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ORIGINAL RESEARCH ARTICLE

Risk of acute kidney injury in dapagliflozin users with type 2 diabetes: A nationwide propensity score-matched cohort study in Korea

Hee-Jin Kim[1] | Heehyun Won[1] | Suvin Park[1] | Hui-Eon Lee[2] | Haerin Cho[1] | Jeong Ah. Kim[1] | Na-Young Jeong[1] | HoJin Shin[3] | Ye-Jee Kim[4] | Nam-Kyong Choi[1,2]

[1]Department of Health Convergence, Ewha Womans University, Seoul, Korea

[2]Department of Industrial Pharmaceutical Science, Ewha Womans University, Seoul, Korea

[3]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA

[4]Department of Clinical Epidemiology and Biostatistics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Correspondence
Nam-Kyong Choi, Department of Health Convergence, Ewha Womans University and Graduate School of Industrial Pharmaceutical Science, College of Pharmacy, Ewha Womans University, 52 Ewhayeodae-gil, Seodaemun-gu, Seoul 03760, Korea.
Email: nchoi@ewha.ac.kr

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Abstract

Background: Several previous studies have identified a potential risk of acute kidney injury (AKI) associated with sodium-glucose cotransporter-2 (SGLT-2) inhibitors, based on adverse event reports. However, recent European observational studies have shown conflicting results.

Objective: To evaluate the risk of AKI in patients with type 2 diabetes (T2DM) who were treated with dapagliflozin compared with sitagliptin.

Method: We conducted a retrospective cohort study on patients with T2DM who were newly prescribed dapagliflozin or sitagliptin between September 1, 2014, and June 30, 2021, using the nationwide National Health Insurance Review and Assessment (HIRA) Service database in Korea. Propensity scores were estimated using a multivariable logistic regression model, and matching was performed at a 1:1 ratio to balance the dapagliflozin and sitagliptin groups. The outcome of interest was the occurrence of AKI hospitalization 90 days post-exposure, captured by a validated algorithm based on the International Classification of Diseases 10th Revision (ICD-10) code: N17. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated using a Cox proportional hazards model.

Results: Among 94,977 dapagliflozin users matched to sitagliptin users, AKI events occurred in 132 dapagliflozin users versus 198 sitagliptin users, with incidence rates of 2.92 and 8.93 per 1000 person-years, respectively. The risk of AKI events was 34% lower in dapagliflozin users (HR: 0.66, 95% CI: 0.53–0.83) compared with sitagliptin users. This protective effect remained consistent in sensitivity analyses.

Conclusion: Contrary to the United States Food and Drug Administration's safety warning, our findings suggest that dapagliflozin may have a protective effect against AKI in patients with T2DM. This is consistent with recent findings from European post-marketing safety studies and may serve as supportive evidence.

KEYWORDS
acute kidney injury, cohort study, dipeptidyl peptidase 4 inhibitor, sodium-glucose transporter 2 inhibitors

1 | BACKGROUND

Dapagliflozin, a sodium-glucose cotransporter-2 (SGLT-2) inhibitor used to treat type 2 diabetes mellitus (T2DM), lowers blood glucose levels by blocking the reabsorption of glucose in the kidneys, prompting its excretion in the urine.[1] This drug was effective in lowering blood glucose levels, but several safety issues were identified during clinical trials. When the European Medicines Agency (EMA) first approved dapagliflozin in November 2012, they required additional non-interventional post-authorization safety studies (PASS) to address unresolved safety concerns from clinical trials, including urinary tract infections, acute kidney injury (AKI), acute liver injury, and bladder cancer.[2]

AKI is characterized by a sudden decline in kidney function, resulting in the accumulation of waste products and potential electrolyte imbalances in the body. Although SGLT-2 inhibitors, including dapagliflozin, have been effective in managing blood glucose levels, safety concerns about AKI have been raised because of its biological mechanism of action on the kidneys. By blocking the reabsorption of glucose in the kidney, elevated glucose concentration in nephron segments can lead to osmotic diuresis, natriuresis, and volume depletion, ultimately leading to renal vasoconstriction and decreased renal perfusion.[3,4] The reduction in renal perfusion pressure can potentially contribute to renal ischemia causing AKI, particularly in patients with preexisting renal impairment or other risk factors for AKI.[5,6] This concern was further strengthened by both a meta-analysis conducted in 2013 and a warning issued based on the United States Food and Drug Administration (FDA) adverse effect reporting system (FAERS) in June 2016.[7,8] According to a disproportionality analysis of acute renal failure (ARF) cases submitted to the FAERS between January 2013 and September 2016, cases involving SGLT-2 inhibitors showed a significantly higher proportion of ARF compared to cases without SGLT2 inhibitors in patients with T2DM.[9] In contrast, the recently completed EMA PASS reported that dapagliflozin reduced the risk of AKI by 30% compared to other glucose-lowering drugs and by 31% compared to the placebo group.[10,11]

In Korea, dapagliflozin was first approved on November 26, 2013; post-marketing surveillance was conducted to identify potential adverse events among 3371 patients who started treatment with dapagliflozin over 6 years of post-approval, and several cases of acute pyelonephritis were identified from this surveillance.[12,13] However, the absence of a comparison group in Korean case reports made it difficult to conclude the association between AKI and dapagliflozin. In addition, several observational studies conducted in Asia have shown conflicting results.[14,15] Therefore, this study aimed to investigate the association between dapagliflozin use and the risk of AKI in patients with T2DM using large-scale, nationwide claims data from Korea.

2 | METHODS

2.1 | Data source

This study utilized the nationwide health insurance claims database of the Health Insurance Review and Assessment (HIRA) from September 1, 2013, to December 31, 2021. HIRA claims data are collected when health-care providers in Korea request reimbursement for health-care services covered by the National Health Insurance Service (NHIS). Korea operates a single-payer public health insurance system, with approximately 97% of the Korean population enrolled in the NHIS. Under this system, insured citizens pay only 5%–30% of the health-care services they receive, and health-care providers submit claims to HIRA for reimbursement of the remaining health-care costs. HIRA reviews these claims to ensure the quality, appropriateness, and accuracy of the medical services provided. Information related to patient demographics, disease details, treatment details, surgical procedures, and more are accumulated in the HIRA database throughout this process.[16] These data are de-identified to protect patient privacy and provided to researchers for research purposes. Patient consent was not required for analyses of secondary claims data from de-identified human records, and we received confirmation of research ethics exemption from the Institutional Review Board of Ewha Womans University (IRB number ewha-202204-0008-01).

2.2 | Study design and population

This study utilized a retrospective cohort study design, entering patients aged over 18 years who initiated a single component of either dapagliflozin or sitagliptin between September 1, 2014 (the date of Korean insurance coverage initiation for dapagliflozin) and June 30, 2021. The start date of treatment with either dapagliflozin or sitagliptin was set as the index date for each patient. Patients were excluded if they had ever taken an SGLT-2 inhibitor, including dapagliflozin, or a dipeptidyl peptidase 4 (DPP-4) inhibitor, including sitagliptin, before the index date. Those without a diagnosis code of T2DM (International Classification of Diseases 10th Revision [ICD-10] code: E11) or those diagnosed with type 1 diabetes (ICD-10 code: E10) before the index date were also excluded. Finally, patients who had a prescription for both dapagliflozin and sitagliptin concurrently on the index date, or those with

a history of AKI within 1 year before or on the index date, were excluded from the study population. The study design with the inclusion and exclusion criteria for selecting eligible study participants is shown in Figure S1. The dapagliflozin and sitagliptin treatment groups were matched in a 1:1 ratio based on propensity scores (PS) of covariates to achieve a balance between the two groups.

2.3 | Exposures and outcomes

The exposure drug was single-component dapagliflozin, and the comparator drug was single-component sitagliptin. Fixed-dose combination drugs containing dapagliflozin or sitagliptin, such as those combined with metformin, were excluded from both the exposure and comparator drugs. Other glucose-lowering drugs, if taken separately and not as fixed-dose combinations, were also excluded. Sitagliptin is a drug that lowers blood sugar in patients with T2DM by inhibiting DPP-4, an enzyme that degrades glucagon-like peptide-1 (GLP-1), a hormone that stimulates insulin secretion to lower blood sugar levels. Sitagliptin has been used for a long time since its first approval in Korea in September 2007 and has been demonstrated by international studies not to be associated with AKI.[17,18] In addition, it was selected as the comparator drug for dapagliflozin because it was the most commonly used second-line treatment for T2DM in Korea during our study period. The outcome of interest was the occurrence of AKI, defined as a first hospitalization with ICD-10 code 'N17' as a primary or secondary diagnosis.[19,20] All patients were followed from the index date until the earliest of the following events: AKI onset, 90 days of post-exposure, the end of the database period (December 31, 2021), or a drug switch from dapagliflozin to DPP-4 inhibitors or from sitagliptin to SGLT-2 inhibitors. Our primary exposure assessment window was 90 days from the index date, and we varied the window to the following periods in sensitivity analyses: 30, 180, 270, and 365 days.

2.4 | Covariates

Baseline characteristics measured on or before the index date of our study population, including age, sex, health insurance status, type of medical institution, Charlson Comorbidity Index (CCI), and co-medication status, were selected as covariates. Comorbidity conditions using the CCI were assessed during the 365 days before the index date.[21] Co-medication status was assessed within 365 days before the index date for medications known to be associated with AKI, as well as other anti-diabetic drugs, excluding SGLT-2 inhibitors and DPP-4 inhibitors. The assessed medications included beta-blockers, bisphosphonates, calcium channel blockers, digoxin, nitrates, anticonvulsants, nonsteroidal anti-inflammatory drugs (NSAIDs), antidepressants, immunosuppressants, antiarrhythmic agents, diuretics, angiotensin receptor blocker (ARB), angiotensin-converting enzyme inhibitor (ACEI), antiplatelet agents, anti-ulcer agents, anticoagulants, agents for gout, antineoplastic agents, antibiotics, antifungals, and other anti-diabetic drugs (biguanides, sulfonylureas, meglitinides, thiazolidinedione [TZDs], alpha-glucosidase inhibitors, GLP-1 agonists, insulin).[22–24]

2.5 | Statistical analysis

Descriptive analyses were conducted to compare the baseline characteristics of the dapagliflozin and sitagliptin groups. For categorical variables, a chi-square test was performed to analyze differences in distributions, and for continuous variables, a *t*-test was used. The balance between the two groups was assessed using overlaid histograms and absolute standardized differences (aSD), considering values <0.1 as indicative of proper balance. To minimize potential confounding factors, PS for each group was computed using multivariate logistic regression models with all baseline characteristics as independent variables and treatment drugs including dapagliflozin and sitagliptin as the dependent variables. The calculated PS were then matched using the greedy matching method in a 1:1 ratio. The Cox proportional hazards model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for balanced groups regarding the risk of AKI occurrence. Two-sided p-values < 0.05 were considered statistically significant. The proportional hazards assumption was verified using a Cox proportional hazards model that included an interaction term between the treatment drug and the logarithm of time to check for normality. If the interaction term was not significant (p-value > 0.05), it supported the proportional hazards assumption, indicating that the treatment effect was consistent over time. Furthermore, sensitivity analyses were conducted to test the robustness of our findings by modifying the follow-up period from 90 to 30 days, 180, 270, and 365 days. Subgroup analyses were performed based on characteristics known as major risk factors for AKI, including age, insulin use, presence of chronic kidney disease, gender, and CCI. All analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina) and visualization using R studio (version 2023.06.1). This article follows the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines.[25]

3 | RESULTS

3.1 | Basic characteristics of the study population

We identified 107,512 patients with T2DM who initiated dapagliflozin therapy and 182,466 patients who initiated sitagliptin therapy between September 1, 2014, and June 30, 2021. Before PS matching, dapagliflozin users were younger, had lower CCI, and were more likely to have experienced calcium channel blockers and antiplatelet agents use within 1 year prior to treatment initiation compared to sitagliptin users. The proportion of beta-blockers, bisphosphonates, anticonvulsants, antidepressants, diuretics, antineoplastic agents, sulfonylurea, and insulin use was higher in the sitagliptin group. The gender distribution was similar

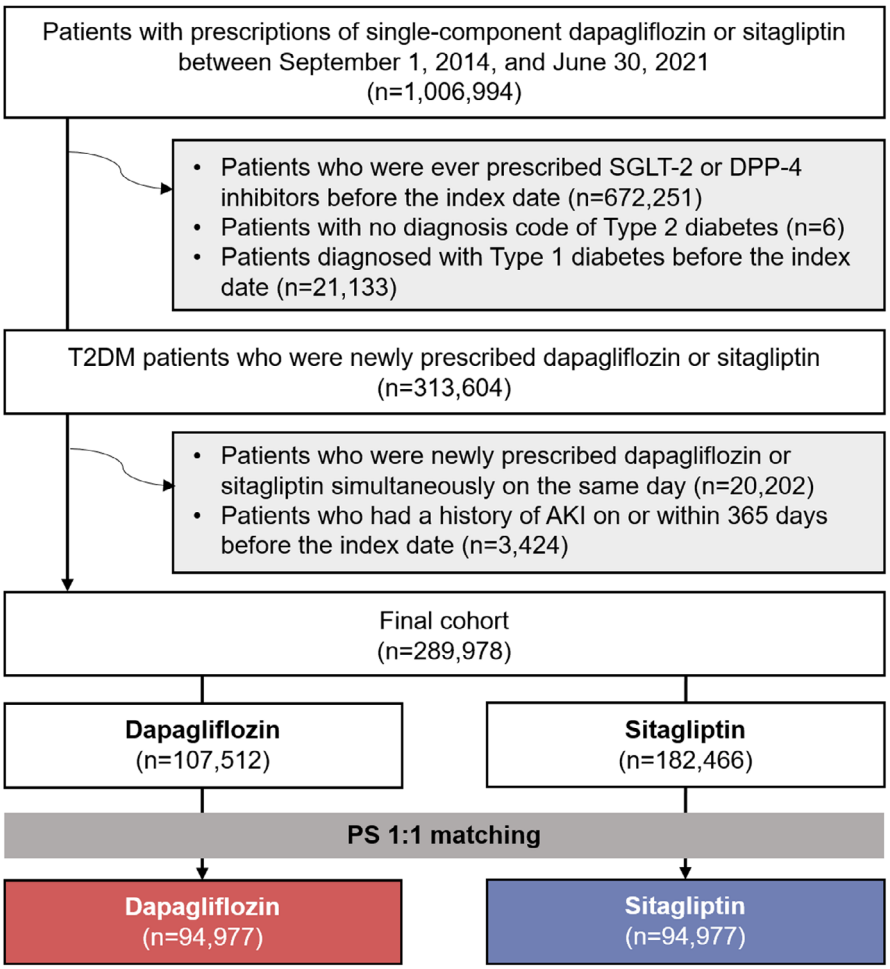

FIGURE 1 Flow chart of the study population. Study populations were selected and matched 1:1 based on the propensity score calculated by the logistic regression including covariates. AKI, acute kidney injury; DPP-4, dipeptidyl peptidase-4; SGLT-2, sodium-glucose cotransporter-2; T2DM, type 2 diabetes mellitus.

between the two groups, with males comprising a higher proportion than females in both groups. After PS matching, 94,977 dapagliflozin users were matched 1:1 to sitagliptin users (Figure 1). The baseline characteristics between the two groups were well balanced, with absolute standardized differences <0.1 for all characteristics (Table 1) (Figure S2).

3.2 | Association between dapagliflozin treatment and hospitalized AKI events

In primary analysis among the matched study population, 132 cases of hospitalized AKI occurred within 90 days after the initiation of dapagliflozin treatment, and 198 hospitalized AKI cases occurred in the sitagliptin group. The incidence rates per 1000 person-years (PY) were 5.92 and 22.18, respectively. Because the proportional hazards assumption was fully satisfied ($p=0.862$), we performed the analysis to estimate the HRs for AKI hospitalization using the Cox proportional hazard model, showing that the dapagliflozin group had a 34% lower risk of hospitalization for AKI within 90 days compared to the sitagliptin group (HR 0.66; 95% CI 0.53–0.83) (Figure 2). In sensitivity analyses, where the follow-up windows were varied to 30, 180, 270, and 365 days, the protective effects of dapagliflozin were consistently maintained. In subgroup analyses, the primary outcome of dapagliflozin's effect on AKI showed inconsistency across different strata including age, gender, CCI, history of chronic kidney disease (CKD)CC, and previous insulin use. Although individuals aged 65 years or older, females, those with a CCI of 5 or higher, and those with previous insulin use showed HR estimates below the null, their confidence intervals spanned the null. In patients with preexisting CKD before initiating dapagliflozin, no protective effect against AKI was observed (HR 1.11, 95% CI 0.58–2.11) (Figure 3). However, a consistent protective effect against AKI was noted in both users and non-users of metformin, ARBs/ACEIs, and diuretics.

4 | DISCUSSION

We conducted a retrospective cohort study using nationwide claims data to assess whether the risk of AKI differed between patients with T2DM who initiated dapagliflozin or sitagliptin between September 1, 2014, and June 30, 2021. In a cohort of 94,977 dapagliflozin users and their 1:1 matched sitagliptin comparators, our results showed a 34% reduction in the risk of AKI hospitalization within 90 days of dapagliflozin initiation, with this reduction remaining consistent across various follow-up periods.

Most previous trials and studies have reported that SGLT-2 inhibitors do not increase the risk of AKI. In a large clinical trial,

TABLE 1 Basic characteristics of study population at index date or baseline (dapagliflozin vs. sitagliptin).

	Before PS matching			After PS matching		
	Dapagliflozin (*n* = 107,512)	Sitagliptin (*n* = 182,466)		Dapagliflozin (*n* = 94,977)	Sitagliptin (*n* = 94,977)	
	N (%)	*N* (%)	SD	*N* (%)	*N* (%)	aSD
Age, years						
Mean (std)	54.3 (13.3)	61.9 (13.3)	−0.570	56.3 (12.4)	56.3 (12.8)	0.002
<45	24,498 (22.8)	18,002 (9.9)	−0.469	15,976 (16.8)	16,411 (17.3)	−0.018
45–54	28,415 (26.4)	34,375 (18.8)		25,166 (26.5)	25,589 (26.9)	
55–64	30,982 (28.8)	50,966 (27.9)		30,256 (31.9)	28,677 (30.2)	
≥65	23,617 (22.0)	79,123 (43.4)		23,579 (24.8)	24,300 (25.6)	
Gender						
Male	60,595 (56.4)	102,314 (56.3)	0.006	53,659 (56.5)	54,175 (57.0)	−0.011
CCI						
Mean (std)	0.93 (1.29)	1.24 (1.68)	−0.212	1.0 (1.3)	1.0 (1.4)	−0.001
≥5	2135 (2.0)	8243 (4.5)	−0.143	2072 (2.2)	2486 (2.6)	−0.029
Health insurance status						
Medical aid	5391 (5.0)	12,427 (6.8)	−0.076	5039 (5.3)	5092 (5.4)	−0.003
Medical institution						
Tertiary hospital	47,858 (44.5)	71,861 (39.4)	−0.084	40,064 (42.2)	39,688 (41.8)	0.000
Secondary hospital	7131 (6.6)	24,698 (13.5)		7027 (7.4)	6995 (7.4)	
Clinic	51,596 (48.0)	82,540 (45.2)		46,959 (49.4)	47,363 (49.9)	
Public health care	937 (0.9)	3367 (1.9)		927 (1.0)	931 (1.0)	
Medication status						
Beta-blocker	62,564 (58.2)	112,005 (61.4)	−0.065	55,396 (58.3)	55,294 (58.2)	0.002
Bisphosphonates	2442 (2.3)	8487 (4.7)	−0.131	2434 (2.6)	2396 (2.5)	0.003
Calcium channel blockers	40,116 (40.7)	74,241 (37.3)	−0.069	35,703 (37.6)	35,609 (37.5)	0.002
Digoxin	3226 (1.3)	1386 (1.8)	−0.039	1290 (1.4)	1291 (1.4)	0.000
Nitrates	6822 (6.4)	9315 (5.1)	0.053	5677 (6.0)	5682 (6.0)	0.000
Anticonvulsants	9003 (8.4)	21,880 (12.0)	−0.120	8425 (8.9)	8500 (9.0)	−0.003
NSAIDs	89,321 (83.1)	155,371 (85.2)	−0.057	79,229 (83.4)	79,024 (83.2)	0.006
Antidepressants	35,183 (32.7)	73,152 (40.1)	−0.154	32,247 (34.0)	32,125 (33.8)	0.003
Immunosuppressants	1069 (1.0)	2788 (1.5)	−0.048	1020 (1.1)	1060 (1.1)	−0.004
Antiarrhythmic agents	6026 (5.6)	12,460 (6.8)	−0.051	5459 (5.8)	5466 (5.8)	0.000
Diuretics	15,076 (14.0)	33,657 (18.5)	−0.120	13,773 (14.5)	13,818 (14.6)	−0.001
ARB/ACEI	58,406 (54.3)	98,301 (53.9)	0.009	51,413 (54.1)	51,270 (54.0)	0.003
Antiplatelet agents	73,068 (68.0)	111,204 (61.0)	0.147	63,616 (67.0)	63,669 (67.0)	−0.001
Anti-ulcer agents	86,865 (80.8)	152,541 (83.6)	−0.073	77,313 (81.4)	77,141 (81.2)	0.005
Anticoagulants	7819 (7.3)	16,695 (9.2)	−0.068	7035 (7.4)	7061 (7.4)	−0.001
Agents for gout	3498 (3.3)	5606 (3.1)	0.010	3005 (3.2)	3021 (3.2)	−0.001
Antineoplastic agents	1658 (1.5)	7382 (4.1)	−0.152	1636 (1.7)	1701 (1.8)	−0.005
Antibiotics	69,178 (64.3)	122,108 (66.9)	−0.054	61,243 (64.5)	61,094 (64.3)	0.003
Antifungal	32,108 (29.9)	61,240 (33.6)	−0.080	28,795 (30.3)	28,791 (30.3)	0.000
Other Ads						
Biguanide	79,252 (73.7)	134,864 (73.9)	−0.005	70,084 (73.8)	69,922 (73.6)	0.004
Sulfonylurea	35,622 (33.1)	78,477 (43.0)	−0.204	33,598 (35.4)	34,285 (36.1)	−0.015

TABLE 1 (Continued)

	Before PS matching			After PS matching		
	Dapagliflozin (*n* = 107,512)	Sitagliptin (*n* = 182,466)		Dapagliflozin (*n* = 94,977)	Sitagliptin (*n* = 94,977)	
	N (%)	*N* (%)	SD	*N* (%)	*N* (%)	aSD
Meglitinide	639 (0.6)	1585 (0.9)	−0.031	624 (0.7)	625 (0.7)	0.000
TZD	8210 (7.6)	12,219 (6.7)	0.036	7193 (7.6)	7319 (7.7)	−0.005
Alpha-glucosidase inhibitor	3948 (3.7)	8273 (4.5)	−0.044	3741 (3.9)	3780 (4.0)	−0.002
GLP-1 agonist	445 (0.4)	139 (0.1)	0.068	138 (0.2)	133 (0.1)	0.001
Insulin	16,121 (15.0)	41,546 (22.8)	−0.200	15,041 (15.8)	15,084 (15.9)	−0.001

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; Ads, anti-diabetic agents; ARB, angiotensin receptor blocker; aSD, absolute standard difference; CCI, Charlson comorbidity index; GLP-1, glucagon-like peptide-1; NSAIDS, nonsteroidal anti-inflammatory drug; PS, Propensity score; SD, standard difference; std., Standard deviation; TZD, thiazolidinedione.

Follow-up period	Dapagliflozin			Sitagliptin			HR (95% CI)
	No. of events	1000PYs	IR	No. of events	1000PYs	IR	
30 days	55	7.67	7.17	78	7.64	10.21	0.70 (0.50-0.99)
90 days	132	22.31	5.92	198	22.18	8.93	0.66 (0.53-0.83)
180 days	219	43.18	5.07	303	43.03	7.04	0.72 (0.61-0.86)
270 days	281	62.59	4.49	398	62.77	6.34	0.71 (0.61-0.82)
365 days	326	81.18	4.02	486	82.14	5.92	0.68 (0.59-0.78)

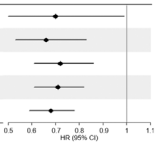

FIGURE 2 Risk of AKI with dapagliflozin compared to sitagliptin. Risks of AKI occurrence with dapagliflozin compared to sitagliptin were calculated according to the follow-up period after the index date using a Cox proportional hazard model. The incidence rate per 1000 person-years was estimated by dividing the number of AKI cases by the total person-years and multiplying by 1000 in each cohort. CI, confidence interval; HR, hazard ratio; IR, incidence ratio; PY, person year.

the Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58), dapagliflozin use was associated with a lower incidence of AKI events compared to placebo.[11] Early studies conducted for 1207 and 4778 SGLT-2 inhibitor users in the United States and Canada, respectively, using data from electronic medical records found a trend toward a reduced risk of AKI in SGLT-2 inhibitor users compared to non-users or other oral glucose-lowering drugs (oGLDs) users, though the results were not statistically significant.[26,27] Recent large-scale observational studies across diverse racial groups have reported a protective effect of dapagliflozin against AKI. In Europe, a PASS analyzing data from approximately 34,000 dapagliflozin users found a 30% reduction in AKI risk compared to all oGLDs and a 22% reduction compared to DPP-4 inhibitors.[10] A Taiwanese study including a total of 29,116 dapagliflozin-treated patients derived from a national claims database also demonstrated a 39% reduction in AKI risk with dapagliflozin compared to DPP-4 inhibitors.[15] Our findings align with these results in terms of trends and the magnitude of estimates, further reinforcing evidence of the protective effects of SGLT-2 inhibitors.

Older age and male gender are well-known risk factors for AKI.[28–30] A previous Japanese study found that characteristics such as being over 65 years of age, male, having comorbidities, and low estimated glomerular filtration rate (eGFR) levels contribute to a higher incidence of AKI among users of SGLT-2 inhibitors.[14] However, the Japanese study did not include a comparison group for SGLT-2 inhibitors and did not exclude a history of AKI prior to taking SGLT-2 inhibitors, making it difficult to determine whether SGLT-2 inhibitors truly contributed to AKI incidence. According to our research, dapagliflozin contributes to the reduction of AKI, with a particularly strong protective effect observed in men. The mechanism behind the gender-specific effects of dapagliflozin remains unknown, so further research is needed. Additionally, although the Japanese study reported a significant increase in AKI risk when SGLT-2 inhibitors were used in combination with diuretics, our study results showed no difference in AKI risk based on diuretic use.

In our study, the only patient group with an HR point estimate for AKI exceeding 1 was the group with CKD. The Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease (DAPA-CKD) randomized clinical trials, which evaluated the efficacy and safety of canagliflozin and dapagliflozin in patients with CKD, reported initial mean eGFR reductions of 3.7 mL/min/1.73 m^2 within 3 weeks and 4.0 mL/min/1.73 m^2 within 2 weeks after dapagliflozin treatment, respectively. However, importantly, in patients with CKD, the incidence of AKI was significantly lower in the dapagliflozin-treatment group compared to the placebo group (HR 0.68, 95% CI 0.49–0.94).[31–33] Likewise, systematic meta-analyses have indicated that SGLT-2 inhibitors provide a protective effect against AKI in

	Dapagliflozin		Sitagliptin		HR
	No. of events	1000PYs	No. of events	1000PYs	(95% CI)
Age, years					
<65	39	16.82	83	16.51	0.46 (0.32-0.68)
≥65	93	5.49	115	5.67	0.84 (0.64-1.10)
Sex					
Male	64	12.61	116	12.65	0.55 (0.41-0.75)
Female	68	9.70	82	9.53	0.82 (0.59-1.12)
CCI					
<5	113	21.84	167	21.61	0.67 (0.53-0.85)
≥5	19	0.47	31	0.57	0.74 (0.42-1.32)
CKD					
Yes	17	0.60	20	0.77	1.11 (0.58-2.11)
No	115	21.72	178	21.41	0.64 (0.50-0.81)
Insulin					
Yes	60	3.47	80	3.38	0.73 (0.52-1.02)
No	72	18.84	118	18.80	0.61 (0.45-0.82)
ARB/ACEI					
Yes	111	12.09	154	12.00	0.72 (0.56-0.91)
No	21	10.22	44	10.18	0.48 (0.28-0.80)
Diuretic					
Yes	82	3.19	115	3.18	0.71 (0.53-0.94)
No	44	19.12	67	19.00	0.60 (0.42-0.85)
Metformin					
Yes	19	16.49	31	16.33	0.67 (0.51-0.87)
No	50	5.82	83	5.85	0.66 (0.45-0.97)

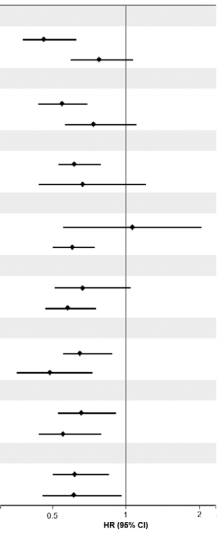

FIGURE 3 Risk of AKI with dapagliflozin compared to sitagliptin stratified by baseline characteristics. The risk of AKI with dapagliflozin and sitagliptin was calculated using the Cox proportional hazards model after stratifying by baseline characteristics. The incidence rate per 1000 person-years was estimated by dividing the number of AKI cases by the total person-years and multiplying by 1000 in each cohort. CCI was identified for each patient until 365 days before the index date, including the index date. CKD prevalence, insulin use, ARB/ACEI use, diuretic use, and metformin use were identified for each patient until 365 days before the index date, excluding the index date. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCI, Charlson comorbidity index; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; PY, person year.

patients with CKD compared to placebo (Relative risk, RR 0.82, 95% CI 0.72–0.93, $p=0.003$).[34–36] Contrary to this evidence, our result did not show a protective effect with dapagliflozin in patients with CKD, with a wide confidence interval (HR 1.11, 95% CI 0.58–2.11). Overall, these results are important for clinical practice, suggesting that dapagliflozin can be safely used in patients with CKD without increasing the risk of AKI. Therefore, the use of SGLT-2 inhibitors in patients with CKD should not be discontinued or rejected.

Our study has several limitations that should be considered when interpreting the findings. First, because the claims database lacks laboratory data and information on disease staging or severity, AKI occurrence was defined using ICD-10 codes. To minimize misclassification, this study identified AKI cases based on hospital admissions where AKI was recorded as either a primary or secondary diagnosis. Instead, this restriction may have led to an underestimation of milder AKI cases that did not require clinical treatment. If the outcome definition is highly specific, bias is likely to be minimal, and estimates are toward the null. Despite this, the current study demonstrated a protective effect of dapagliflozin compared to sitagliptin. Second, the exposure group was assigned based on dapagliflozin prescription status on the index date, without accounting for the prescription duration, adherence, or dosage. Although prescription duration and adherence were not considered, their impact is likely minimal given the relatively short follow-up period. Moreover, sensitivity analyses with both shorter and longer follow-up durations consistently yielded similar results. Most patients are likely to start with the low dose, and the impact of dose titration on the outcome might be minimal given the short follow-up period. However, as little is known about the association between dapagliflozin dosage and AKI risk, further research may be warranted. Finally, despite using PS matching to balance observed confounders between treatment groups, residual confounding remains a possibility. Variables such as baseline kidney function, body mass index, and lifestyle factors (e.g., smoking and physical activity) were not available in the claims data and may have influenced the observed associations. However, both SGLT-2 inhibitors and DPP-4 inhibitors are primarily second-line therapies in Korea and are more expensive than metformin or sulfonylureas. As a result, these drugs are likely to be prescribed to patients at similar stages of T2DM. Selecting appropriate comparison groups, combined with a new-user design and 1:1 PS matching on multiple proxies of diabetes severity and duration, has been shown to significantly reduce bias.[37] Accordingly, our methods minimize concerns regarding unmeasured confounding.

Nevertheless, the strength of our study lies in the use of a large research population, including approximately 95,000 dapagliflozin users in Korea, which enhances the robustness and generalizability of our findings. This large sample size allowed for subgroup analyses based on patient characteristics, revealing potential variations in the effects on AKI according to age, gender, comorbidities, insulin use, and CKD history.

5 | CONCLUSIONS

Compared to sitagliptin, dapagliflozin was associated with a lower risk of AKI-related hospitalization in patients with T2DM. This

finding is consistent with multinational studies from Taiwan, the United States, Europe, and Canada, suggesting generalizability across different ethnicities and populations. However, stratified analyses indicated potential variations in effects based on baseline factors such as age, sex, and comorbidities. Although the confidence intervals were wide, the observed trends highlight the need for further research to confirm these potential differences.

AUTHOR CONTRIBUTIONS

All authors attest they meet the ICMJE criteria for authorship. **Conceptualization:** Hee-Jin Kim, HoJin Shin, Ye-Jee Kim, Nam-Kyong Choi; **Investigation:** Heehyun Won, Suvin Park, Hui-Eon Lee, Haerin Cho, Jeong Ah Kim; **Methodology:** Hee-Jin Kim, Hui-Eon Lee, HoJin Shin, Ye-Jee Kim, Nam-Kyong Choi; **Data curation:** Hee-Jin Kim; **Formal analysis:** Hee-Jin Kim; **Writing-original draft:** Hee-Jin Kim; **Writing-review & editing:** Hee-Jin Kim, Na-Young Jeong, HoJin Shin, Ye-Jee Kim; **Supervision:** Nam-Kyong Choi.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The database is not available due to the privacy policy.

ORCID

Hee-Jin Kim https://orcid.org/0000-0003-0424-8874
Heehyun Won https://orcid.org/0000-0001-9601-3786
Suvin Park https://orcid.org/0000-0003-4292-049X
Hui-Eon Lee https://orcid.org/0000-0002-6351-2674
Haerin Cho https://orcid.org/0009-0001-7221-4265
Jeong Ah. Kim https://orcid.org/0000-0001-5429-759X
Na-Young Jeong https://orcid.org/0000-0003-2130-1286
HoJin Shin https://orcid.org/0000-0002-2032-6134
Ye-Jee Kim https://orcid.org/0000-0002-3307-2970
Nam-Kyong Choi https://orcid.org/0000-0003-1153-9928

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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