

# Effect of the addition of thiazolidinedione to sodium-glucose cotransporter 2 inhibitor therapy on lipid levels in type 2 diabetes mellitus: a retrospective study using Korean National Health Insurance Service data

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**Background:** Dyslipidemia is common in patients with type 2 diabetes mellitus (T2D) and contributes to an increased risk of cardiovascular disease. Previous studies have shown that treatment with thiazolidinediones (TZDs) and sodium-glucose cotransporter-2 inhibitors (SGLT2-i) may help to improve dyslipidemia in T2D patients. In this study, we investigated whether patients treated with TZD and SGLT2-i showed greater improvement in high-density lipoprotein cholesterol (HDL-C) levels than those treated with only SGLT2-i.

**Methods:** From the National Health Insurance Service database of Korea, we extracted all patients who first received SGLT2-i from 2014 to 2016. Propensity score matching was performed to balance the two groups: group A (SGLT2-i and TZD, regardless of other antidiabetic medications) and group B (SGLT2-i only without TZD, regardless of other antidiabetic medications). Posttreatment HDL-C levels were compared by the Student t-test.

**Results:** In total, 1,400 T2D patients (700 in each group) were matched by propensity score matching. There was a significant post-treatment increase in HDL-C in group A ( $49.54 \pm 20.03$  to  $51.6 \pm 12.92$  mg/dL,  $P=0.007$ ), but not in group B ( $49.14 \pm 13.52$  to  $49.1 \pm 2.15$  mg/dL,  $P=0.937$ ). Group A also showed significantly higher posttreatment HDL-C levels than group B ( $51.4 \pm 12.92$  vs.  $49.1 \pm 12.15$  mg/dL,  $P<0.001$ ). Regarding the secondary endpoints, posttreatment triglyceride levels were lower ( $P<0.001$ ), but total cholesterol ( $P=0.131$ ) and low-density lipoprotein cholesterol levels ( $P=0.054$ ) were not different after treatment.

**Conclusions:** The combination of SGLT2-i and TZD may be more effective in ameliorating dyslipidemia in T2D patients than SGLT2-i alone. However, further studies are needed to confirm this finding.

**Keywords:** Type 2 diabetes mellitus; Dyslipidemias; Sodium-glucose transporter 2 inhibitors; Thiazolidinedione; Drug combination

**Received:** July 6, 2022; **Accepted:** July 19, 2022

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## INTRODUCTION

Type 2 diabetes (T2D) is a significant risk factor for cardiovascular disease (CVD). Coronary artery disease and stroke are the main causes of death in T2D patients [1–4]. Dyslipidemia is a major modifiable factor for CVD prevention [3,4]. Therefore, the management of dyslipidemia is necessary to reduce mortality due to CVD in patients with T2D [5,6].

Low levels of high-density lipoprotein cholesterol (HDL-C) are a key feature of diabetic dyslipidemia [6–9], as well as a major independent risk factor for CVD [10]. While statins are the mainstay of dyslipidemia management, they have limited effects on HDL-C [11]. A previous study found that HDL-C levels increased when sodium-glucose cotransporter-2 inhibitors (SGLT2-i) and thiazolidinediones (TZDs) were administered alone or in combination [4,7,12–19]. Therefore, it was expected that a combination of TZD and SGLT2-i would increase HDL-C levels more than treatment with only SGLT2-i.

Some clinical trials have added SGLT2-i to background TZD treatment [7,17,18,20], but to our knowledge, there have been no clinical trials in which TZD was added to SGLT2-i treatment. In this study, using national health insurance data, we aimed to investigate whether treatment with a combination of TZD and SGLT2-i resulted in a greater improvement in HDL-C levels than treatment with SGLT2-i alone.

## METHODS

### Ethical statement

This study was approved by the Institutional Review Board of Sungkyunkwan University (No. 2021-05-017). Participants who underwent national health checkup examinations provided written informed consent for the use of their data for research purposes. All personal information was deleted, and only de-identified data were included in the analysis.

### Study setting and data source

Korea has a mandatory social health insurance system, called the National Health Insurance Service (NHIS), which is run by the government (i.e., the Ministry of Health and Welfare). The entire Korean population is covered by the NHIS, except for the lowest-income segment of the popu-

lation (approximately 3%), who are covered by medical aid. In Korea, all medical providers are compulsorily designated by the NHIS, and the providers must register all disease diagnoses, medical procedures, and drug prescription information for reimbursement from the NHIS. All administrative procedures for NHIS subscribers and the medical aid population are performed by the NHIS, which is a public corporation.

The Korean government also operates the National Health Screening Program (NHSP). All insured adults are eligible for a regular health checkup every 2 years. In 2014, the target population's participation rate in the program's general health examination was 74.8% [21]. Currently, Korea's NHSP is the world's most extensive health screening program.

This retrospective study used the NHIS database. The NHIS maintains five databases: the qualification database, the national health checkup database, the medical use database, the long-term care insurance database (since 2014), and the healthcare provider database [22]. The NHIS operates the National Health Information Sharing Service to support policies and academic research by providing information (Wonju, NHIS; <https://nhiss.nhis.or.kr>). The NHIS databases have been extensively used for medical and health policy research.

For this research, we used a custom NHIS database, which was designed according to the researchers' needs [22]. Data extraction was performed by medical record technicians at the NHIS Center, who had no conflicts of interest related to this study.

### Study population

We extracted 129,666 T2D patients (International Classification of Diseases 10th revision [ICD-10] codes, E10–E14) who were first prescribed SGLT2-i from the NHIS database from October 1, 2014 to December 31, 2016. Of these, 127,066 adults aged 30 years or older were selected.

The index date was the first prescription date for T2D patients who first received SGLT2-i between 2014 and 2016. As of the index date, T2D patients who had not received a medical examination during the previous 2 years and within 2 years thereafter were excluded. We also excluded patients with type 1 diabetes mellitus (ICD-10, E10) and gestational diabetes mellitus (ICD-10, O244 and O249) from January 1, 2002 to the index date.

The group with TZD prescriptions was defined as patients who were also prescribed TZD at the time of the first prescription of SGLT2-i, and it excluded patients who received only SGLT2-i. Subsequently, we performed propensity score matching (PSM), which is known to reduce confound-

ing in observational studies [23]. All possible covariates, including demographic and medical information (Table 1) were included in PSM, and logistic regression analysis was performed to calculate the propensity scores in a logistic model. We set the caliper for nearest-neighbor matching

**Table 1.** PSM in patients treated with SGLT2-i with or without TZDs

Variable	Before PSM			After PSM		
	Group A (n=702)	Group B (n=45,850)	ASD	Group A (n=700)	Group B (n=700)	ASD
Index year						
2014	108 (15.38)	5,164 (11.26)	0.1215	107 (15.29)	112 (16.00)	0.0195
2015	331 (47.15)	19,434 (42.39)	0.0958	330 (47.14)	337 (48.14)	0.0200
2016	263 (37.46)	21,252 (46.35)	0.1809	263 (37.57)	251 (35.86)	0.0355
Hypertension	455 (64.81)	29,175 (63.63)	0.0246	453 (64.71)	455 (65.00)	0.0061
Dyslipidemia	514 (73.22)	32,360 (70.58)	0.0588	513 (73.29)	520 (74.29)	0.0227
Income (lowest 20%)	122 (17.38)	8,811 (19.22)	0.0476	122 (17.43)	132 (18.86)	0.0371
Smoke						
Nonsmoker	343 (48.86)	25,627 (55.89)	0.1411	343 (49.00)	332 (47.43)	0.0314
Ex-smoker	190 (27.07)	9,794 (21.36)	0.1336	189 (27.00)	201 (28.71)	0.0382
Current smoker	169 (240.7)	10,429 (22.75)	0.0312	168 (24.00)	167 (23.86)	0.0033
Alcohol drinking						
None	393 (55.98)	27,052 (59.00)	0.0611	393 (56.14)	382 (54.57)	0.0316
Mild	247 (35.19)	15,114 (32.96)	0.0471	246 (35.14)	261 (37.29)	0.0447
Heavy	62 (8.83)	3,684 (8.03)	0.0288	61 (8.71)	57 (8.14)	0.0205
Regular exercise	153 (21.79)	9,693 (21.14)	0.0158	153 (21.86)	148 (21.14)	0.0175
Medication when first prescribed SGLT2-i						
Insulin	52 (7.41)	3,283 (7.16)	0.0096	51 (7.29)	37 (5.29)	0.0824
GLP-1	2 (0.28)	6 (0.01)	0.071	2 (0.29)	2 (0.29)	0.0000
≥3 Oral agents	614 (87.46)	15,798 (34.46)	1.294	612 (87.43)	608 (86.86)	0.0170
Medication during 1 yr prior to the first SGLT2-i prescription						
Insulin	114 (16.24)	6,396 (13.95)	0.064	113 (16.14)	104 (14.86)	0.0354
Sulfonylurea	451 (64.25)	25,342 (55.27)	0.1839	450 (64.29)	464 (66.29)	0.0420
Metformin	627 (89.32)	40,632 (88.62)	0.0223	626 (89.43)	645 (92.14)	0.0938
Meglitinides	10 (1.42)	368 (0.80)	0.0592	10 (1.43)	9 (1.29)	0.0121
TZD	604 (86.04)	7,259 (15.83)	1.9727	602 (86.00)	604 (86.29)	0.0084
DPP4-i	556 (79.20)	28,523 (62.21)	0.38	556 (79.43)	575 (82.14)	0.0688
AGI	58 (8.26)	2,201 (4.80)	0.1404	57 (8.14)	68 (9.71)	0.0551
GLP-1	2 (0.28)	153 (0.33)	0.0091	2 (0.29)	5 (0.71)	0.0596
Male sex	464 (66.10)	25,195 (54.95)	0.2296	462 (66.00)	457 (65.29)	0.0150
Age (yr)	56.34±9.97	55.62±10.13	0.0716	56.33±9.96	55.67±10.14	0.0658
Height (cm)	165.02±9.26	163.63±9.17	0.1506	165.02±9.27	164.88±8.72	0.0154
Weight (kg)	72.83±14.82	73.30±14.04	0.0323	72.83±14.87	73.13±13.56	0.0212
Body mass index (kg/m <sup>2</sup> )	26.61±4.02	27.26±4.00	0.162	26.61±4.02	26.79±3.79	0.0460
Waist circumference (cm)	89.12±9.95	89.73±9.84	0.0623	89.10±9.95	89.31±9.36	0.0210
Systolic blood pressure (mmHg)	126.95±14.27	127.62±14.39	0.0463	126.94±14.29	127.28±14.44	0.0236
Diastolic blood pressure (mmHg)	77.89±9.81	78.59±9.74	0.0719	77.90±9.82	77.94±9.20	0.0042
Glucose (mg/dL)	166.19±58.77	157.49±54.34	0.1536	166.25±58.79	170.96±58.98	0.0801
Total cholesterol (mg/dL)	175.97±44.05	182.61±48.75	0.1429	176.01±44.08	176.48±41.25	0.0110
HDL-C (mg/dL)	49.51±20.01	48.86±13.21	0.0385	49.54±20.03	49.14±13.52	0.0235

(Continued to the next page)

**Table 1.** Continued

Variable	Before PSM			After PSM		
	Group A (n=702)	Group B (n=45,850)	ASD	Group A (n=700)	Group B (n=700)	ASD
LDL-C (mg/dL)	96.20±51.49	100.30±44.32	0.0854	94.90±36.15	95.62±37.01	0.0199
Aspartate aminotransferase (U/L)	26.84 (25.41–27.83)	28.22 (28.03–28.34)	0.1097	26.58 (25.16–27.56)	26.84 (25.50–27.77)	0.0203
Alanine aminotransferase (U/L)	29.08 (27.25–30.35)	31.50 (31.24–31.67)	0.1366	28.79 (26.98–30.05)	29.08 (27.22–30.38)	0.0043
Triglyceride (mg/dL)	141.17 (132.47–147.26)	148.41 (147.27–149.18)	0.083	141.17 (132.45–147.26)	141.17 (132.31–147.37)	0.0047
rGTP (IU/L)	37.34 (34.26–39.53)	38.86 (38.47–39.12)	0.0578	37.34 (34.26–39.53)	36.97 (34.07–39.02)	0.0085
GFR (mL/min/1.73 m <sup>2</sup> )	90.41±25.79	91.16±29.32	0.0272	90.41±25.82	91.31±25.59	0.0350
Fatty liver index	49.39±26.90	52.96±26.69	0.1332	49.39±26.89	49.99±26.29	0.0254
Diabetes mellitus duration (yr)	9.05±4.06	7.07±4.72	0.4497	9.05±4.07	9.29±4.10	0.0586
Previous index date (day)	353.92±230.97	347.79±230.95	0.0265	354.09±230.94	345.30±223.00	0.0387
Next index date (day)	330.82±215.76	329.50±214.20	0.0061	330.71±216.06	345.45±226.62	0.0666

Values are presented as number (%), mean±standard deviation, or geometric mean (95% confidence interval).

PSM, propensity score matching; SGLT2-i, sodium-glucose cotransporter-2 inhibitors; TZD, thiazolidinedione; ASD, absolute standardized difference; GLP-1, glucagon-like peptide-1; DPP4-i, dipeptidyl peptidase-4 inhibitors; AGI, alpha-glucosidase inhibitors; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; rGTP, gamma-glutamyl transpeptidase; GFR, glomerular filtration rate.

within the first 4 to 8 digits, allowing PSM at a 1:1 ratio. Finally, 700 patients were obtained for each group: group A (SGLT2i and TZD, regardless of other antidiabetic medications) and group B (SGLT2i only without TZD, regardless of other antidiabetic medications) (Fig. 1).

### Study endpoint

The primary endpoint was the posttreatment HDL-C level. The secondary endpoints were posttreatment triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and total cholesterol (TC) levels.

### Statistical analysis

The absolute value of the standardized mean difference (ASD) was used to determine the balance before and after PSM, and an ASD <0.1 was used to determine whether all covariates were sufficiently balanced through PSM. Since PSM was performed and baseline characteristics of groups A and B were comparable, differences in the study endpoints between groups A and B were compared with the Student t-test without consideration of the baseline characteristics. In addition, the paired t-test was used to analyze differences between the pre- and posttreatment values within each group. All statistical analyses were performed using SAS ver. 9.4 (SAS Institute Inc., Cary, NC, USA), and P-values less than 0.05 were considered statistically

significant.

## RESULTS

### Patient disposition and baseline characteristics

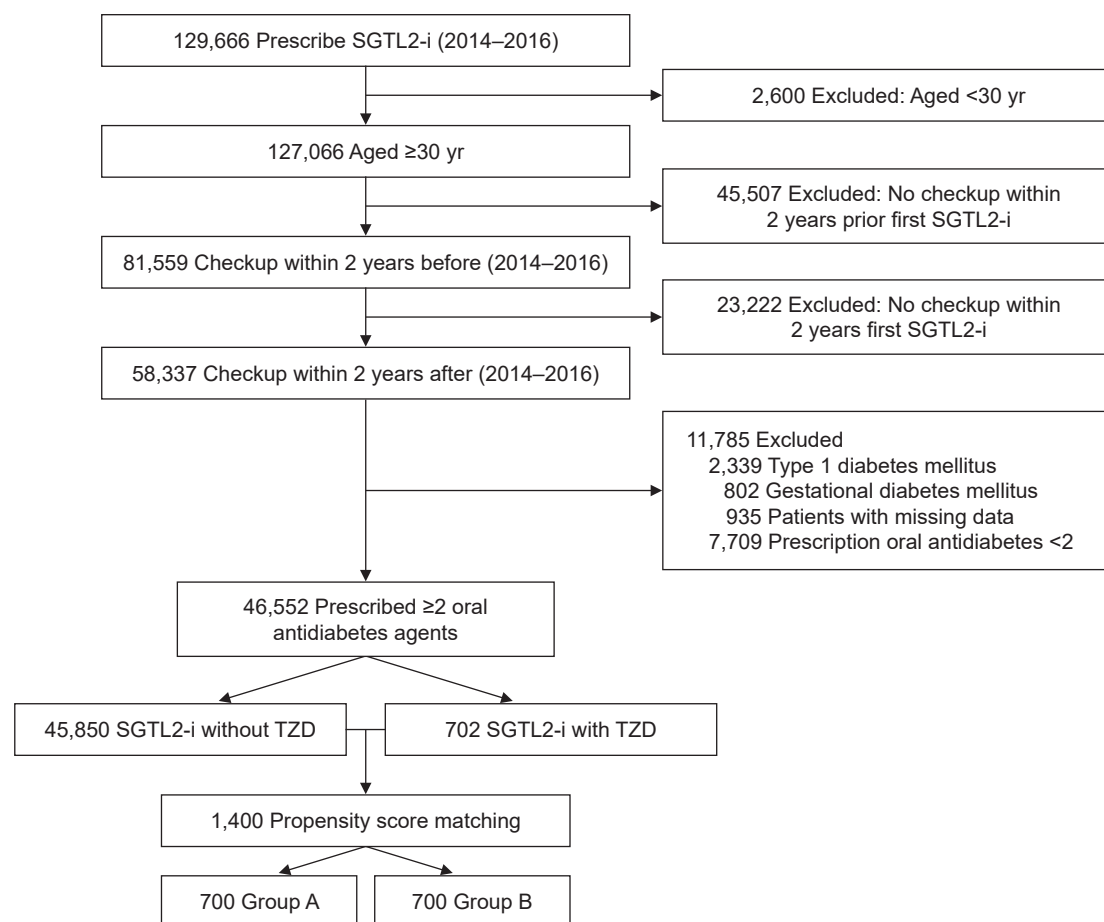
After PSM, 1,400 patients (700 patients in each group) were included in the analysis. The characteristics of groups A and B before and after PSM are compared in Table 1. The ASDs of all covariates were below 0.1, indicating that the two groups were sufficiently balanced after PSM (Table 1).

### Comparison of the primary outcome HDL-C

In the posttreatment comparison conducted using the Student t-test, group A showed significantly higher HDL-C levels (51.4±12.92 vs. 49.1±12.15 mg/dL,  $P<0.001$ ) than group B. When comparing the pretreatment and posttreatment HDL-C levels within each group, a significant increase was found in group A (49.54±20.03 to 51.6±12.92 mg/dL,  $P=0.007$ ), whereas no significant change was observed in group B (49.14±13.52 to 49.1±2.15 mg/dL,  $P=0.937$ ) (Table 2).

### Changes in the secondary outcomes

In the posttreatment comparison conducted using the Student t-test, group A showed significantly lower TG levels than group B (120.51 mg/dL, 95% confidence in-



**Fig. 1.** Patient disposition. SGLT2-i, sodium-glucose cotransporter-2 inhibitors; TZD, thiazolidinedione.

**Table 2.** Effect of sodium-glucose cotransporter-2 inhibitors with or without thiazolidinedione treatment in propensity score-matched type 2 diabetes patients (n=1,400)

Variable	Pretreatment	Posttreatment	P-value	P-value <sup>a)</sup>
HDL cholesterol (mg/dL)				
Group A	49.54±20.03	51.60±12.92	0.007	<0.001
Group B	49.14±13.52	49.10±12.15	0.937	
Triglyceride (mg/dL)				
Group A	141.53 (135.71–147.60)	120.51 (115.60–125.62)	<0.001	<0.001
Group B	141.15 (135.21–147.34)	135.59 (129.98–141.43)	0.056	
Total cholesterol (mg/dL)				
Group A	176.01±44.08	167.40±41.49	<0.001	0.131
Group B	176.48±41.25	165.85±40.71	<0.001	
LDL cholesterol (mg/dL)				
Group A	94.90±36.15	88.23±36.05	<0.001	0.054
Group B	95.62±37.01	86.13±33.76	<0.001	

Values are presented as mean±standard deviation or geometric mean (95% confidence interval). The Student t-test was used to compare posttreatment differences between groups A and B. Pretreatment values after propensity score matching were assumed to be the same.

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

<sup>a)</sup>Student t-test.



terval [CI] 115.6–126.62 mg/dL vs. 135.59 mg/dL, 95% CI 129.98–141.43 mg/dL;  $P<0.001$ ). When comparing the pretreatment and posttreatment TG levels within each group, a significant decrease was observed in group A (141.53 mg/dL [95% CI, 135.71–147.6 mg/dL] to 120.51 mg/dL [95% CI, 115.6–125.62 mg/dL];  $P<0.001$ ), but not in group B (141.15 mg/dL [95% CI, 135.7–147.6 mg/dL] to 135.59 mg/dL [95% CI, 129.98–141.43 mg/dL];  $P=0.056$ ).

No statistically significant differences were found between groups A and B in the posttreatment comparisons of TC levels ( $167.4\pm41.49$  mg/dL vs.  $165.85\pm40.71$  mg/dL,  $P=0.479$ ) and LDL-C levels ( $88.23\pm36.05$  mg/dL vs.  $86.13\pm33.76$  mg/dL,  $P=0.261$ ) using the Student t-test. However, both groups showed significant decreases in these parameters in comparisons between pretreatment and posttreatment values. TC levels decreased from  $176.01\pm44.08$  to  $167.4\pm41.49$  mg/dL ( $P<0.001$ ) in group A and from  $176.48\pm41.25$  to  $165.85\pm40.71$  mg/dL ( $P<0.001$ ) in group B. LDL-C levels decreased from  $94.9\pm36.15$  to  $88.23\pm36.05$  mg/dL ( $P<0.001$ ) in group A and from  $95.62\pm37.01$  to  $86.13\pm33.76$  mg/dL ( $P<0.001$ ) in group B (Table 2).

## DISCUSSION

In this study, we tried to determine whether dyslipidemia could be improved by using TZD in combination with SGTL2-i. Although our study was an observational study, we tried to reduce the differences between the groups by using PSM, and our real-world data might be useful considering that no clinical trial data regarding this question are available yet.

An increase in HDL-C levels was observed only in patients who were prescribed SGLT2-i and TZD (group A), who had higher posttreatment HDL-C levels than patients who were prescribed SGLT2-i only (group B). These results suggest that the combination of TZD and SGLT2-i might be helpful for the improvement of HDL-C. Many previous studies have confirmed that TZD significantly increases HDL-C levels [12,15,16,24]. Although it has been accepted that the increase in HDL-C levels with TZD treatment is entirely due to an increase in the HDL3 subfraction, the mechanism by which TZD induces alterations in the HDL3 subfraction remains unclear [25].

SGTL2-i medications are generally considered to improve HDL-C, but unexpectedly, the present study using NHIS

data found no increase in HDL-C levels with SGTL2-i treatment. A possible explanation might be that previous studies inconsistent results were reported regarding the effects of different SGLT2-i drugs on HDL-C levels [22–24], which is relevant since group B in our real-world study used various types of SGTL2-i (dapagliflozin, empagliflozin, and ipragliflozin). In addition, treatment persistence and/or adherence might not have been optimal in this study population compared to a clinical trial. Limitations of insurance benefits for SGTL2-i and TZD may also be a factor (Fig. 2).

TG is also an important aspect of diabetic dyslipidemia and a substantial risk factor for atherosclerotic CVD in patients with T2D [26]. In patients who were prescribed SGLT2-i and TZD (group A), the posttreatment TG levels were lower than in those who were prescribed SGLT2-i only (group B). This is in line with the results of previous studies showing a decrease in TG with TZD treatment [15,27,28].

LDL-C and TC levels decreased after treatment within groups A and B, but the posttreatment comparison between groups A and B did not yield significant results. TZD showed a consistent LDL-C reduction effect [15,28], while SGLT2-i slightly increased LDL-C levels [14], although differences were observed depending on the specific drugs or doses. Variations in the types and doses of SGTL2-i were not considered in this study, but should be investigated in future research.

There are several limitations of this study. First, the National Health Insurance Research Database (NHIRD) was created for entitlement and reimbursement management; therefore, it lacks clinical information, such as why patients were prescribed specific antidiabetic drugs. While we tried to balance the two groups with PSM, there could have still been some unmeasured confounders. Second, the number of patients in each group was small, at 700. Currently, the reimbursement of oral antidiabetic drugs is limited to two drugs, and the patient must pay for a third drug. As most people are prescribed metformin as the first-line drug, the number of patients who are prescribed both SGLT2-i and TZD is limited. Therefore, although this was a nationwide study, the sample size was only 700 patients and a more detailed analysis was not possible. Third, our endpoint of the lipid profile is only a proxy marker of CVD. Fourth, information about the concomitant use of anti-hyperlipidemic drugs was lacking. Further research is needed to clarify whether improving the lipid profile could lead to a reduced

		MET	SU	Meglitinide	a-GI	TZD	DPP4-i	SGLT2-i		
								Dapagliflozin	Ipragliflozin	Empagliflozin
MET			✓	✓	✓	✓	✓	✓	✓	✓
SU		✓			✓	✓	✓			
Meglitinide		✓			✓	✓				
a-GI		✓	✓	✓						
TZD		✓	✓	✓			✓		(Pioglitazone)	MET+ (Pioglitazone)
DPP4-i		✓	✓			✓		Sitagliptin MET+Sitagliptin /Saxagliptin	MET+ Sitagliptin	MET+ Liniagliptin
SGLT2-i	Dapagliflozin	✓					Sitagliptin MET+Sitagliptin /Saxagliptin			
	Ipragliflozin	✓				Pioglitazone	MET+ Sitagliptin			
	Empagliflozin	✓ MET+SU				MET+ Pioglitazone	MET+ Liniagliptin			

**Fig. 2.** Insurance benefits for antidiabetic agents in Korea based on the Health Insurance Review and Assessment Service. Pioglitazone is 100% covered by the patient. MET, metformin; SU, sulfonylurea; a-GI, alpha-glucosidase inhibitors; TZD, thiazolidinedione; DPP4-i, dipeptidyl peptidase-4 inhibitors; SGLT2-i, sodium-glucose cotransporter 2 inhibitors.

risk of coronary artery disease.

In conclusion, our study results suggest that a combination of SGLT2-i and TZD might be more effective for improving dyslipidemia than SGLT2-i alone in T2D patients. Our findings are consistent with the recommendations for using TZD in the American Diabetes Association guidelines for T2D patients with a higher CVD risk, but further studies are needed to confirm these findings.

## ARTICLE INFORMATION

### Ethical statements

This study was approved by the Institutional Review Board of Sungkyunkwan University (No. 2021-05-017). Participants who underwent national health checkup examinations provided written informed consent for the use of their data for research purposes. All personal information was deleted, and only de-identified data were included in the analysis.

### Conflicts of interest

The authors have no conflicts of interest to declare.

### Funding

None.

### Author contributions

Conceptualization: TP, KH, DS; Data curation: KH, TP; Formal analysis: KH, TP; Methodology: DS, TP, KH; Project administration: DS, TG, HK; Supervision: DS; Validation: DS, TP, KH, JP; Writing–original draft: TP, KH, DS, JP; Writing–review & editing: TP, JP, KH, DS.

All authors read and approved the final manuscript.

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