Original Article

Real-World Prescription Patterns and Barriers Related to the Use of Sodium-Glucose Cotransporter 2 Inhibitors among Korean Patients with Type 2 Diabetes Mellitus and Cardiovascular Disease

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Background: To evaluate prescription trends and clinical factors of the sodium-glucose cotransporter 2 inhibitors (SGLT2i) use according to the presence of atherosclerotic cardiovascular disease (ASCVD) or heart failure (HF) in Korean patients with type 2 diabetes mellitus (T2DM).

Methods: Prescription patterns of SGLT2i use between 2015 and 2019 were determined using the Korean National Health Insurance Service database of claims.

Results: Of all patients with T2DM ($n=4{,}736{,}493$), the annual prescription rate of SGLT2i increased every year in patients with ASCVD (from 2.2% to 10.7%) or HF (from 2.0% to 11.1%). After the first hospitalization for ASCVD ($n=518{,}572$), 13.7% ($n=71{,}259$) of patients initiated SGLT2i with a median of 10.6 months. After hospitalization for HF ($n=372{,}853$), 11.2% ($n=41{,}717$) of patients initiated SGLT2i after a median of 8.8 months. In multivariate regression for hospitalization, older age (per 10 years, odds ratio [OR], 0.57; 95% confidence interval [CI], 0.56 to 0.57), lower household income (OR, 0.93; 95% CI, 0.92 to 0.95), rural residents (OR, 0.95; 95% CI, 0.93 to 0.97), and dipeptidyl peptidase-4 inhibitor (DPP-4i) users (OR, 0.82; 95% CI, 0.81 to 0.84) were associated with lesser initiation of SGLT2i in ASCVD. Additionally, female gender (OR, 0.97; 95% CI, 0.95 to 0.99) was associated with lesser initiation of SGLT2i in HF.

Conclusion: The prescription rate of SGLT2i increased gradually up to 2019 but was suboptimal in patients with ASCVD or HF. After the first hospitalization for ASCVD or HF, older age, female gender, low household income, rural residents, and DPP-4i users were less likely to initiate SGLT2i.

Keywords: Asians; Cardiovascular diseases; Diabetes mellitus, type 2; Healthcare disparities; Heart failure; Sodium-glucose transporter 2 inhibitors

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is commonly complicated by atherosclerotic cardiovascular disease (ASCVD) and heart failure (HF). Patients with T2DM and cardiovascular disease (CVD) have a higher risk for recurrent CVD events than those with prior CVD without diabetes [1]. Among antidiabetic drugs, sodium-glucose cotransporter 2 inhibitor (SGLT2i) and glucagon-like peptide-1 (GLP-1) analogues reduced the risk of major adverse cardiovascular events (MACE) [2-5]. Particularly, SGLT2i reduced CVD risk with the largest benefit for reducing hospitalization for HF [6]. In addition, cardiovascular (CV) benefits independent of the presence of ASCVD, glycemic control status, or baseline renal function have been observed [7]. Accordingly, recent recommendations in the main guidelines for diabetes treatment are shifting their importance from glycemic control to prevention and management of MACE according to the presence or risk of ASCVD. The updated American Diabetes Association guidelines [8] and Korean Diabetes Association guidelines [9] now recommend prioritizing antidiabetic drugs with a proven benefit for CVD in patients with established ASCVD or HF.

According to the United States and Europe nationwide cohort study [10-12], the proportion of SGLT2i use has increased globally in patients with T2DM and in those with concomitant T2DM and CVD. Among United States patients with concomitant T2DM and established CVD between 2014 and 2018, the proportion of those taking SGLT2i had increased from 2.0% in 2014 to 7.2% in 2018 [10]. Austria region-wide diabetes registry data between 2012 and 2018 (n=10,875) showed that the overall prescription rate of SGLT2i in patients with T2DM had increased from 3.7% in 2012 to 11.7% in 2018 [11]. A Danish nationwide population-based study compared the initiation rate between SGLT2i and dipeptidyl peptidase-4 inhibitor (DPP-4i) between 2014 and 2017 and found that SGLT2i initiators had increased 3.6-fold in 2017 compared to that in 2014 (from 53/100,000 to 172/100,000 per year) [12].

Several factors can affect the use of SGLT2i in eligible patients with CV risk. According to medical and pharmacy claims data from the United States between 2013 and 2016 [13], SGLT2i users were younger and more likely to have commercial health insurance. The United States claims database of commercially health insured population for T2DM between 2015 and 2019 (n=934,737) showed that black and female patients and those with low socioeconomic status were indepen-

dently associated with lower rates of SGLT2i use [14].

It is important to decide which subjects to prescribe and start SGLT2i treatment to expect clinical benefits. However, there are scarce population-based data on when SGLT2i is initiated after the first onset of ASCVD or HF. In addition, few studies have analyzed clinical factors affecting the prescription of SGLT2i as secondary prevention therapy. SGLT2i has been covered by the Korean National Health Insurance Service (KNHIS) and reimbursed under regulation since 2015 in Korea. Korean population-based healthcare databases provide an opportunity to characterize SGLT2i utilization trends in the Korean population and describe all individuals with an incident case of SGLT2i use after the first onset of ASCVD or HF. Therefore, the aim of this study was to examine trends in annual prescription rate of SGLT2i and compare the overall prescription rate to other cardioprotective medications and antidiabetic drugs according to the presence of ASCVD or HF. Additionally, clinical characteristics and prescribing patterns of other antidiabetic and cardioprotive drugs were compared to determine whether SGLT2i was prescribed or not after the first hospitalization for ASCVD or HF. Clinical factors associated with SGLT2i initiation after the onset of ASCVD or HF were also assessed.

METHODS

Data sources
Data from the KNHIS datasets of claims from 2015 to 2019, including diagnosis, demographic factors, prescription records, and comorbidities, were analyzed. The KNHIS, a single-payer system for all residents in Korea, covers 97.1% of Koreans (approximately 50 million individuals) [15]. The KNHIS datasets include an eligibility database (age, sex, socioeconomic variables, type of eligibility, household income level), a medical treatment claims database (based on medical bills that were claimed by medical service providers for their medical expenses), and a medical care institution database (type of medical care institutions). Adult patients aged more than 20 years were included in this study. These datasets have been established since 2002. Written informed consent by the patients was waived due to a retrospective nature of our study. This study was approved by the Institutional Review Board of Gyeongsang National University Changwon Hospital (IRB no. GNUCH 2021-08-021).

Study population and definitions

The diagnosis was classified using the International Classification of Disease, 10th Revision (ICD-10). Operational definition of diabetes and its related comorbidities were applied for further analysis (Supplementary Table 1). Patients with T2DM were defined when ICD-10 codes for T2DM (E11–E14) as the principal diagnosis or up to a fourth additional diagnosis were present with a prescription of at least one antidiabetic drug in a given year [16]. The presence of hypertension was defined according to at least one claim in a given year for the prescription of antihypertensive drugs under ICD-10 codes I10–I13 and I15 [16]. The presence of dyslipidemia was defined as at least one claim for lipid-lowering agents in a given year under the corresponding ICD-10 code (E78) [16]. Drugs corresponding to each class are summarized in Supplementary Table 2. Urban residents were defined as cases where prescriptions were made in seven metropolitan cities, including Seoul. In the classification of medical institutions, a hospital was defined as a case of more than a general hospital, including secondary and tertiary hospitals. Household income level was recruited through the annual contribution amount for health insurance, and dichotomized at the lower 25th percentile or divided into quartiles. ASCVD comprised ischemic heart disease and stroke. Ischemic heart disease was defined as the presence of ICD-10 codes of I20–I25 and/or the accompanied procedure for percutaneous coronary intervention or coronary artery bypass graft [16]. Stroke was defined as the presence of ICD-10 code of I50 with computed tomography/magnetic resonance imaging scan [16].

Baseline demographic variables, socioeconomic factors, concomitant use of other medications (antidiabetic drugs, CV medications), and comorbidities were defined differently according to prevalent and incident cases. For prevalent cases, the presence of ASCVD or HF was determined based on whether there were claim data with corresponding ICD-10 codes within the whole study period or a given year, regardless of hospitalization. The use of each class of drugs was defined as whether drugs were prescribed at least once in a given year. Demographic variables such as age, sex, region, and prescribed medical institutions were determined based on when the first claim data were sent to Health Insurance Review Agency (HIRA) for each diagnostic code (e.g., T2DM, ASCVD, HF) in a given year. Meanwhile, for incident cases, a 12-year washout period (from January 2002 to December 2014) was set to confirm incident cases during 2015 to 2019. In addition, the presence of ASCVD or HF was determined when the billing data with each corresponding ICD-10 code was present with hospitalization during the study period. The use of each medication, demographic factors, income levels, residents, prescribed medical institutions, and comorbidities were determined based on the first claim data sent to HIRA after the first diagnosis and hospitalization for ASCVD or HF during 2015 to 2019.

Statistical analysis

Baseline characteristics are presented as mean with standard deviation or numbers and percentages. Clinical parameters between SGLT2i users and non-users were compared using one-way analysis of variance for continuous variables and the chi-square test for categorical variables. Multivariate logistic regression analysis was conducted to evaluate associations between the initiation of SGLT2i after the first hospitalization for ASCVD or HF and clinical parameters including age, gender, residents, income levels, concomitant antidiabetic drugs, comorbidities, and CV medications. These results are presented as odds ratio (OR) and 95% confidence interval (CI). All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) and R version 3.2.5 (The R Foundation for Statistical Computing, Vienna, Austria; http://www.Rproject.org). All statistical tests were two-tailed, and significance level was set at $P < 0.05$.

RESULTS

Prevalent case

Among all Korean patients with T2DM enrolled between 2015 to 2019 ($n = 4,736,493$), 1,720,996 (36.1%) patients had ASCVD (ICD-10 code corresponding to ASCVD exists at least once), and 783,378 (16.5%) patients had HF (Supplementary Table 3). Annual proportion of patients with concomitant T2DM and ASCVD ranged from 24.3% to 24.5% (Supplementary Fig. 1). Annual prescription rate of SGLT2i in total T2DM patients increased steadily from 2.4% ($n = 74,805$) in 2015 to 11.0% ($n = 435,179$) in 2019. These trends were consistent independent of the presence of ASCVD (from 2.2% to 10.7%) or HF (from 2.0% to 11.1%) (Fig. 1).

Among all patients with T2DM ($n = 3,975,145$) based on the latest data in 2019, 370,082 patients had concomitant T2DM and HF, 973,685 patients had concomitant T2DM and ASCVD, respectively (Fig. 2). Angiotensin-converting enzyme inhibitor
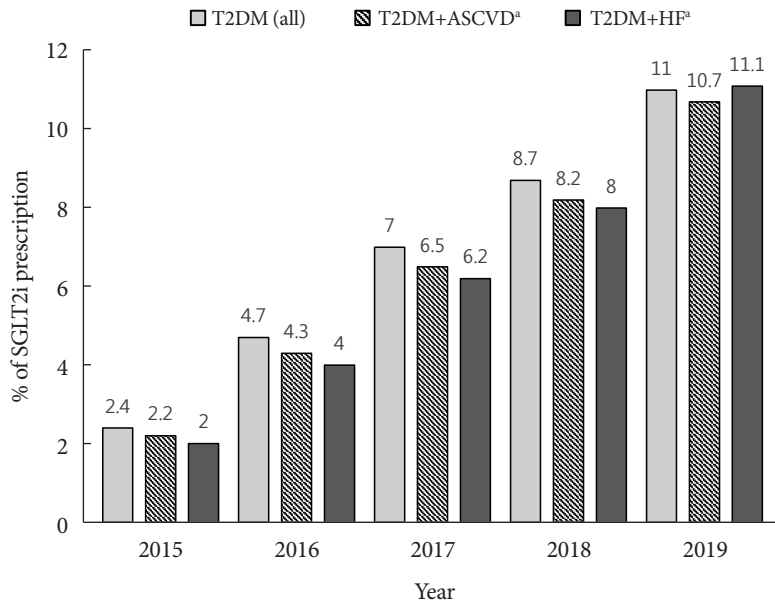
Fig. 1. Annual prescription rate of sodium-glucose cotransporter 2 inhibitor (SGLT2i) in patients with type 2 diabetes mellitus (T2DM) according to the presence of atherosclerotic cardiovascular disease (ASCVD) or heart failure (HF). [a]The presence of AS-CVD or HF was determined whether the corresponding International Classification of Disease, 10th Revision (ICD-10) code presents in a given year regardless of hospitalization.
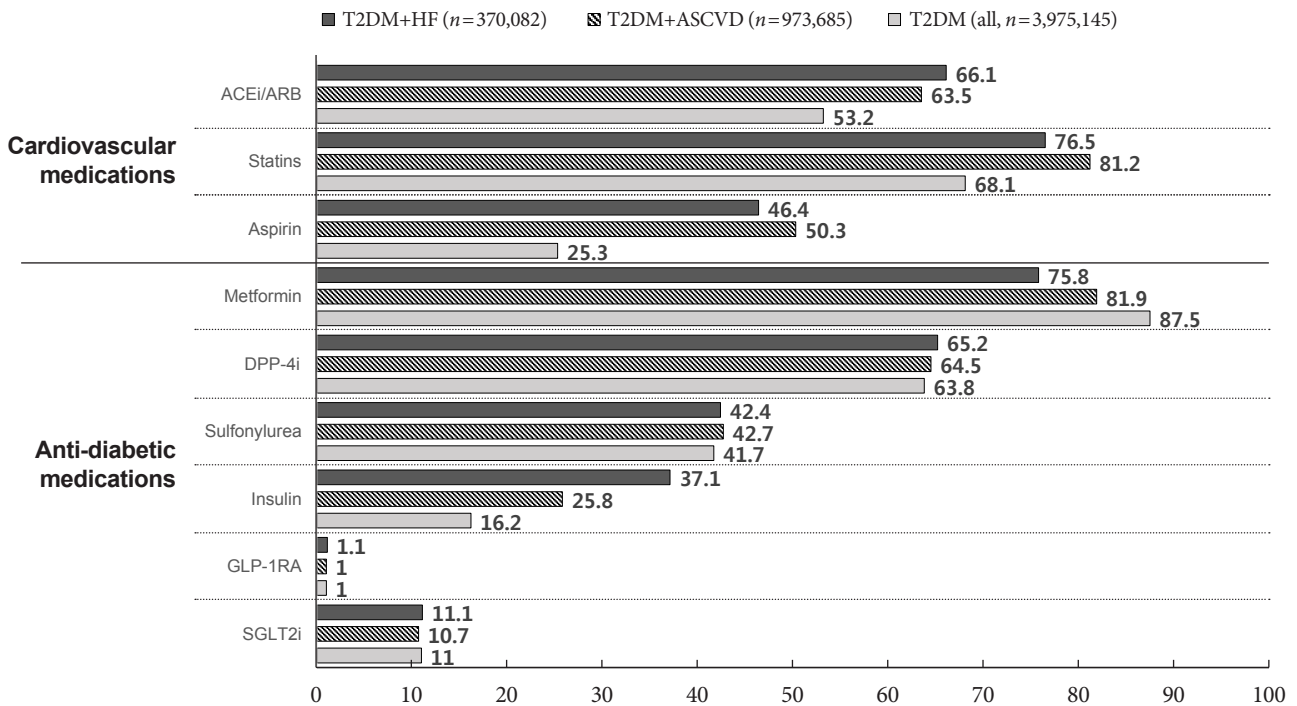
Fig. 2. Use of cardiovascular and antidiabetic medications among patients with type 2 diabetes mellitus (T2DM) and atherosclerotic cardiovascular disease (ASCVD) or heart failure (HF) in 2019. Data were presented as percentage (%). ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockade; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

(ACEi)/angiotensin receptor blockade (ARB) was used more frequently in patients with T2DM accompanied ASCVD (63.5%; $n=618,100$) or HF (66.1%; $n=244,629$) than in all patients with T2DM (53.2%; $n=2,114,946$). Similarly, statins and aspirin were used more in patients with ASCVD (81.2% were on statins, 50.3% were on aspirin) or HF (76.5% were on statins, 46.4% were on aspirin) than in all patients with T2DM. Regarding antidiabetic drugs used in all patients with T2DM, 11% ($n=435,179$) of patients were prescribed SGLT2i, and 63.8% ($n=2,536,481$) were prescribed DPP-4i. Meanwhile, SGLT2 prescription rates were similar in patients accompanied by AS-CVD (10.7%; $n=103,761$) or HF (11.1%; $n=41,008$) compared to all patients (11.0%; $n=435,179$). Among patients with concomitant T2DM and ASCVD in 2019, there was no regional difference in the prescription rate of SGLT2i (Supplementary Fig. 2).

When prescription rates of SGLT2i were compared according to age, gender, and household income levels as of 2019, male gender (12.2% vs. 8.7% in females, $P<0.001$) and younger patients (26.0% in 30 to 49 years old vs. 15.0% in 50 to 69 years old and 5.9% in 70 years old or higher, $P<0.001$) were prescribed SGLT2i more frequently in patients with T2DM and ASCVD. However, the prescription rate of SGLT2i was not significantly different according to household income level (10.6% vs. 10.6%, $P=0.647$) (Supplementary Fig. 3).

Incident case: ASCVD

During 2015 to 2019, a total of 518,572 patients were hospitalized with the first diagnosis of ASCVD, and 71,259 patients (13.7%) initiated SGLT2i treatment with a median of 10.6 months after discharge. Baseline demographic, socioeconomic, and medication differences between those who were prescribed an SGLT2i and those who were not are summarized in Table 1. SGLT2i was initially prescribed the most by hospitals ($n=52,332$, 73.4%), followed by local clinics ($n=18,497$, 26.0%). Patients who initiated SGLT2i after the first hospitalization for ASCVD were younger (mean 61.6 years vs. 69.8 years, $P<0.001$). In addition, patients who initiated SGLT2i after the onset of ASCVD also had higher proportions of male gender (63.4% vs. 54.6%, $P<0.001$) and urban residents (42.3% vs. 40.7%, $P<0.001$) than those who did not initiate. Overall, 7.4% ($n=38,192$) of patients who were first hospitalized for ASCVD between 2015 and 2019 initiated SGLT2i therapy within a year, which increased from 2.5% ($n=2,272$) in 2015 to 12.9% ($n=13,455$) in 2019 (Fig. 3).

In multivariate analyses (Fig. 4A, Supplementary Table 4), older age (per 10 years, OR, 0.57; 95% CI, 0.56 to 0.57; $P<0.001$), rural residents (OR, 0.95; 95% CI, 0.93 to 0.97; $P<0.001$), lower income level (OR, 0.93; 95% CI, 0.92 to 0.95; $P<0.001$), the use of DPP-4i (OR, 0.82; 95% CI, 0.81 to 0.84; $P<0.001$) and the presence of hypertension (OR, 0.92; 95% CI, 0.89 to 0.95; $P<0.001$) were independently associated with lesser initiation of SGLT2i after the first hospitalization for AS-CVD. Meanwhile, the presence of dyslipidemia (OR, 1.52; 95% CI, 1.44 to 1.61; $P<0.001$), use of metformin (OR, 1.83; 95% CI, 1.79 to 1.87; $P<0.001$), sulfonylurea (OR, 1.51; 95% CI, 1.49 to 1.54; $P<0.001$), ACEi/ARB (OR, 1.28; 95% CI, 1.24 to 1.31; $P<0.001$), statins (OR, 1.37; 95% CI, 1.29 to 1.45; $P<0.001$), and aspirin (OR, 1.38; 95% CI, 1.36 to 1.41; $P<0.001$) were also associated with SGLT2i use. Additionally, ischemic heart disease as a cause of ASCVD (OR, 1.69; 95% CI, 1.66 to 1.74; $P<0.001$) was associated with SGLT2i use compared to stroke.

Incident case: HF

Of 372,853 patients hospitalized with the first diagnosis of HF during 2015 to 2019, 41,717 (11.2%) patients initiated SGLT2i treatment with a median of 8.8 months after discharge. Baseline demographic, socioeconomic, and medication differences between those who were prescribed an SGLT2i and those who were not are summarized in Table 2. Similarly, for incident AS-CVD cases, SGLT2i users were younger (63.4 years vs. 71.8 years, $P<0.001$) and male-dominant (59.4% vs. 51.8%, $P<0.001$). They were more likely to be urban residents (41.8% vs. 39.9%, $P<0.001$). Hypertension (83.9% vs. 83.3%, $P=0.002$) and dyslipidemia (84.0% vs. 65.9%, $P<0.001$) were more common in patients who were prescribed an SGLT2i than in those who were not. Insulin was prescribed less in patients who used an SGLT2i than in those who did not (20.6% vs. 31.6%, $P<0.001$). Overall, 6.6% ($n=24,562$) of patients who were first hospitalized for HF between 2015 and 2019 initiated SGLT2i therapy within a year, which increased from 1.9% ($n=642$) in 2015 to 10.3% ($n=9,763$) in 2019 (Fig. 3).

Older age (per 10 years; OR, 0.57; 95% CI, 0.57 to 0.58; $P<0.001$), female gender (OR, 0.97; 95% CI, 0.95 to 0.99; $P=0.004$), rural resident (OR, 0.93; 95% CI, 0.91 to 0.95; $P<0.001$), and lower income level (OR, 0.95; 95% CI, 0.93 to 0.98; $P<0.001$) were independently associated with lesser initiation of SGLT2i after the first hospitalization for HF. Additionally, the use of DPP-4i (OR, 0.75; 95% CI, 0.74 to 0.77; $P<0.001$) and insulin (OR, 0.73; 95% CI, 0.71 to 0.75; $P<0.001$) were as-

Table 1. Baseline characteristics according to initiation of SGLT2i prescription after the first hospitalization for atherosclerotic cardiovascular disease

Characteristic	All	SGLT2i treatment		P value
		No	Yes	
Number	518,572	447,313	71,259	
Age, yr	68.7±12.1	69.8±11.8	61.6±11.7	<0.001
Male sex	289,347 (55.8)	244,192 (54.6)	45,155 (63.4)	<0.001
Time to initiation, mo	-	-	10.6 (1.2–26.8)	
Urban residents	212,152 (40.9)	182,017 (40.7)	30,135 (42.3)	<0.001
Incomes (low 25%)	152,749 (29.5)	132,390 (29.6)	20,359 (28.6)	<0.001
Prescription				
Hospitals	-	-	52,332 (73.4)	
Clinics	-	-	18,497 (26.0)	
Etc.	-	-	430 (0.6)	
Comorbidities				
Hypertension	425,037 (82.0)	367,326 (82.1)	57,711 (81.0)	<0.001
Dyslipidemia	393,162 (75.8)	330,498 (73.9)	62,664 (87.9)	<0.001
Antidiabetic drugs[a]				
Metformin	360,462 (69.5)	301,817 (67.5)	58,645 (82.3)	<0.001
DPP-4i	235,352 (45.4)	202,327 (45.2)	33025 (46.4)	<0.001
Insulin	134,654 (26.0)	121,148 (27.1)	13,506 (19.0)	<0.001
Sulfonylureas	192,135 (37.1)	160,143 (35.8)	31,992 (44.9)	<0.001
TZD	30,799 (5.9)	25,912 (5.8)	4,887 (6.9)	<0.001
AGI	14,107 (2.7)	12,545 (2.8)	1,562 (2.2)	<0.001
Meglitinide	3,693 (0.7)	3,455 (0.8)	238 (0.3)	<0.001
SGLT2i	14,516 (2.8)	0	14,516 (20.4)	<0.001
GLP-1RA	833 (0.2)	598 (0.1)	235 (0.3)	<0.001
Cardiovascular medications				
ACEi/ARB	347,273 (67.0)	296,864 (66.4)	50,409 (70.7)	<0.001
Statins	393,010 (75.8)	330,815 (74.0)	62,195 (87.3)	<0.001
ASA	341,707 (65.9)	289,442 (64.7)	52,265 (73.4)	<0.001

Values are presented as mean±standard deviation, number (%), or median (range).
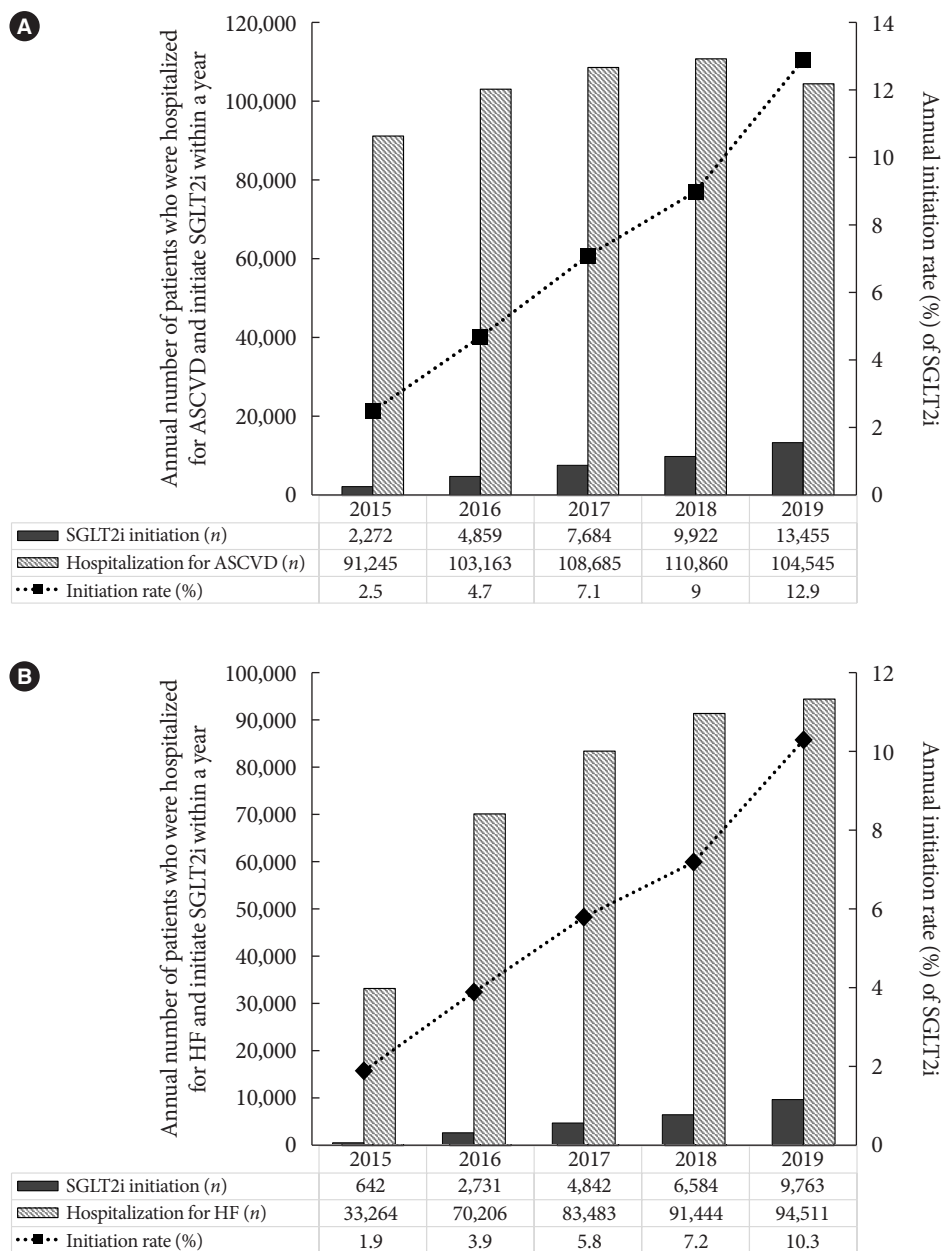SGLT2i, sodium-glucose cotransporter 2 inhibitor; DPP-4i, dipeptidyl peptidase-4 inhibitor; TZD, thiazolidinedione; AGI, alpha-glucosidase inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockade; ASA, aspirin.
[a]Drug that was first prescribed and billed after hospitalization for atherosclerotic cardiovascular disease.

sociated with SGLT2i non-users. Meanwhile, the use of metformin (OR, 1.97; 95% CI, 1.92 to 2.03; P<0.001), sulfonylurea (OR, 1.49; 95% CI, 1.45 to 1.52; P<0.001), ACEi/ARB (OR, 1.30; 95% CI, 1.26 to 1.34; P<0.001), and beta-blockers (OR, 1.16; 95% CI, 1.14 to 1.19; P<0.001) were associated with SGLT2i use (Fig. 4B, Supplementary Table 5).

DISCUSSION

In this nationwide Korean population cohort study, the rate of SGLT2i prescription in patients with T2DM increased steadily. However, the rate was not different according to the presence of ASCVD or HF. Additionally, the overall prescription rate of SGLT2i use as secondary prevention therapy was insufficient
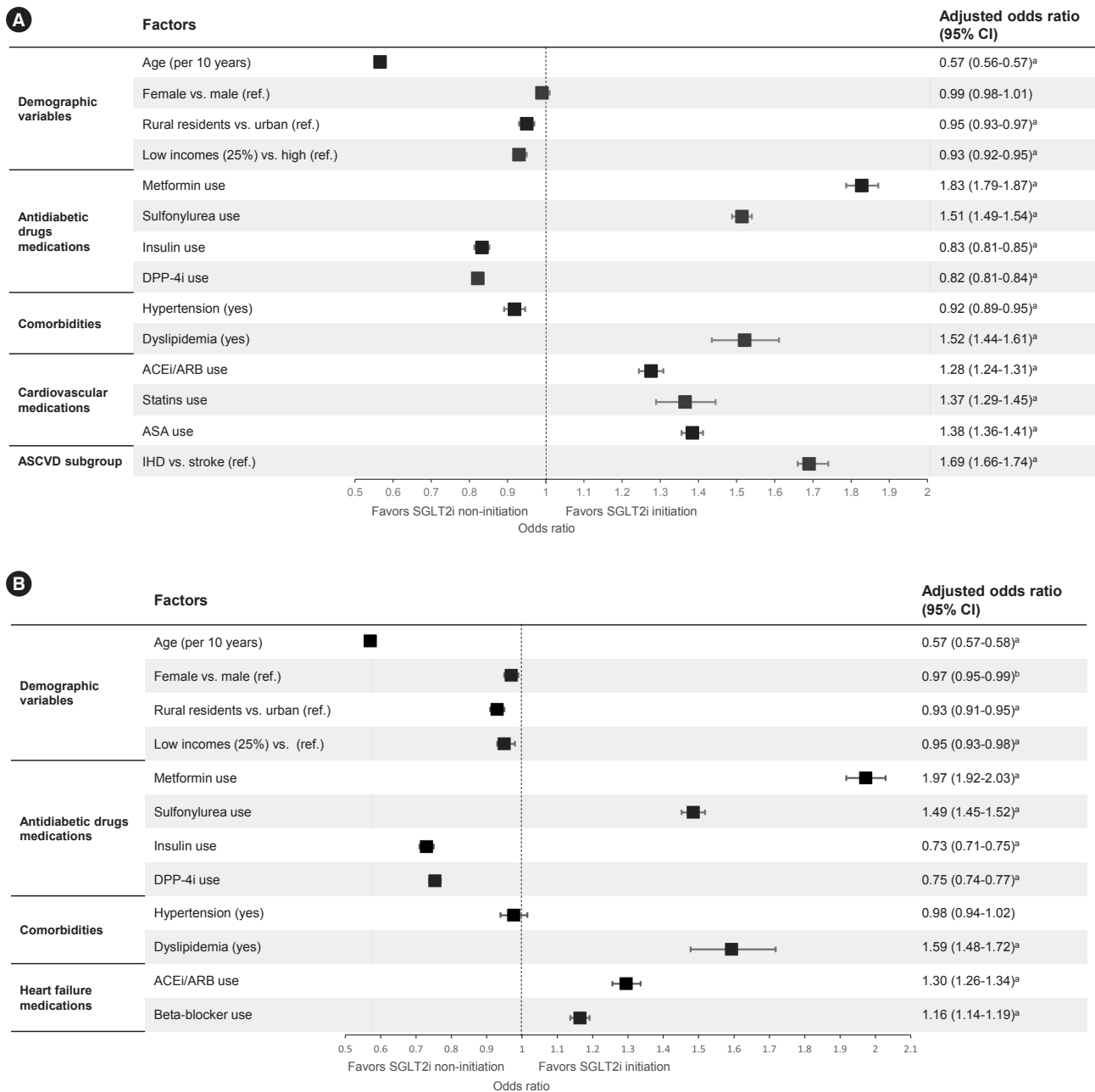
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Fig. 3. Annual initiation rate of sodium-glucose cotransporter 2 inhibitor (SGLT2i) within a year after the first hospitalization for (A) atherosclerotic cardiovascular disease (ASCVD) or (B) heart failure (HF).

compared to other CV medications. Among patients who were first diagnosed and hospitalized for ASCVD or HF, older age, female gender, DPP-4i users, rural residents, and low-income households were independently associated with lower initiation rates of SGLT2i treatment.

According to this nationwide population-based cohort data, although the rate of SGLT2i use among patients with T2DM had steadily increased every year, the proportion of SGLT2i

use in eligible patients with high CV risk was suboptimal. Globally, national cohort studies through 2019 have shown that CVD presence or risk has little effect on the decision to use SGLT2i in patients with T2DM. A United States cohort study has demonstrated that the use of antidiabetic drugs with proven CV benefits (SGLT2i, GLP-1 analogues) is suboptimal compared to other cardioprotective medications such as statins or ACEi in T2DM patients with high CV risk [17]. According

Fig. 4. Factors associated with sodium-glucose cotransporter 2 inhibitors (SGLT2i) initiation after the first hospitalization for (A) atherosclerotic cardiovascular disease (ASCVD) or (B) heart failure (HF) in patients with type 2 diabetes mellitus. DPP-4i, dipeptidyl peptidase-4 inhibitor; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockade; ASA, aspirin; IHD, ischemic heart disease; CI, confidence interval. [a]$P<0.001$, [b]$P<0.01$.

to a Danish population-based study, among all patients with T2DM who initiated SGLT2i, a minor increase was observed in proportion with ASCVD by year (from 28% in 2014 to 30% in 2017) [12]. In addition, 1- and 2-year cumulative incidence proportions of SGLT2i initiation after CVD onset were only

10.2% and 10.7%, respectively [18]. However, considering the fact that updated guidelines [8,9] have recently emphasized the selection of antidiabetic drugs according to CV risk and trends of gradual increase in the initiation rate of SGLT2i therapy since 2015, future studies with an additional follow-up are

Table 2. Baseline characteristics according to initiation of SGLT2i prescription after the first hospitalization for heart failure

Characteristic	All	SGLT2i treatment		P value
		No	Yes	
Number	372,853	331,136	41,717	
Age, yr	70.8±12.3	71.8±12.0	63.4±12.5	<0.001
Male sex	196,458 (52.7)	171,668 (51.84)	24,790 (59.42)	<0.001
Time to initiation, mo	-	-	8.8 (0.3–22.5)	
Urban residents	149,452 (40.1)	132,026 (39.9)	17,426 (41.8)	<0.001
Incomes (low 25%)	114,650 (30.8)	101,692 (30.7)	12,958 (31.1)	0.142
Prescription				
Hospitals			31,419 (75.3)	
Clinics			10,048 (24.1)	
Etc.			250 (0.6)	
Comorbidities				
Hypertension	310,925 (83.4)	275,917 (83.3)	35,008 (83.9)	0.002
Dyslipidemia	253,174 (67.9)	218,124 (65.9)	35,050 (84.0)	<0.001
Antidiabetic drugs[a]				
Metformin	235,753 (63.2)	202,742 (61.2)	33,011 (79.1)	<0.001
Sulfonylureas	130,540 (35.0)	112,159 (33.9)	18,381 (44.1)	<0.001
DPP-4i	171,984 (46.1)	152,549 (46.1)	19,435 (46.6)	0.045
Insulin	113,093 (30.3)	104,491 (31.6)	8,602 (20.6)	<0.001
SGLT2i	9,841 (2.6)	0	9,841 (23.6)	<0.001
TZD	23,525 (6.3)	20,409 (6.2)	3,116 (7.5)	<0.001
AGI	9,370 (2.5)	8,566 (2.6)	804 (1.9)	<0.001
Meglitinide	2,671 (0.7)	2,554 (0.8)	117(0.3)	<0.001
HF medications				
ACEi/ARB	247,070 (66.3)	217,021 (65.5)	30,049 (72.0)	<0.001
Statins	251,300 (67.4)	216,675 (65.4)	34,625 (83.0)	<0.001
ASA	196,245 (52.6)	170,509 (51.5)	25,736 (61.7)	<0.001

Values are presented as mean±standard deviation, number (%), or median (range).
SGLT2i, sodium-glucose cotransporter 2 inhibitor; DPP-4i, dipeptidyl peptidase-4 inhibitor; TZD, thiazolidinedione; AGI, alpha-glucosidase inhibitor; HF, heart failure; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockade; ASA, aspirin.
[a]Drug that was first prescribed and billed after hospitalization for heart failure.

needed to determine whether the guideline-recommended SGLT2i therapy is applied according to the presence or risk of CVD.

In patients who were first diagnosed and hospitalized for ASCVD or HF between 2015 and 2019, 13.7% (with ASCVD) and 11.2% (with HF) of patients initiated SGLT2i therapy. Among SGLT2i users, 53.6% (n=38,192) of patients with AS-CVD (median 10.6 months) and 58.9% (n=24,562) of those with HF (median 8.8 months) were prescribed within a year after the first hospitalization. A previous study showed that the

time to initiation of SGLT2i after the onset of CVD was gradually shortened from 2012 (4.6 years to reach 15% of SGLT2i/GLP-1 analogues use) to 2018 (0.5 years to reach 15% of use) in a Danish population [18]. Meanwhile, Sun and Yan [19] have reported that early initiation of SGLT2i within 12 months is associated with significantly lower MACE, especially in patients with known ASCVD or additional CV risk factors. In addition, a recent randomized control study demonstrated that early initiation of sotagliflozin (dual SGLT1/2 inhibitor) after the hospitalization for worsening HF lower the risk of death

from CVD and hospitalization for HF [20]. Considering the safety and potential efficacy, it may be necessary to consider early initiation of SGLT2i after hospitalization for ASCVD or HF for eligible high-risk patients.

Elderly patients were less likely to initiate SGLT2i treatment after the first diagnosis and hospitalization for ASCVD or HF. Older patients with T2DM are at a particularly high-risk of CVD [21]. However, other conditions that can increase the risk of frailty [22], fracture [23], and renal failure [24] also coexist in elderly patients. Although SGLT2i is well-tolerated, there are concerns related to volume depletion by the diuretic effect of SGLT2i that can lead to postural hypotension and syncope, especially in patients with older age. However, since CV protective effects of SGLT2i are maintained in both older and younger patients [25,26], it is necessary to actively prescribe SGLT2i with careful monitoring and management of concurrent conditions.

This study confirmed that the rate of SGLT2i use was low in females, consistent with findings of other nationwide cohort studies. Although whether poorer provider communication [27] and/or slower adoption of new guideline-directed therapies in females [14] might affect gender inequity remains unknown, concerns about side effects associated with a higher risk of genital infections [28], especially in women, might have acted as one of the barriers to prescribing SGLT2i in the high-risk group with CVD.

We also found that the use of DPP-4i was independently associated with a lower rate of SGLT2i initiation after the onset of ASCVD or HF. Globally, DPP-4i, which has neutral effects on CV outcomes, is still more widely used than SGLT2i even in CVD, HF, and chronic kidney disease [10,29]. Based on the United States claims data, patients with a history of CVD, HF, and nephropathy who could get the most benefit from SGLT2i therapy were less likely to initiate SGLT2i compared to DPP-4i [30]. In Korea, DPP-4i occupies a high proportion of total antidiabetic drugs market shares. The combination of metformin and DPP-4i is the most common dual combination therapy since 2014, while DPP-4i is the third most frequently prescribed drug after metformin and sulfonylurea among monotherapy [31]. Because the combination therapy of SGLT2i and DPP-4i was not covered by national health insurance, healthcare providers were required to consider out-of-pocket payments to initiate or switch to SGLT2i therapy. Institutional efforts to expand the insurance coverage for a combination of antidiabetic therapy are also required to ease the decision in choosing antidiabetic drugs according to CV risk.

Patients with lower income levels or rural residents were less likely to initiate SGLT2i treatment after the onset of ASCVD or HF. Income level was a strong predictor of unmet healthcare needs [29], and lower income households are associated with a reduced rate of SGLT2i treatment in the United States population [32]. Meanwhile, although low-income households were exempted from cost or had access to discounted copayment rates in Korea, the unfavorable gap in accessibility to hospitals according to income levels continued [33] due to limited benefit coverage [34].

This study has some limitations. Due to the nature of an insurance claims-based database, although the presence or initiation of each prescription was identified, adherence to or duration of treatment was unavailable. In addition, the actual usage rate might have been underestimated when the prescription was not covered by or claimed by the KNHIS. We were unable to identify clinical factors such as glycosylated hemoglobin or renal function. The use of SGLT2i is limited in T2DM patients with impaired renal function, especially in those with concomitant CVD. Until August 2019 in Korea, the use of SGLT2i was approved in patients with preserved renal function (estimated glomerular filtration rate [eGFR] >60 mL/min/1.73 m^2). Meanwhile, the overall prevalence of chronic kidney disease (albuminuria or low eGFR [<60 mL/min/1.73 m^2]) in patients diagnosed with CVD was 17.3%, which was higher than the general population (8.2%), according to the Korean National Health and Nutrition Examination Survey in 2011 to 2013 [35]. We could not account for intolerance, contraindications, comorbidities, or other barriers to choosing medical therapy. In addition, more detailed clinician- and patient-related factors and interactions that might affect the decision were not evaluated. Despite these limitations, this nationwide population-based data minimized the selection bias and offered nationwide prescription trends. In addition, this study offers a clue to provide more detailed and appropriate treatment for patients with T2DM who are vulnerable to or at high-risk for CVD in the future.

In conclusion, this Korean population-based cohort study demonstrated that the rate of SGLT2i use in patients with T2DM had increased steadily from 2015 to 2019. However, the accompanying ASCVD or HF did not affect the prescription rate of SGLT2i, and the prescription rate of SGLT2i was insufficient compared to that of other CV protective medications. There were age, gender, socioeconomic, and medication-relat-

ed inequalities in prescribing an SGLT2i after the hospitalization for ASCVD or HF. More attention and efforts are needed to address factors affecting inequality in the prescription of SGLT2i with proven CV protection. Considering benefits and risks, it is necessary to actively consider the prescription of SGLT2i in the high-risk group for CVD.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2022.0002.

CONFLICTS OF INTEREST

Seung-Hyun Ko has been executive editor of the *Diabetes & Metabolism Journal* since 2022. She was not involved in the review process of this article. Otherwise, there was no conflict of interest.

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