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Comparative Risk of Incident Autoimmune Diseases by First Add-on Antidiabetic Drug Class After Metformin: A Population-Based Active-Comparator, New-User Cohort Study

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Research Article

Keywords: Type 2 diabetes mellitus, Autoimmune rheumatic diseases, Sodium–glucose cotransporter 2 inhibitors, Dipeptidyl peptidase 4 inhibitors

Posted Date: November 18th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11564075/v1

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Additional Declarations: No competing interests reported.

Abstract

Purpose

To compare the incidence of autoimmune rheumatic diseases among patients with type 2 diabetes initiating different oral glucose-lowering drug classes as the first add-on to metformin.

Methods

This active-comparator, new-user cohort study used the Korean National Health Insurance Service–National Sample Cohort. Adults who initiated metformin monotherapy and subsequently added a dipeptidyl peptidase-4 (DPP-4) inhibitor, sodium–glucose cotransporter-2 (SGLT-2) inhibitor, sulfonylurea, or thiazolidinedione between January 2014 and June 2023 were included. Patients with a history of autoimmune rheumatic disease were excluded. The primary outcome was incident autoimmune rheumatic disease identified using diagnostic codes. Multivariable Cox regression was used to estimate adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs), with DPP-4 inhibitors as the reference.

Results

The cohort included 14,463 patients: 9,279 receiving DPP-4 inhibitors, 2,339 receiving SGLT-2 inhibitors, 2,434 receiving sulfonylureas, and 411 receiving thiazolidinediones. The incidence rates of autoimmune rheumatic disease were 15.32, 13.16, 16.67, and 10.97 per 1,000 person-years, respectively. Compared with DPP-4 inhibitors, SGLT-2 inhibitors were associated with lower risks of autoimmune rheumatic disease (aHR, 0.80; 95% CI, 0.65–0.99) and rheumatoid arthritis (aHR, 0.79; 95% CI, 0.63–0.99). The corresponding aHRs for overall autoimmune rheumatic disease were 1.11 (95% CI, 0.94–1.29) for sulfonylureas and 0.65 (95% CI, 0.42–1.01) for thiazolidinediones.

Conclusion

Among patients adding a second oral agent to metformin, SGLT-2 inhibitor initiation was associated with a lower incidence of autoimmune rheumatic disease than DPP-4 inhibitor initiation. Residual confounding and claims-based outcome ascertainment limit causal interpretation.

Introduction

Type 2 diabetes mellitus (T2DM) is increasingly recognized as a disease characterized not only by chronic hyperglycemia but also by chronic low-grade inflammation. Pro-inflammatory cytokines, including IL-6, TNF-α, and IL-1β, and pathways involving Toll-like receptors, the NLRP3 inflammasome, and the JNK signaling cascade disrupt insulin signaling, impair β-cell function, and perpetuate insulin resistance [1–3]. Aberrant CD4 + T-helper cell activity and dysregulated cytokine networks have also

been implicated in sustaining this “meta-inflammatory” state in T2DM [4–6]. This inflammatory milieu, together with reports of altered regulatory T-cell (Treg) populations and circulating islet-reactive autoantibodies in a subset of patients, has led investigators to propose that autoimmune mechanisms may contribute to the inflammatory response in T2DM [7, 8].

Given this pathophysiological overlap, several oral antidiabetic agents have demonstrated anti-inflammatory effects beyond their glucose-lowering actions, raising the possibility that drug selection may influence autoimmune disease risk in patients with T2DM. Because many patients prefer to avoid injectable therapies, oral agents remain central to T2DM management. Clarifying the immunomodulatory profiles of individual oral drug classes is therefore clinically relevant.

Dipeptidyl peptidase-4 (DPP-4) inhibitors are commonly used in combination with metformin. However, DPP-4, also known as CD26, is expressed on multiple immune cell types and participates in immune regulation, T-cell costimulation, and tissue remodeling after injury, providing a plausible mechanism through which DPP-4 inhibition could affect autoimmune disease risk [9]. Population-based cohort studies have yielded conflicting findings. Several large cohorts have reported associations between DPP-4 inhibitor use and lower risks of composite autoimmune disease and rheumatoid arthritis (RA) compared with non-DPP-4 inhibitor regimens [9, 10]. In contrast, a population-based study using Israeli health system data found that DPP-4 inhibitor use was associated with higher prevalences of Crohn’s disease, psoriasis, and Hashimoto’s thyroiditis than in matched controls [11]. These inconsistent findings, together with the potential immunomodulatory effects of DPP-4 inhibition, warrant further investigation of alternative oral regimens.

Sodium–glucose cotransporter-2 (SGLT-2) inhibitors have demonstrated anti-inflammatory and immunomodulatory effects in preclinical and clinical studies, including reductions in circulating C-reactive protein, IL-6, ferritin, and leptin, as well as increases in adiponectin [12, 13]. These findings raise the possibility that SGLT-2 inhibitors may be associated with a lower incidence of autoimmune disease than DPP-4 inhibitors. However, a population-based cohort study using administrative health data from a setting with universal health coverage found no significant difference in overall autoimmune rheumatic disease risk between these drug classes, although SGLT-2 inhibitor use was associated with a lower risk of systemic autoimmune rheumatic diseases [14]. A separate nationwide Korean cohort study comparing SGLT-2 inhibitors with sulfonylureas (SUs), rather than DPP-4 inhibitors, reported an 11% lower risk of incident autoimmune rheumatic disease among SGLT-2 inhibitor users [15, 16].

The comparative associations between these drug classes and autoimmune disease risk may vary across populations. Compared with Western populations, East Asian populations, including Korean patients with T2DM, more often exhibit a phenotype characterized by reduced pancreatic β-cell mass and impaired insulin secretory capacity at a relatively lower body mass index (BMI) [17]. This difference may be immunologically relevant because insulin has anti-inflammatory effects independent of glycemic control, including suppression of NF-κB activation, downregulation of ICAM-1, MCP-1, and TNF-α, promotion of nitric oxide-mediated vasodilation, and inhibition of Toll-like receptor expression [18].

Reduced endogenous insulin secretory capacity in Korean patients with T2DM could therefore alter the inflammatory milieu and potentially modify the relative immunomodulatory effects of different antidiabetic drug classes.

Accordingly, the comparative association of SGLT-2 inhibitors versus DPP-4 inhibitors with incident autoimmune rheumatic disease in Korean patients with T2DM remains unclear. This study aimed to compare the risk of incident autoimmune rheumatic disease among Korean patients with T2DM initiating SGLT-2 inhibitors versus DPP-4 inhibitors as the first add-on to metformin.

Methods

Data Source

We conducted a population-based retrospective cohort study using the National Health Insurance Service–National Sample Cohort (NHIS-NSC), a nationally representative sample of approximately 1 million individuals randomly selected from the Korean population [19]. The cohort is refreshed annually to account for deaths and new entrants, supporting its continued representativeness of the national population [20]. In Korea, the NHIS operates a mandatory health insurance system covering nearly the entire population. The sample database contains sociodemographic characteristics, insurance eligibility and income information, inpatient and outpatient healthcare utilization, diagnoses, prescription records, and dates of death [19, 20]. Diagnoses are coded according to the International Classification of Diseases, 10th Revision (ICD-10), established by the World Health Organization [19, 20]. The study covered the period from 2014 to 2023. The Institutional Review Board (IRB) of CHA Bundang Medical Center exempted the study from review because it used existing data and individuals could not be directly identified or identified through linked identifiers (Nos. CHAMC 2023-05-061 and CHAMC 2026-01-030).

Study Population and Study Design

We used an active-comparator, new-user cohort design, which emulates a randomized trial of treatment initiation and can reduce confounding by indication and healthy-user bias compared with prevalent-user designs [21]. We identified adults aged 18 years or older with T2DM (ICD-10 codes E11–E14) who initiated metformin monotherapy and subsequently received their first add-on antidiabetic agent from one of four classes: DPP-4 inhibitors, SGLT-2 inhibitors, SUs, or thiazolidinediones (TZDs). Eligible prescriptions occurred between January 1, 2014, and June 30, 2023. The four mutually exclusive exposure groups were defined by the class of the first add-on agent: metformin plus DPP-4 inhibitors (reference group), metformin plus SGLT-2 inhibitors, metformin plus SUs, and metformin plus TZDs. The index date was the date of the first add-on prescription.

To identify new users, we applied an 11-year baseline (washout) period from January 1, 2002, through December 31, 2013. We excluded patients with any diagnosis of type 1, type 2, or gestational diabetes

mellitus, or any prescription for metformin or any of the four add-on drug classes, during this period. We also excluded patients with a diagnosis of any autoimmune disease of interest before the index date and those without a recorded BMI measurement. The final cohort therefore comprised patients initiating their first add-on antidiabetic drug class who had no recorded history of the autoimmune diseases of interest and had available baseline anthropometric data.

Exposure and Outcomes

The index date was defined as the date of the first antidiabetic agent added to metformin. Patients were classified according to the class of this first add-on agent and analyzed using an intention-to-treat approach, irrespective of subsequent treatment changes. Follow-up began on the day after the index date and continued until the earliest occurrence of the outcome, death, loss of insurance eligibility, or the end of the study period (December 31, 2023).

The primary outcome was incident autoimmune rheumatic disease, defined as the first recorded diagnosis after the index date of any of the following conditions, identified using ICD-10 codes: RA (M05, M06), systemic lupus erythematosus (SLE; M32), Sjögren syndrome (M35.0), systemic sclerosis (M34), inflammatory myositis (M33), vasculitis (M30, M31), ankylosing spondylitis/spondyloarthritis (M45), or psoriatic arthritis (M07) [22]. Each condition was also analyzed separately as an individual outcome.

Covariates

Baseline covariates were assessed at or before the index date. Demographic and socioeconomic characteristics included age, sex, insurance type (National Health Insurance or medical aid), geographic region (capital or non-capital region), and household income level. Comorbidity burden was assessed using the Charlson Comorbidity Index (CCI), both as an overall score and by individual component conditions [23]. We also assessed the interval between the initial diagnosis of diabetes mellitus and initiation of second-line therapy, as well as BMI recorded at the index date. Medication use during the baseline period included antihypertensive and lipid-lowering agents.

Statistical Analysis

Baseline characteristics were summarized as means and standard deviations for continuous variables and frequencies and percentages for categorical variables. Differences across the four exposure groups were assessed using standardized mean differences (SMDs). Covariates with absolute SMDs greater than 0.05 were considered imbalanced and adjusted for in the Cox proportional hazards models.

For each outcome, incidence rates per 1,000 person-years and corresponding 95% confidence intervals (CIs) were calculated assuming a Poisson distribution. Crude and adjusted hazard ratios (aHRs) with 95% CIs were estimated using Cox proportional hazards models, with SGLT-2 inhibitors, SUs, and TZDs each compared with DPP-4 inhibitors as the reference group.

Subgroup analyses were conducted according to sex (male or female), prior use of antihypertensive agents (yes or no), prior use of lipid-lowering agents (yes or no), and age group (less than 50, 50–59, 60–69, and 70 years or older). All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Characteristics of the Study Population

Between 2014 and June 2023, 188,874 patients aged 18 years or older with newly diagnosed diabetes mellitus were identified after excluding those diagnosed during the 2002–2013 baseline period. Of these, 44,086 received metformin, and 28,852 subsequently initiated a second-line antidiabetic agent. After excluding patients with prior use of a second-line agent before the index date, those without a BMI measurement within 1 year of the index date, and those with pre-existing autoimmune disease, 14,463 patients remained: 9,279 in the DPP-4 inhibitor group, 2,339 in the SGLT-2 inhibitor group, 2,434 in the SU group, and 411 in the TZD group (Fig. 1).

Baseline characteristics of the four groups are presented in Table 1. The mean age was 53.7 ± 12.1 years, and 9,618 patients (66.5%) were male. The mean interval from diabetes diagnosis to initiation of second-line therapy was 395.0 ± 685.9 days, the mean BMI was 26.8 ± 4.2 kg/m², and the mean CCI was 1.7 ± 1.6. The interval from diabetes diagnosis to second-line therapy, BMI, age, sex, CCI, and prior use of antihypertensive and lipid-lowering agents had absolute SMDs greater than 0.05 and were included as adjustment variables in the Cox proportional hazards models.

Table 1

Baseline characteristics of the study population

Variable	Total (N = 14,463)	DPP-4 inhibitors (N = 9,279)	SGLT-2 inhibitors (N = 2,339)	SUs (N = 2,434)	TZDs (N = 411)	SMD
	N (%)	*N (%)*	*N (%)*	*N (%)*	*N (%)*	
Time from diabetes diagnosis to second-line therapy, days						
Mean ± SD	395.0 ± 685.9	374.2 ± 673.8	513.6 ± 781.4	330.7 ± 601.6	572.3 ± 737.0	0.206
BMI at index date, kg/m²						
Mean ± SD	26.8 ± 4.2	26.5 ± 4.1	28.2 ± 4.4	26.6 ± 4.2	26.6 ± 4.2	0.205
Age, years						
Mean ± SD	53.7 ± 12.1	54.4 ± 12.0	50.0 ± 11.7	54.0 ± 12.1	55.5 ± 12.0	0.236
≤ 49	5,367 (37.1)	3,207 (34.6)	1,154 (49.3)	878 (36.1)	128 (31.1)	0.234
50–59	4,579 (31.7)	2,985 (32.2)	695 (29.7)	773 (31.8)	126 (30.7)	
60–69	3,057 (21.1)	2,052 (22.1)	371 (15.9)	524 (21.5)	110 (26.8)	
≥ 70	1,460 (10.1)	1,035 (11.2)	119 (5.1)	259 (10.6)	47 (11.4)	
Sex						
Male	9,618 (66.5)	6,131 (66.1)	1,554 (66.4)	1,664 (68.4)	269 (65.5)	0.032
Female	4,845 (33.5)	3,148 (33.9)	785 (33.6)	770 (31.6)	142 (34.5)	
Insurance type						
National Health Insurance	14,177 (98.0)	9,098 (98.0)	2,303 (98.5)	2,383 (97.9)	393 (95.6)	0.087

Data are presented as mean ± standard deviation or N (%). Variables with absolute standardized mean differences > 0.05 were included as covariates in adjusted Cox proportional hazards models.

Abbreviations: BMI, body mass index; DPP-4, dipeptidyl peptidase-4; SGLT-2, sodium–glucose cotransporter-2; SU, sulfonylurea; TZD, thiazolidinedione; COPD, chronic obstructive pulmonary disease; SMD, standardized mean difference; SD, standard deviation.

Variable	Total (N = 14,463)	DPP-4 inhibitors (N = 9,279)	SGLT-2 inhibitors (N = 2,339)	SUs (N = 2,434)	TZDs (N = 411)	SMD
	N (%)	*N (%)*	*N (%)*	*N (%)*	*N (%)*	
Medical aid	286 (2.0)	181 (2.0)	36 (1.5)	51 (2.1)	18 (4.4)	
Geographic region						
Capital region	9,806 (67.8)	6,327 (68.2)	1,608 (68.7)	1,592 (65.4)	279 (67.9)	0.037
Non-capital regions	4,657 (32.2)	2,952 (31.8)	731 (31.3)	842 (34.6)	132 (32.1)	
Income level						
Mean ± SD	5.9 ± 3.0	5.9 ± 3.0	6.0 ± 3.0	5.9 ± 2.9	6.1 ± 3.0	0.046
Low (0–3)	3,827 (26.5)	2,502 (27.0)	591 (25.3)	638 (26.2)	96 (23.4)	0.057
Middle (4–7)	5,310 (36.7)	3,364 (36.3)	862 (36.9)	930 (38.2)	154 (37.5)	
High (8–10)	5,326 (36.8)	3,413 (36.8)	886 (37.9)	866 (35.6)	161 (39.2)	
Comorbidities						
Charlson Comorbidity Index						
Mean ± SD	1.7 ± 1.6	1.6 ± 1.6	1.7 ± 1.5	1.7 ± 1.6	2.1 ± 1.7	0.169
0–1	7,789 (53.9)	5,114 (55.1)	1,210 (51.7)	1,303 (53.5)	162 (39.4)	0.177
2–3	5,131 (35.5)	3,216 (34.7)	882 (37.7)	854 (35.1)	179 (43.6)	
≥ 4	1,543 (10.7)	949 (10.2)	247 (10.6)	277 (11.4)	70 (17.0)	
Myocardial infarction	152 (1.1)	79 (0.9)	47 (2.0)	21 (0.9)	5 (1.2)	0.055

Data are presented as mean ± standard deviation or N (%). Variables with absolute standardized mean differences > 0.05 were included as covariates in adjusted Cox proportional hazards models.

Abbreviations: BMI, body mass index; DPP-4, dipeptidyl peptidase-4; SGLT-2, sodium–glucose cotransporter-2; SU, sulfonylurea; TZD, thiazolidinedione; COPD, chronic obstructive pulmonary disease; SMD, standardized mean difference; SD, standard deviation.

Variable	Total (N = 14,463)	DPP-4 inhibitors (N = 9,279)	SGLT-2 inhibitors (N = 2,339)	SUs (N = 2,434)	TZDs (N = 411)	SMD
	N (%)	*N (%)*	*N (%)*	*N (%)*	*N (%)*	
Congestive heart failure	470 (3.2)	286 (3.1)	106 (4.5)	61 (2.5)	17 (4.1)	0.065
Peripheral vascular disorders	1,348 (9.3)	854 (9.2)	198 (8.5)	241 (9.9)	55 (13.4)	0.083
Cerebrovascular disease	713 (4.9)	472 (5.1)	103 (4.4)	104 (4.3)	34 (8.3)	0.088
Dementia	160 (1.1)	105 (1.1)	27 (1.2)	22 (0.9)	6 (1.5)	0.026
COPD	2,754 (19.0)	1,776 (19.1)	421 (18.0)	463 (19.0)	94 (22.9)	0.061
Peptic ulcer disease	2,457 (17.0)	1,579 (17.0)	340 (14.5)	444 (18.2)	94 (22.9)	0.113
Mild liver disease	4,518 (31.2)	2,829 (30.5)	787 (33.6)	750 (30.8)	152 (37.0)	0.079
Hemiplegia or paraplegia	61 (0.4)	49 (0.5)	2 (0.1)	6 (0.2)	4 (1.0)	0.072
Renal disease	182 (1.3)	107 (1.2)	37 (1.6)	31 (1.3)	7 (1.7)	0.028
Malignancy	437 (3.0)	284 (3.1)	64 (2.7)	79 (3.2)	10 (2.4)	0.028
Metastatic cancer	58 (0.4)	33 (0.4)	6 (0.3)	16 (0.7)	3 (0.7)	0.041
Metastatic solid tumor	61 (0.4)	41 (0.4)	6 (0.3)	12 (0.5)	2 (0.5)	0.020
Previous medication use						
Antihypertensive agents	6,276 (43.4)	3,920 (42.2)	1,090 (46.6)	1,057 (43.4)	209 (50.9)	0.097
Lipid-lowering agents	4,264 (29.5)	2,643 (28.5)	825 (35.3)	630 (25.9)	166 (40.4)	0.180

Data are presented as mean ± standard deviation or N (%). Variables with absolute standardized mean differences > 0.05 were included as covariates in adjusted Cox proportional hazards models.

Abbreviations: BMI, body mass index; DPP-4, dipeptidyl peptidase-4; SGLT-2, sodium–glucose cotransporter-2; SU, sulfonylurea; TZD, thiazolidinedione; COPD, chronic obstructive pulmonary disease; SMD, standardized mean difference; SD, standard deviation.

Primary Outcome: Overall Autoimmune Rheumatic Disease

Incidence rates and HRs for overall autoimmune rheumatic disease are presented in Table 2. The incidence rates per 1,000 person-years were 15.32 (95% CI, 14.16–16.57) in the DPP-4 inhibitor group, 13.16 (95% CI, 10.82–16.01) in the SGLT-2 inhibitor group, 16.67 (95% CI, 14.57–19.08) in the SU group, and 10.97 (95% CI, 7.15–16.82) in the TZD group. Compared with the DPP-4 inhibitor group, the adjusted HRs were 0.80 (95% CI, 0.65–0.99) for the SGLT-2 inhibitor group, 1.11 (95% CI, 0.94–1.29)for the SU group, and 0.65 (95% CI, 0.42–1.01) for the TZD group.

Table 2

Incidence rates and hazard ratios for autoimmune rheumatic disease outcomes

	No. of patients	No. of events	PYs	IR per 1,000 PYs (95% CI)	HR (95% CI)	aHR (95% CI)
Overall autoimmune rheumatic disease						
DPP-4 inhibitors	9,279	617	40,279.9	15.32 (14.16–16.57)	Reference	Reference
SGLT-2 inhibitors	2,339	100	7,598.1	13.16 (10.82–16.01)	0.85 (0.68–1.04)	0.80 (0.65–0.99)
SUs	2,434	211	12,655.6	16.67 (14.57–19.08)	1.10 (0.94–1.28)	1.11 (0.94–1.29)
TZDs	411	21	1,914.3	10.97 (7.15–16.82)	0.72 (0.47–1.11)	0.65 (0.42–1.01)
Rheumatoid arthritis						
DPP-4 inhibitors	9,279	548	40,477.4	13.54 (12.45–14.72)	Reference	Reference
SGLT-2 inhibitors	2,339	88	7,636.3	11.52 (9.35–14.20)	0.84 (0.67–1.05)	0.79 (0.63–0.99)
SUs	2,434	189	12,728.6	14.85 (12.88–17.12)	1.10 (0.94–1.30)	1.11 (0.94–1.32)
TZDs	411	21	1,915.2	10.96 (7.15–16.82)	0.81 (0.53–1.25)	0.74 (0.48–1.15)
Systemic lupus erythematosus						

Adjusted hazard ratios were estimated using Cox proportional hazards models, with the DPP-4 inhibitor group as the reference and adjustment for covariates with absolute standardized mean differences > 0.05 in Table 1. Cell counts below 5 are masked (< 5) in accordance with the data provider's policy to protect against re-identification. Results for additional individual autoimmune rheumatic diseases were not shown because event counts were too small to permit stable estimation.

Abbreviations: CI, confidence interval; HR, hazard ratio; aHR, adjusted hazard ratio; IR, incidence rate; PYs, person-years; DPP-4, dipeptidyl peptidase-4; SGLT-2, sodium–glucose cotransporter-2; SU, sulfonylurea; TZD, thiazolidinedione.

No. of patients	No. of events	PYs	IR per 1,000 PYs (95% CI)	HR (95% CI)	aHR (95% CI)	
Overall autoimmune rheumatic disease						
DPP-4 inhibitors	9,279	34	42095.4	0.81 (0.58–1.13)	Reference	Reference
SGLT-2 inhibitors	2,339	5	7833.4	0.64 (0.27–1.53)	0.77 (0.30–1.98)	0.72 (0.28–1.86)
SUs	2,434	11	13351.9	0.82 (0.46–1.49)	1.03 (0.52–2.04)	1.04 (0.53–2.06)
TZDs	411	< 5	1967.8	0.51 (0.07–3.61)	0.63 (0.09–4.58)	0.60 (0.08–4.43)
Sjögren syndrome						
DPP-4 inhibitors	9,279	20	42150.5	0.47 (0.31–0.73)	Reference	Reference
SGLT-2 inhibitors	2,339	< 5	7829.8	0.51 (0.19–1.36)	1.07 (0.36–3.15)	1.01 (0.34–3.04)
SUs	2,434	5	13361.6	0.37 (0.16–0.90)	0.79 (0.29–2.10)	0.82 (0.30–2.19)
TZDs	411	< 5	1968.7	0.51 (0.07–3.61)	1.07 (0.14–7.96)	0.81 (0.11–6.03)
Ankylosing spondylitis/spondyloarthritis						
DPP-4 inhibitors	9,279	43	42083.1	1.02 (0.76–1.38)	Reference	Reference
SGLT-2 inhibitors	2,339	10	7815.6	1.28 (0.69–2.38)	1.20 (0.60–2.40)	1.14 (0.56–2.30)
SUs	2,434	16	13316.2	1.20 (0.74–1.96)	1.21 (0.68–2.15)	1.21 (0.68–2.15)

Adjusted hazard ratios were estimated using Cox proportional hazards models, with the DPP-4 inhibitor group as the reference and adjustment for covariates with absolute standardized mean differences > 0.05 in Table 1. Cell counts below 5 are masked (< 5) in accordance with the data provider's policy to protect against re-identification. Results for additional individual autoimmune rheumatic diseases were not shown because event counts were too small to permit stable estimation.

Abbreviations: CI, confidence interval; HR, hazard ratio; aHR, adjusted hazard ratio; IR, incidence rate; PYs, person-years; DPP-4, dipeptidyl peptidase-4; SGLT-2, sodium–glucose cotransporter-2; SU, sulfonylurea; TZD, thiazolidinedione.

	No. of patients	No. of events	PYs	IR per 1,000 PYs (95% CI)	HR (95% CI)	aHR (95% CI)	
Overall autoimmune rheumatic disease							
TZDs	411	< 5		1968.7	0.51 (0.07–3.61)	0.50 (0.07–3.62)	0.45 (0.06–3.27)
Adjusted hazard ratios were estimated using Cox proportional hazards models, with the DPP-4 inhibitor group as the reference and adjustment for covariates with absolute standardized mean differences > 0.05 in Table 1. Cell counts below 5 are masked (< 5) in accordance with the data provider's policy to protect against re-identification. Results for additional individual autoimmune rheumatic diseases were not shown because event counts were too small to permit stable estimation.							
Abbreviations: CI, confidence interval; HR, hazard ratio; aHR, adjusted hazard ratio; IR, incidence rate; PYs, person-years; DPP-4, dipeptidyl peptidase-4; SGLT-2, sodium–glucose cotransporter-2; SU, sulfonylurea; TZD, thiazolidinedione.							

Individual Autoimmune Rheumatic Diseases

HRs for individual autoimmune rheumatic diseases with sufficient event counts are presented in Table 2. For RA, which accounted for the largest number of events, the adjusted HRs compared with the DPP-4 inhibitor group were 0.79 (95% CI, 0.63–0.99) for the SGLT-2 inhibitor group, 1.11 (95% CI, 0.94–1.32) for the SU group, and 0.74 (95% CI, 0.48–1.15) for the TZD group. Among the other individual outcomes reported in Table 2—SLE, Sjögren syndrome, and ankylosing spondylitis/spondyloarthritis—event counts were small. Additional individual autoimmune rheumatic disease outcomes were not tabulated because event counts were too small to permit stable estimation.

Subgroup Analyses

Subgroup analyses of overall autoimmune rheumatic disease by sex, prior use of antihypertensive agents, prior use of lipid-lowering agents, and age group (less than 50, 50–59, 60–69, and 70 years or older) are presented in Table 3. Subgroup-specific adjusted HRs for the SGLT-2 inhibitor, SU, and TZD groups, each compared with the DPP-4 inhibitor group, are reported in Table 3.

Table 3

Subgroup analyses for overall autoimmune rheumatic disease

	No. of patients	No. of events	PYs	IR per 1,000 PYs (95% CI)	HR (95% CI)	aHR (95% CI)
Sex						
Male						
DPP-4 inhibitors	6,131	315	26,959.0	11.68 (10.46–13.05)	Reference	Reference
SGLT-2 inhibitors	1,554	52	4,971.7	10.46 (7.97–13.73)	0.89 (0.66–1.19)	0.82 (0.61–1.10)
SUs	1,664	118	8,827.1	13.37 (11.16–16.01)	1.15 (0.93–1.42)	1.15 (0.93–1.42)
TZDs	269	12	1,249.5	9.60 (5.45–16.91)	0.82 (0.46–1.46)	0.73 (0.41–1.30)
Female						
DPP-4 inhibitors	3,148	302	13,320.9	22.67 (20.25–25.38)	Reference	Reference
SGLT-2 inhibitors	785	48	2,626.4	18.28 (13.77–24.25)	0.80 (0.59–1.08)	0.78 (0.57–1.06)
SUs	770	93	3,828.5	24.29 (19.82–29.77)	1.08 (0.86–1.36)	1.07 (0.84–1.35)
TZDs	142	9	664.8	13.54 (7.04–26.02)	0.60 (0.31–1.17)	0.58 (0.30–1.13)
Prior use of antihypertensive agents						
No						

Adjusted hazard ratios were estimated using Cox proportional hazards models, with the DPP-4 inhibitor group as the reference and adjustment for covariates with absolute standardized mean differences > 0.05 in Table 1. Cell counts below 5 are masked (< 5) to protect against re-identification.

Abbreviations: CI, confidence interval; HR, hazard ratio; aHR, adjusted hazard ratio; IR, incidence rate; PYs, person-years; DPP-4, dipeptidyl peptidase-4; SGLT-2, sodium–glucose cotransporter-2; SU, sulfonylurea; TZD, thiazolidinedione.

No. of patients	No. of events	PYs	IR per 1,000 PYs (95% CI)	HR (95% CI)	aHR (95% CI)	
Sex						
DPP-4 inhibitors	5,359	323	23,980.8	13.47 (12.08–15.02)	Reference	Reference
SGLT-2 inhibitors	1,249	46	4,123.4	11.16 (8.36–14.89)	0.82 (0.60–1.12)	0.77 (0.56–1.05)
SUs	1,377	104	7,397.8	14.06 (11.60–17.04)	1.05 (0.84–1.31)	1.06 (0.85–1.33)
TZDs	202	9	976.8	9.21 (4.79–17.71)	0.68 (0.35–1.32)	0.64 (0.33–1.24)
Yes						
DPP-4 inhibitors	3,920	294	16,299.1	18.04 (16.09–20.22)	Reference	Reference
SGLT-2 inhibitors	1,090	54	3,474.7	15.54 (11.90–20.29)	0.85 (0.63–1.13)	0.83 (0.62–1.11)
SUs	1,057	107	5,257.8	20.35 (16.84–24.60)	1.14 (0.92–1.43)	1.15 (0.92–1.44)
TZDs	209	12	937.5	12.80 (7.27–22.54)	0.71 (0.40–1.27)	0.67 (0.38–1.20)
Prior use of lipid-lowering agents						
No						
DPP-4 inhibitors	6,636	432	30,036.4	14.38 (13.09–15.80)	Reference	Reference

Adjusted hazard ratios were estimated using Cox proportional hazards models, with the DPP-4 inhibitor group as the reference and adjustment for covariates with absolute standardized mean differences > 0.05 in Table 1. Cell counts below 5 are masked (< 5) to protect against re-identification.

Abbreviations: CI, confidence interval; HR, hazard ratio; aHR, adjusted hazard ratio; IR, incidence rate; PYs, person-years; DPP-4, dipeptidyl peptidase-4; SGLT-2, sodium–glucose cotransporter-2; SU, sulfonylurea; TZD, thiazolidinedione.

No. of patients	No. of events	PYs	IR per 1,000 PYs (95% CI)	HR (95% CI)	aHR (95% CI)	
Sex						
SGLT-2 inhibitors	1,514	57	4,946.1	11.52 (8.89–14.94)	0.79 (0.60–1.04)	0.74 (0.56–0.99)
SUs	1,804	149	9,717.6	15.33 (13.06–18.00)	1.07 (0.89–1.29)	1.07 (0.89–1.29)
TZDs	245	13	1,219.6	10.66 (6.19–18.36)	0.74 (0.43–1.29)	0.68 (0.39–1.18)
Yes						
DPP-4 inhibitors	2,643	185	10,243.5	18.06 (15.64–20.86)	Reference	Reference
SGLT-2 inhibitors	825	43	2,651.9	16.21 (12.03–21.86)	0.89 (0.64–1.24)	0.89 (0.64–1.24)
SUs	630	62	2,937.9	21.10 (16.45–27.07)	1.18 (0.89–1.58)	1.20 (0.90–1.60)
TZDs	166	8	694.8	11.51 (5.76–23.02)	0.63 (0.31–1.29)	0.61 (0.30–1.24)
Age, years						
≤ 49						
DPP-4 inhibitors	3,207	188	14,725.2	12.77 (11.07–14.73)	Reference	Reference
SGLT-2 inhibitors	1,154	47	3,826.3	12.28 (9.23–16.35)	0.95 (0.69–1.31)	0.87 (0.62–1.20)

Adjusted hazard ratios were estimated using Cox proportional hazards models, with the DPP-4 inhibitor group as the reference and adjustment for covariates with absolute standardized mean differences > 0.05 in Table 1. Cell counts below 5 are masked (< 5) to protect against re-identification.

Abbreviations: CI, confidence interval; HR, hazard ratio; aHR, adjusted hazard ratio; IR, incidence rate; PYs, person-years; DPP-4, dipeptidyl peptidase-4; SGLT-2, sodium–glucose cotransporter-2; SU, sulfonylurea; TZD, thiazolidinedione.

No. of patients	No. of events	PYs	IR per 1,000 PYs (95% CI)	HR (95% CI)	aHR (95% CI)	
Sex						
SUs	878	59	4,654.4	12.68 (9.82–16.36)	0.99 (0.74–1.33)	1.02 (0.76–1.37)
TZDs	128	< 5	645.1	6.20 (2.33–16.52)	0.48 (0.18–1.30)	0.44 (0.17–1.20)
50–59						
DPP-4 inhibitors	2,985	216	12,992.5	16.63 (14.55–19.00)	Reference	Reference
SGLT-2 inhibitors	695	34	2,296.6	14.80 (10.58–20.72)	0.89 (0.62–1.28)	0.85 (0.59–1.23)
SUs	773	74	4,048.5	18.28 (14.55–22.95)	1.10 (0.84–1.43)	1.10 (0.84–1.43)
TZDs	126	6	596.7	10.06 (4.52–22.38)	0.60 (0.27–1.36)	0.56 (0.25–1.25)
60–69						
DPP-4 inhibitors	2,052	134	8,357.8	16.03 (13.54–18.99)	Reference	Reference
SGLT-2 inhibitors	371	16	1,165.9	13.72 (8.41–22.40)	0.83 (0.49–1.39)	0.72 (0.42–1.21)
SUs	524	47	2,695.8	17.43 (13.10–23.20)	1.11 (0.80–1.55)	1.17 (0.83–1.63)
TZDs	110	9	496.2	18.14 (9.44–34.86)	1.14 (0.58–2.23)	1.05 (0.53–2.08)

Adjusted hazard ratios were estimated using Cox proportional hazards models, with the DPP-4 inhibitor group as the reference and adjustment for covariates with absolute standardized mean differences > 0.05 in Table 1. Cell counts below 5 are masked (< 5) to protect against re-identification.

Abbreviations: CI, confidence interval; HR, hazard ratio; aHR, adjusted hazard ratio; IR, incidence rate; PYs, person-years; DPP-4, dipeptidyl peptidase-4; SGLT-2, sodium–glucose cotransporter-2; SU, sulfonylurea; TZD, thiazolidinedione.

No. of patients	No. of events	PYs	IR per 1,000 PYs (95% CI)	HR (95% CI)	aHR (95% CI)	
Sex						
≥ 70						
DPP-4 inhibitors	1,035	79	4,204.5	18.79 (15.07–23.43)	Reference	Reference
SGLT-2 inhibitors	119	< 5	309.3	9.70 (3.13–30.08)	0.49 (0.16–1.57)	0.46 (0.14–1.49)
SUs	259	31	1,256.9	24.66 (17.35–35.07)	1.35 (0.89–2.05)	1.28 (0.84–1.95)
TZDs	47	< 5	176.3	11.34 (2.84–45.35)	0.60 (0.15–2.42)	0.54 (0.13–2.21)

Adjusted hazard ratios were estimated using Cox proportional hazards models, with the DPP-4 inhibitor group as the reference and adjustment for covariates with absolute standardized mean differences > 0.05 in Table 1. Cell counts below 5 are masked (< 5) to protect against re-identification.

Abbreviations: CI, confidence interval; HR, hazard ratio; aHR, adjusted hazard ratio; IR, incidence rate; PYs, person-years; DPP-4, dipeptidyl peptidase-4; SGLT-2, sodium–glucose cotransporter-2; SU, sulfonylurea; TZD, thiazolidinedione.

Discussion

This study evaluated the association between SGLT-2 inhibitor use and incident autoimmune rheumatic disease compared with DPP-4 inhibitor use among Korean patients with T2DM. SGLT-2 inhibitor use was associated with a lower hazard of overall autoimmune rheumatic disease, with a similar association observed for rheumatoid arthritis.

These findings suggest that SGLT-2 inhibitors may have a more favorable association with autoimmune rheumatic disease incidence than DPP-4 inhibitors in patients with T2DM. If confirmed in further studies, these findings could inform research into whether autoimmune disease risk should be considered alongside established cardiovascular and renal benefits when selecting glucose-lowering therapy for appropriate patients with T2DM.

The anti-inflammatory and immunometabolic effects of SGLT-2 inhibitors provide biological plausibility for the observed associations, particularly that involving RA. Preclinical studies suggest that SGLT-2 inhibitors can suppress NLRP3 inflammasome activation and downstream IL-1β, IL-6, and IL-17 signaling, partly through β-hydroxybutyrate-mediated inflammasome inhibition, and promote a shift from pro-inflammatory M1 to reparative M2 macrophage polarization [24–26]. In T cells, these agents have

been reported to modulate ERK and mTORC1 signaling, potentially affecting T-cell activation, proliferation, and effector function while shifting the Th17/Treg balance toward a regulatory phenotype [27–29]. These mechanisms overlap with pathways implicated in RA pathogenesis, including NLRP3/IL-1β-mediated synovitis and Th17/Treg imbalance [30]. Thus, the lower hazard of RA observed among SGLT-2 inhibitor users relative to DPP-4 inhibitor users is biologically plausible, although the present observational findings do not establish a causal mechanism.

For SLE, the mechanistic rationale is also supported by experimental evidence, although the association in the present study was not statistically significant. In MRL/lpr lupus-prone mice, empagliflozin reduced anti-dsDNA IgG titers, downregulated genes related to the NLRP3 inflammasome, complement activation, and oxidative injury, and attenuated podocyte damage through mTORC1 inhibition and enhanced autophagy [31, 32]. However, these findings have not been consistently reproduced. One study using an active-disease MRL/lpr model found no improvement in proteinuria, glomerular filtration rate, or histologic lupus nephritis activity with empagliflozin. Clinical evidence in patients with established lupus nephritis has also been mixed, with some cohorts reporting reduced proteinuria and glucocorticoid-sparing effects, whereas others have found no measurable renal benefit [33]. Given this heterogeneity and the small number of incident SLE events in the present cohort, the absence of a statistically significant association should be interpreted as inconclusive rather than as evidence against a potential protective association. Larger studies are needed to clarify this relationship.

In subgroup analyses, the association between SGLT-2 inhibitor initiation and lower autoimmune rheumatic disease risk was statistically significant among patients without prior lipid-lowering medication use (aHR, 0.74; 95% CI, 0.56–0.99), but not among those with prior use (aHR, 0.89; 95% CI, 0.64–1.24). However, differences in statistical significance between subgroups do not establish effect modification, particularly in the absence of a reported formal interaction test. Furthermore, prior medication use does not necessarily indicate ongoing lipid-lowering therapy or a confirmed diagnosis of dyslipidemia. These exploratory findings therefore do not establish pharmacodynamic synergy or support preferential use of SGLT-2 inhibitors according to lipid-lowering medication history.

This study has some limitations. First, detailed laboratory and biomarker data, including measures of glycemic control, renal function, lipid profiles, inflammatory markers, and autoantibodies, were unavailable in the NHIS data, limiting our ability to account fully for differences in disease severity and metabolic or inflammatory status. Second, healthcare services and medications not captured in reimbursed insurance claims were unavailable, and follow-up was censored when individuals lost insurance eligibility. These limitations may have contributed to exposure, covariate, or outcome misclassification. Third, residual and unmeasured confounding cannot be excluded despite the active-comparator, new-user design and multivariable adjustment. Although the study period was restricted to an era in which the study drug classes were available for routine clinical use, treatment patterns and clinical practice may have evolved over time. Differences in prescribing preferences, healthcare utilization, and other unmeasured clinical characteristics may therefore have influenced the observed associations. Finally, because the study used the NHIS-NSC rather than the full nationwide database, the

numbers of exposed patients and outcome events were limited for some treatment groups and individual autoimmune rheumatic diseases, resulting in imprecise estimates for less common outcomes. Accordingly, disease-specific and subgroup findings should be interpreted cautiously and validated in larger nationwide cohorts.

Conclusions

Among Korean patients with T2DM, SGLT-2 inhibitor use was associated with a lower risk of incident autoimmune rheumatic disease, particularly RA, than DPP-4 inhibitor use. This association is biologically plausible given the reported anti-inflammatory and immunomodulatory effects of SGLT-2 inhibitors; however, the observational design precludes causal conclusions, and further epidemiological and mechanistic studies are needed. These findings provide a basis for further investigation of autoimmune rheumatic disease risk as a potential consideration in antidiabetic treatment selection, rather than supporting preferential use of SGLT-2 inhibitors for autoimmune disease prevention.

Declarations

Competing Interests

The authors have no competing interests to declare that are relevant to the content of this article.

Ethics Approval

The Institutional Review Board of CHA Bundang Medical Center determined that the study was exempt from review (CHAMC 2023-05-061 and CHAMC 2026-01-030).

Clinical trial number

Not applicable.

Consent to Participate

Not applicable; this study analyzed existing de-identified administrative claims data.

Funding

The authors did not receive support from any organization for the submitted work.

Author Contribution

Seung-Hun You and Hyounggyoon Yoo contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Seung-Hun You. The first draft of the manuscript was written by Seung-Hun You and Wonsuk Shin. Yil-Seob Lee and Hyounggyoon Yoo critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Acknowledgement

The authors thank the members of the Big Data Working Group and the Medical Big Data Research Center at CHA Bundang Medical Center for methodological discussions and support.

Data Availability

The data analyzed in this study were obtained from the Korean National Health Insurance Service–National Sample Cohort. These third-party data are not distributed by the authors. Eligible researchers may request access through the National Health Insurance Data Sharing Service (https://nhiss.nhis.or.kr), subject to its review and approval procedures.

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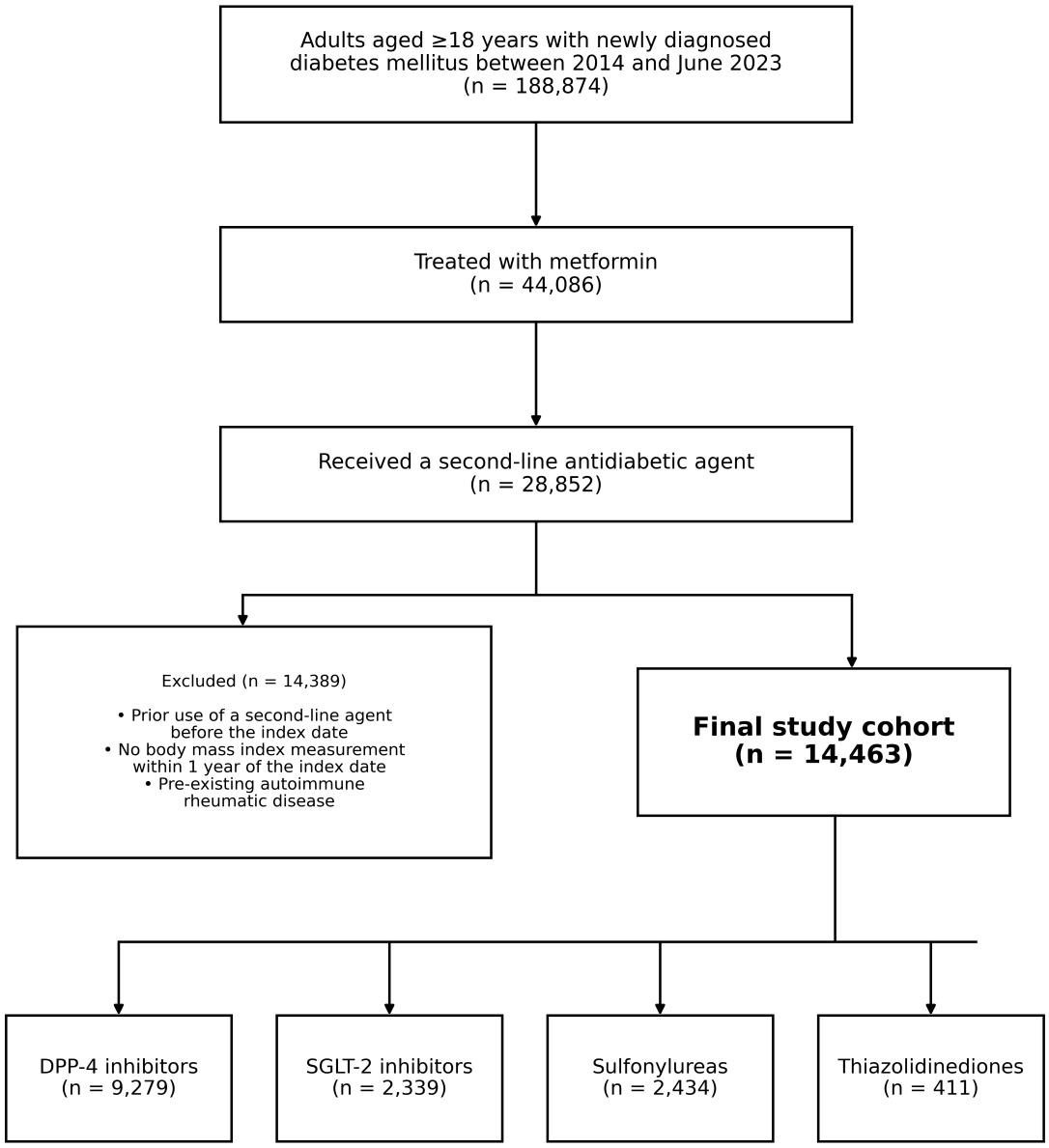
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Figures

Fig. 1 Flowchart of study population selection



Abbreviations: DPP-4, dipeptidyl peptidase-4; SGLT-2, sodium–glucose cotransporter-2; SU, sulfonylurea; TZD, thiazolidinedione.

Figure 1

Flowchart of study population selection