesartan medoxomil 20mg
	5200	amlodipine besylate (as amlodipine 10mg)
	5200	hydrochlorothiazide 12.5mg
	5200	olmesartan medoxomil 40mg
	6628	amlodipine camsylate (as amlodipine 5mg)
	6628	losartan potassium (as losartan 45.8mg)
	6628	chlorthalidone 12.5mg

Drug class	Code[a]	Active ingredient
ARBs + CCBs + Diuretics (Continued)		
	6629	amlodipine camsylate (as amlodipine 5mg)
	6629	losartan potassium (as losartan 91.6mg)
	6629	chlorthalidone 12.5mg
	6630	amlodipine camsylate (as amlodipine 5mg)
	6630	losartan potassium (as losartan 91.6mg)
	6630	chlorthalidone 25mg
	6635	amlodipine besylate (as amlodipine 5mg)
	6635	hydrochlorothiazide 12.5mg
	6635	telmisartan 40mg
	6636	amlodipine besylate (as amlodipine 5mg)
	6636	hydrochlorothiazide 12.5mg
	6636	telmisartan 80mg
	6637	amlodipine besylate (as amlodipine 10mg)
	6637	hydrochlorothiazide 12.5mg
	6637	telmisartan 80mg
	6638	amlodipine besylate (as amlodipine 10mg)
	6638	hydrochlorothiazide 25mg
	6638	telmisartan 80mg
	6827	amlodipine besylate (as amlodipine 5mg)
	6827	chlorthalidone 12.5mg
	6827	telmisartan 40mg
	6828	amlodipine besylate (as amlodipine 5mg)
	6828	chlorthalidone 12.5mg
	6828	telmisartan 80mg
	6829	amlodipine besylate (as amlodipine 5mg)
	6829	chlorthalidone 25mg
	6829	telmisartan 80mg
	7075	amlodipine besylate (as amlodipine 5mg)
	7075	fimasartan potassium trihydrate (as fimasartan potassium 30mg)
	7075	hydrochlorothiazide 12.5mg
	7076	amlodipine besylate (as amlodipine 5mg)
	7076	fimasartan potassium trihydrate (as fimasartan potassium 60mg)
	7076	hydrochlorothiazide 12.5mg
	7077	amlodipine besylate (as amlodipine 10mg)
	7077	fimasartan potassium trihydrate (as fimasartan potassium 60mg)
	7077	hydrochlorothiazide 12.5mg
	7107	amlodipine besylate (as amlodipine 5mg)
	7107	fimasartan potassium trihydrate (as fimasartan potassium 60mg)
	7107	hydrochlorothiazide 25mg

[a]The 4-digit code represents the first four digits of the original active ingredients code indexed in the reimbursable drugs list, available at: https://www.hira.or.kr/bbsDummy.do?pgmid=HIRAA030014050000.
ACE; Angiotensin-Converting Enzyme, ARB: Angiotensin II Receptor Blocker, CCB: Calcium Channel Blocker.

Appendix 6. List of pharmaceutical code of oral lipid-lowering agents

Drug class	Code[a]	Active ingredient
Cholesterol absorption inhibitor		
	4622	ezetimibe
PPAR-α agonists		
	1171	bezafibrate
	1577	fenofibrate pellet
	1650	gemfibrozil
	1949	fenofibrate granule(micronized)
	5203	fenofibric acid
	6423	choline fenofibrate
Omega-3 fatty acids		
	6794	omega-3-acid ethyl esters90
Bile acid sequestrants		
	1323	cholestyramine resin
	2154	polystyrene sulfonate calcium
HMG-CoA reductase inhibitors		
	1115	atorvastatin calcium
	1624	fluvastatin
	1858	lovastatin
	2166	pravastatin sodium
	2278	simvastatin
	4540	rosuvastatin calcium
	4709	pitavastatin calcium
	5022	atorvastatin strontium pentahydrate
	4239	ulinastatin
Cholesterol absorption inhibitor + PPAR-α agonists		
	7028	ezetimibe
	7028	fenofibrate
HMG-CoA reductase inhibitors + Cholesterol absorption inhibitor		
	4710	ezetimibe
	4710	simvastatin
	4711	ezetimibe
	4711	simvastatin
	5078	ezetimibe
	5078	simvastatin
	6338	atorvastatin calcium
	6338	ezetimibe
	6339	atorvastatin calcium
	6339	ezetimibe

Drug class	Code[a]	Active ingredient
HMG-CoA reductase inhibitors + Cholesterol absorption inhibitor (Continued)		
	6346	atorvastatin calcium
	6346	ezetimibe
	6348	atorvastatin calcium
	6348	ezetimibe
	6407	ezetimibe
	6407	rosuvastatin calcium
	6408	ezetimibe
	6408	rosuvastatin calcium
	6409	ezetimibe
	6409	rosuvastatin calcium
	7011	ezetimibe
	7011	rosuvastatin calcium
	6994	ezetimibe
	6994	pitavastatin calcium
	6995	ezetimibe
	6995	pitavastatin calcium
HMG-CoA reductase inhibitors + PPAR-α agonists		
	5193	fenofibrate
	5193	pravastatin sodium
	6793	fenofibrate granule(micronized)
	6793	pitavastatin calcium
HMG-CoA reductase inhibitors + Omega-3 fatty acids		
	6634	omega-3-acid ethyl esters90
	6634	rosuvastatin calcium
	6940	atorvastatin calcium
	6940	omega-3-acid ethyl esters90
	7112	atorvastatin calcium
	7112	omega-3-acid ethyl esters90

[a]The 4-digit code represents the first four digits of the original active ingredients code indexed in the reimbursable drugs list, available at: https://www.hira.or.kr/bbsDummy.do?pgmid=HIRAA030014050000.
PPAR-α: Peroxisome Proliferator-Activated Receptor Alpha, HMG-CoA: 3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase Inhibitors

Appendix 7. List of pharmaceutical code of fixed-dose combination drug for hypertension and dyslipidemia

Drug class	Code[a]	Active ingredient
ARB + HMG-CoA reductase inhibitors		
	5240	atorvastatin calcium (as atorvastatin 10mg)
	5240	irbesartan 0.15g
	5241	atorvastatin calcium (as atorvastatin 20mg)
	5241	irbesartan 0.15g
	5270	atorvastatin calcium (as atorvastatin 20mg)
	5270	irbesartan 0.3g
	5271	atorvastatin calcium (as atorvastatin 10mg)
	5271	irbesartan 0.3g
	5250	rosuvastatin calcium (as rosuvastatin 10mg)
	5250	valsartan 80mg
	5251	rosuvastatin calcium (as rosuvastatin 10mg)
	5251	valsartan 0.16g
	5252	rosuvastatin calcium (as rosuvastatin 20mg)
	5252	valsartan 80mg
	5253	rosuvastatin calcium (as rosuvastatin 20mg)
	5253	valsartan 0.16g
	6297	rosuvastatin calcium (as rosuvastatin 5mg)
	6297	valsartan 80mg
	6298	rosuvastatin calcium (as rosuvastatin 5mg)
	6298	valsartan 160mg
	5263	olmesartan medoxomil 20mg
	5263	rosuvastatin calcium (as rosuvastatin 10mg)
	5264	olmesartan medoxomil 20mg
	5264	rosuvastatin calcium (as rosuvastatin 20mg)
	5265	olmesartan medoxomil 40mg
	5265	rosuvastatin calcium (as rosuvastatin 20mg)
	5269	olmesartan medoxomil 20mg
	5269	rosuvastatin calcium (as rosuvastatin 5mg)
	6441	olmesartan medoxomil 10mg
	6441	rosuvastatin calcium (as rosuvastatin 10mg)
	6442	olmesartan medoxomil 10mg
	6442	rosuvastatin calcium (as rosuvastatin 5mg)
	6532	olmesartan medoxomil 40mg
	6532	rosuvastatin calcium (as rosuvastatin 10mg)
	6299	rosuvastatin calcium (as rosuvastatin 10mg)
	6299	telmisartan 40mg
	6300	rosuvastatin calcium (as rosuvastatin 20mg)
	6300	telmisartan 40mg
	6301	rosuvastatin calcium (as rosuvastatin 10mg)
	6301	telmisartan 80mg

Drug class	Code[a]	Active ingredient
ARB + HMG-CoA reductase inhibitors (Continued)		
	6302	rosuvastatin calcium (as rosuvastatin 20mg)
	6302	telmisartan 80mg
	6316	rosuvastatin calcium (as rosuvastatin 5mg)
	6316	telmisartan 40mg
	6317	rosuvastatin calcium (as rosuvastatin 5mg)
	6317	telmisartan 80mg
	6349	pitavastatin calcium 2mg
	6349	valsartan 160mg
	6350	pitavastatin calcium 2mg
	6350	valsartan 80mg
	6351	pitavastatin calcium 4mg
	6351	valsartan 160mg
	6352	pitavastatin calcium 4mg
	6352	valsartan 80mg
	6547	fimasartan potassium trihydrate (as fimasartan potassium 60mg)
	6547	rosuvastatin calcium (as rosuvastatin 10mg)
	6548	fimasartan potassium trihydrate (as fimasartan potassium 60mg)
	6548	rosuvastatin calcium (as rosuvastatin 5mg)
	6549	fimasartan potassium trihydrate (as fimasartan potassium 30mg)
	6549	rosuvastatin calcium (as rosuvastatin 10mg)
	6550	fimasartan potassium trihydrate (as fimasartan potassium 30mg)
	6550	rosuvastatin calcium (as rosuvastatin 5mg)
	6618	candesartan cilexetil 8mg
	6618	rosuvastatin calcium (as rosuvastatin 5mg)
	6619	candesartan cilexetil 8mg
	6619	rosuvastatin calcium (as rosuvastatin 10mg)
	6620	candesartan cilexetil 16mg
	6620	rosuvastatin calcium (as rosuvastatin 10mg)
	6621	candesartan cilexetil 32mg
	6621	rosuvastatin calcium (as rosuvastatin 20mg)
	6737	candesartan cilexetil 16mg
	6737	rosuvastatin calcium (as rosuvastatin 5mg)
	6881	atorvastatin calcium (as atorvastatin 10mg)
	6881	fimasartan potassium trihydrate (as fimasartan potassium 30mg)
	6882	atorvastatin calcium (as atorvastatin 10mg)
	6882	fimasartan potassium trihydrate (as fimasartan potassium 60mg)
	6883	atorvastatin calcium (as atorvastatin 20mg)
	6883	fimasartan potassium trihydrate (as fimasartan potassium 30mg)
	6884	atorvastatin calcium (as atorvastatin 20mg)
	6884	fimasartan potassium trihydrate (as fimasartan potassium 60mg)
	6885	atorvastatin calcium (as atorvastatin 40mg)
	6885	fimasartan potassium trihydrate (as fimasartan potassium 0.12g)

Drug class	Code[a]	Active ingredient
Beta-blocker + HMG-CoA reductase inhibitors		
	6830	nebivolol hydrochloride (as nebivolol 5mg)
	6830	rosuvastatin calcium (as rosuvastatin 10mg)
	6831	nebivolol hydrochloride (as nebivolol 5mg)
	6831	rosuvastatin calcium (as rosuvastatin 20mg)
	6832	nebivolol hydrochloride (as nebivolol 2.5mg)
	6832	rosuvastatin calcium (as rosuvastatin 10mg)
	6912	nebivolol hydrochloride (as nebivolol 2.5mg)
	6912	rosuvastatin calcium (as rosuvastatin 5mg)
	6930	nebivolol hydrochloride (as nebivolol 1.25mg)
	6930	rosuvastatin calcium (as rosuvastatin 5mg)
	7089	nebivolol hydrochloride (as nebivolol 2.5mg)
	7089	rosuvastatin calcium (as rosuvastatin 20mg)
CCB + HMG-CoA reductase inhibitors		
	4723	amlodipine besylate (as amlodipine 5mg)
	4723	atorvastatin calcium (as atorvastatin 10mg)
	4724	amlodipine besylate (as amlodipine 5mg)
	4724	atorvastatin calcium (as atorvastatin 20mg)
	4725	amlodipine besylate (as amlodipine 5mg)
	4725	atorvastatin calcium (as atorvastatin 40mg)
	5189	amlodipine besylate (as amlodipine 10mg)
	5189	atorvastatin calcium (as atorvastatin 20mg)
	6145	atorvastatin calcium (as atorvastatin 10mg)
	6145	S-amlodipine besylate (as S-amlodipine 2.5mg)
ARB + CCB + HMG-CoA reductase inhibitors		
	6639	amlodipine camsylate (as amlodipine 5mg)
	6639	losartan potassium (as losartan 45.8mg)
	6639	rosuvastatin calcium (as rosuvastatin 5mg)
	6640	amlodipine camsylate (as amlodipine 5mg)
	6640	losartan potassium (as losartan 45.8mg)
	6640	rosuvastatin calcium (as rosuvastatin 10mg)
	6641	amlodipine camsylate (as amlodipine 5mg)
	6641	losartan potassium (as losartan 45.8mg)
	6641	rosuvastatin calcium (as rosuvastatin 20mg)
	6642	amlodipine camsylate (as amlodipine 5mg)
	6642	losartan potassium (as losartan 91.6mg)
	6642	rosuvastatin calcium (as rosuvastatin 5mg)
	6643	amlodipine camsylate (as amlodipine 5mg)
	6643	losartan potassium (as losartan 91.6mg)
	6643	rosuvastatin calcium (as rosuvastatin 10mg)
	6644	amlodipine camsylate (as amlodipine 5mg)
	6644	losartan potassium (as losartan 91.6mg)
	6644	rosuvastatin calcium (as rosuvastatin 20mg)

Drug class	Code[a]	Active ingredient
ARB + CCB + HMG-CoA reductase inhibitors (Continued)		
	6712	amlodipine besylate (as amlodipine 5mg)
	6712	rosuvastatin calcium (as rosuvastatin 5mg)
	6712	telmisartan 40mg
	6713	amlodipine besylate (as amlodipine 5mg)
	6713	rosuvastatin calcium (as rosuvastatin 5mg)
	6713	telmisartan 80mg
	6714	amlodipine besylate (as amlodipine 5mg)
	6714	rosuvastatin calcium (as rosuvastatin 10mg)
	6714	telmisartan 40mg
	6715	amlodipine besylate (as amlodipine 5mg)
	6715	rosuvastatin calcium (as rosuvastatin 10mg)
	6715	telmisartan 80mg
	6717	amlodipine besylate (as amlodipine 10mg)
	6717	rosuvastatin calcium (as rosuvastatin 20mg)
	6717	telmisartan 80mg
	6770	amlodipine besylate (as amlodipine 5mg)
	6770	rosuvastatin calcium (as rosuvastatin 20mg)
	6770	telmisartan 40mg
	6771	amlodipine besylate (as amlodipine 5mg)
	6771	rosuvastatin calcium (as rosuvastatin 20mg)
	6771	telmisartan 80mg
	6739	amlodipine besylate (as amlodipine 5mg)
	6739	rosuvastatin calcium (as rosuvastatin 5mg)
	6740	amlodipine besylate (as amlodipine 5mg)
	6740	rosuvastatin calcium (as rosuvastatin 10mg)
	6741	amlodipine besylate (as amlodipine 5mg)
	6741	rosuvastatin calcium (as rosuvastatin 20mg)
	6786	amlodipine besylate (as amlodipine 10mg)
	6786	rosuvastatin calcium (as rosuvastatin 10mg)
	6773	amlodipine besylate (as amlodipine 5mg)
	6773	olmesartan medoxomil 20mg
	6773	rosuvastatin calcium (as rosuvastatin 5mg)
	6774	amlodipine besylate (as amlodipine 5mg)
	6774	olmesartan medoxomil 20mg
	6774	rosuvastatin calcium (as rosuvastatin 10mg)
	6868	amlodipine besylate (as amlodipine 5mg)
	6868	olmesartan medoxomil 40mg
	6868	rosuvastatin calcium (as rosuvastatin 5mg)
	6869	amlodipine besylate (as amlodipine 5mg)
	6869	olmesartan medoxomil 40mg
	6869	rosuvastatin calcium (as rosuvastatin 10mg)

Drug class	Code[a]	Active ingredient
ARB + CCB + HMG-CoA reductase inhibitors (Continued)		
	6795	amlodipine besylate (as amlodipine 5mg)
	6795	rosuvastatin calcium (as rosuvastatin 10mg)
	6795	valsartan 80mg
	6796	amlodipine besylate (as amlodipine 5mg)
	6796	rosuvastatin calcium (as rosuvastatin 10mg)
	6796	valsartan 0.16g
	6797	amlodipine besylate (as amlodipine 5mg)
	6797	rosuvastatin calcium (as rosuvastatin 5mg)
	6797	valsartan 0.16g
	6803	amlodipine besylate (as amlodipine 5mg)
	6803	rosuvastatin calcium (as rosuvastatin 5mg)
	6803	valsartan 80mg
	6914	amlodipine besylate (as amlodipine 10mg)
	6914	rosuvastatin calcium (as rosuvastatin 10mg)
	6914	valsartan 0.16g
	6915	amlodipine besylate (as amlodipine 10mg)
	6915	rosuvastatin calcium (as rosuvastatin 20mg)
	6915	valsartan 0.16g
	6843	amlodipine besylate (as amlodipine 5mg)
	6843	fimasartan potassium trihydrate (as fimasartan potassium 30mg)
	6843	rosuvastatin calcium (as rosuvastatin 5mg)
	6844	amlodipine besylate (as amlodipine 5mg)
	6844	fimasartan potassium trihydrate (as fimasartan potassium 30mg)
	6844	rosuvastatin calcium (as rosuvastatin 10mg)
	6845	amlodipine besylate (as amlodipine 5mg)
	6845	fimasartan potassium trihydrate (as fimasartan potassium 60mg)
	6845	rosuvastatin calcium (as rosuvastatin 5mg)
	6846	amlodipine besylate (as amlodipine 5mg)
	6846	fimasartan potassium trihydrate (as fimasartan potassium 60mg)
	6846	rosuvastatin calcium (as rosuvastatin 10mg)
	6847	amlodipine besylate (as amlodipine 10mg)
	6847	fimasartan potassium trihydrate (as fimasartan potassium 60mg)
	6847	rosuvastatin calcium (as rosuvastatin 20mg)
	6904	amlodipine besylate (as amlodipine 5mg)
	6904	atorvastatin calcium (as atorvastatin 20mg)
	6904	valsartan 80mg
	6905	amlodipine besylate (as amlodipine 5mg)
	6905	atorvastatin calcium (as atorvastatin 10mg)
	6905	valsartan 80mg
	6906	amlodipine besylate (as amlodipine 5mg)
	6906	atorvastatin calcium (as atorvastatin 20mg)
	6906	valsartan 0.16g

Drug class	Code[a]	Active ingredient
ARB + CCB + HMG-CoA reductase inhibitors (Continued)		
	6907	amlodipine besylate (as amlodipine 5mg)
	6907	atorvastatin calcium (as atorvastatin 10mg)
	6907	valsartan 0.16g
	7063	amlodipine besylate (as amlodipine 5mg)
	7063	atorvastatin calcium (as atorvastatin 10mg)
	7063	candesartan cilexetil 8mg
	7064	amlodipine besylate (as amlodipine 5mg)
	7064	atorvastatin calcium (as atorvastatin 20mg)
	7064	candesartan cilexetil 16mg
	7065	amlodipine besylate (as amlodipine 10mg)
	7065	atorvastatin calcium (as atorvastatin 40mg)
	7065	candesartan cilexetil 16mg
	7066	amlodipine besylate (as amlodipine 5mg)
	7066	atorvastatin calcium (as atorvastatin 20mg)
	7066	candesartan cilexetil 8mg
	7067	amlodipine besylate (as amlodipine 5mg)
	7067	atorvastatin calcium (as atorvastatin 10mg)
	7067	candesartan cilexetil 16mg
ARB + HMG-CoA reductase inhibitors + Cholesterol absorption inhibitor		
	7018	ezetimibe 10mg
	7018	rosuvastatin calcium (as rosuvastatin 10mg)
	7018	telmisartan 80mg
	7019	ezetimibe 10mg
	7019	rosuvastatin calcium (as rosuvastatin 5mg)
	7019	telmisartan 80mg
	7021	ezetimibe 10mg
	7021	rosuvastatin calcium (as rosuvastatin 5mg)
	7021	telmisartan 40mg
	7022	ezetimibe 10mg
	7022	rosuvastatin calcium (as rosuvastatin 10mg)
	7022	telmisartan 40mg
	7020	ezetimibe 10mg
	7020	rosuvastatin calcium (as rosuvastatin 20mg)
	7020	telmisartan 40mg
ARB + CCB + HMG-CoA reductase inhibitors + Cholesterol absorption inhibitor		
	6920	amlodipine besylate (as amlodipine 5mg)
	6920	ezetimibe 10mg
	6920	losartan potassium (as losartan 45.8mg)
	6920	rosuvastatin calcium (as rosuvastatin 5mg)

Drug class	Code[a]	Active ingredient
ARB + CCB + HMG-CoA reductase inhibitors + Cholesterol absorption inhibitor (Continued)		
	6921	amlodipine besylate (as amlodipine 5mg)
	6921	ezetimibe 10mg
	6921	losartan potassium (as losartan 45.8mg)
	6921	rosuvastatin calcium (as rosuvastatin 20mg)
	6922	amlodipine besylate (as amlodipine 5mg)
	6922	ezetimibe 10mg
	6922	losartan potassium (as losartan 45.8mg)
	6922	rosuvastatin calcium (as rosuvastatin 10mg)
	6923	amlodipine besylate (as amlodipine 5mg)
	6923	ezetimibe 10mg
	6923	losartan potassium (as losartan 91.6mg)
	6923	rosuvastatin calcium (as rosuvastatin 5mg)
	6924	amlodipine besylate (as amlodipine 5mg)
	6924	ezetimibe 10mg
	6924	losartan potassium (as losartan 91.6mg)
	6924	rosuvastatin calcium (as rosuvastatin 20mg)
	6925	amlodipine besylate (as amlodipine 5mg)
	6925	ezetimibe 10mg
	6925	losartan potassium (as losartan 91.6mg)
	6925	rosuvastatin calcium (as rosuvastatin 10mg)
	7097	amlodipine besylate (as amlodipine 5mg)
	7097	ezetimibe 10mg
	7097	rosuvastatin calcium (as rosuvastatin 5mg)
	7097	telmisartan 40mg
	7098	amlodipine besylate (as amlodipine 5mg)
	7098	ezetimibe 10mg
	7098	rosuvastatin calcium (as rosuvastatin 10mg)
	7098	telmisartan 40mg
	7100	amlodipine besylate (as amlodipine 5mg)
	7100	ezetimibe 10mg
	7100	rosuvastatin calcium (as rosuvastatin 5mg)
	7100	telmisartan 80mg
	7101	amlodipine besylate (as amlodipine 5mg)
	7101	ezetimibe 10mg
	7101	rosuvastatin calcium (as rosuvastatin 10mg)
	7101	telmisartan 80mg
	7122	ezetimibe 10mg
	7122	rosuvastatin calcium (as rosuvastatin 5mg)
	7122	S-amlodipine besylate (as S-amlodipine 2.5mg)
	7122	telmisartan 40mg

Drug class	Code[a]	Active ingredient
ARB + CCB + HMG-CoA reductase inhibitors + Cholesterol absorption inhibitor (Continued)		
	7124	ezetimibe 10mg
	7124	rosuvastatin calcium (as rosuvastatin 5mg)
	7124	S-amlodipine besylate (as S-amlodipine 5mg)
	7124	telmisartan 40mg
	7125	ezetimibe 10mg
	7125	rosuvastatin calcium (as rosuvastatin 10mg)
	7125	S-amlodipine besylate (as S-amlodipine 5mg)
	7125	telmisartan 40mg

[a]The 4-digit code represents the first four digits of the original active ingredients code indexed in the reimbursable drugs list, available at: https://www.hira.or.kr/bbsDummy.do?pgmid=HIRAA030014050000.
ACE: Angiotensin-Converting Enzyme, ARB: Angiotensin II Receptor Blocker, CCB: Calcium Channel Blocker, PPAR-α: Peroxisome Proliferator-Activated Receptor Alpha, HMG-CoA: 3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase Inhibitors

Appendix 8. List of pharmaceutical code of insulin and GLP-1 receptor agonist

Drug class	Code[a]	Active ingredient
Insulin		
	1701	human insulin
	1704	human insulin(N70/R30)
	1753	insulin lispro
	4413	insulin aspart
	4618	insulin glargine
	4849	insulin glulisine
	4887	insulin detemir
	6267	insulin aspart
	6268	Insulin degludec
GLP-1 receptor agonist		
	6397	dulaglutide
Insulin + GLP-1 receptor agonist		
	6667	insulin glargine
	6667	lixisenatide
	6670	insulin glargine
	6670	lixisenatide
	6939	insuln degludec
	6939	liraglutide

[a]The 4-digit code represents the first four digits of the original active ingredients code indexed in the reimbursable drugs list, available at: https://www.hira.or.kr/bbsDummy.do?pgmid=HIRAA030014050000.
GLP-1: Glucagon-like peptide-1

Appendix 9. Comparison of general characteristics between main and sensitivity analyses

Characteristic	Main analysis		Sensitivity analysis	
Total	**74,867**		**178,001**	
Proportion days covered, %	75.1	[49.3–91.0]	67.1	[41.1–87.7]
Age, years	39.2	± 4.3	37.6	± 5.0
Sex				
Male	57,561	(76.9)	123,110	(73.1)
Female	17,306	(23.1)	54,910	(26.9)
Monthly health insurance premium				
In thousand KRW	71.0	[42.0–110.7]	58.9	[32.0–99.3]
Charlson comorbidity index				
1 or more	18,991	(25.4)	7,438	(19.4)
Taking medication for hypertension	20,529	(27.4)	11,112	(29.0)
Taking medication for dyslipidemia	27,529	(36.8)	13,948	(36.4)

Numbers represent mean ± standard deviation, median [interquartile range], or frequency (%)

Appendix 10. Comparison of the results between main and sensitivity analysis

Adherence	No. at risk	Events	Unadjusted		Adjusted*	
			HR	(95%CI)	HR	(95%CI)
Adherent vs. non-adherent						
Main analysis						
Adherent	33,049	1,491	1.00	(Reference)	1.00	(Reference)
Non-adherent	41,818	2,958	1.33	(1.25–1.42)	1.45	(1.36–1.54)
Sensitivity analysis						
Adherent	64,129	4,746	1.00	(Reference)	1.00	(Reference)
Non-adherent	113,872	12,182	1.28	(1.24–1.32)	1.40	(1.35–1.44)
Adherence group						
Main analysis						
Good	33,049	1,510	1.00	(Reference)	1.00	(Reference)
Moderate	22,623	1,351	1.22	(1.13–1.31)	1.29	(1.20–1.39)
Poor	19,195	1,441	1.46	(1.35–1.57)	1.64	(1.53–1.77)
Sensitivity analysis						
Good	64,129	4,746	1.00	(Reference)	1.00	(Reference)
Moderate	54,074	5,119	1.17	(1.13–1.22)	1.24	(1.20–1.29)
Poor	59,798	7,063	1.38	(1.37–1.66)	1.56	(1.50–1.62)
By quartiles						
Main analysis						
Q4, highest	18,345	798	1.00	(Reference)	1.00	(Reference)
Q3	18,901	957	1.06	(0.97–1.17)	1.11	(1.01–1.22)
Q2	18,716	1,124	1.23	(1.13–1.35)	1.34	(1.22–1.47)
Q1, lowest	18,905	1,423	1.49	(1.35–1.61)	1.69	(1.55–1.85)
Sensitivity analysis						
Q4, highest	44,855	3,211	1.00	(Reference)	1.00	(Reference)
Q3	44,415	3,840	1.09	(1.04–1.14)	1.15	(1.09–1.20)
Q2	44,793	4,480	1.23	(1.18–1.30)	1.35	(1.29–1.42)
Q1, lowest	43,938	5,397	1.42	(1.36–1.48)	1.65	(1.57–1.72)

*Adjusted for sex, age at index, duration from diagnosis to index, index year, socioeconomic status, initial treatment regimen, drug class, taking insulin therapy, taking GLP-1 RA therapy, Charlson comorbidity index, taking medication for hypertension, and taking medication for dyslipidemia,

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ABSTRACT IN KOREAN

젊은 당뇨병 환자의 복약순응도와 심혈관질환 발생 위험

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연구배경 및 목적: 젊은 성인에서 제 2 형 당뇨병(T2DM)의 유병률이 증가하고 있는 것은 심각한 보건 문제이다. 젊은 나이에 당뇨병에 이환되면 높은 혈당에 장기간 노출되어 합병증 발생과 입원 및 사망의 위험도 높아지기 때문에 개인은 물론 사회적 질병 부담이 크게 증가한다. 치료 계획을 준수하고 약물을 지속적으로 복용하는 것은 당뇨병 환자가 최적의 건강 결과를 달성하는 데 중요하나, 젊거나 질병 초기 단계에 있는 환자는 치료제의 복약 순응도가 낮은 경향이 있다. 본 연구는 젊은 제 2 형 당뇨병 환자에서 복약 순응도가 심혈관질환 발생에 미치는 영향을 평가하는 것을 목적으로 수행되었다.

방법: 한국 국민건강보험공단(NHIS) 데이터베이스를 활용하여 2003 년부터 2015 년 동안 약물 치료를 처음 시작한 20~44 세 젊은 제 2 형 당뇨병 환자 233,241 명을 확인하였다. 심뇌혈관질환 과거력이 있거나, 약물치료 시작 후 1 년이내 사망하였거나, 90 일 미만의 약물 처방정보만 있거나, 사회경제적 상태 및 건강검진 수검 데이터가 없는 사람을 제외한 후 총 76,867 명이 분석대상이 되었다. 당뇨병 치료제의 복약순응도는 첫 365 일 동안 약물 처방 비율(proportion of days covered, PDC)로

측정하였다. 주요 결과 변수는 심근경색, 뇌졸중, 심부전으로 인한 입원 및 심혈관 사망을 포함한 복합 심혈관 사건으로 정의하였다. 인구통계학적, 사회경제적, 임상적 및 생활습관 관련 변수를 보정한 Cox 비례위험 모형을 구축하여 복약순응도가 심혈관질환 발생위험에 미치는 영향을 평가하였다.

결과: 연구 대상자의 평균 연령은 39.2 세이며, 76.9%가 남성이었다. 치료 시작 첫 일년간 PDC 80%이상의 순응도를 보인 사람은 44.1%였다. 중위수 8.1 년의 추적 관찰 기간(총 624,000 인년) 동안 4,302 건의 심혈관사건이 관찰되었다. 복약순등도에 따라 심혈관과사건 발생의 위험도가 통계적으로 유의한 차이가 있었다. 순응군(PDC≥ 80%)에 비하여 비순응군(PDC<80%)은 주요 위험요인을 보정하여도 심혈관사건발생 위험이 유의하게 높았다(보정위험도 1.45; 95% 신뢰구간 1.36–1.54). 또한, 복약순응도를 4 분위수로 구분하여 비교한 결과 순응도가 낮을수록 심혈관 위험이 점진적으로 증가하는 용량-반응 관계도 관찰되었다.

결론: 젊은 당뇨병 유병자에서 복약 순응도는 심혈관질환 발생의 중요한 결정요인이다. 당뇨병으로 인한 개인 및 사회적 질병 부담을 줄이기 위해 젊은 당뇨병 환자의 복약순응도를 높일 수 있는 포괄적인 개선방안이 필요하다.

핵심되는 말: 복약순응도, **심혈관질환**, **젊은 당뇨병**