Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Acute kidney injury risk with SGLT2 inhibitors versus sulfonylureas by baseline cardiorenal status in type 2 diabetes: A nationwide cohort study

Eonji Na
Korea Institute of Drug Safety and Risk Management
Hyeri Yang
Korea Institute of Drug Safety and Risk Management
Bonggi Kim
Korea Institute of Drug Safety and Risk Management
Sungho Won
won1@snu.ac.kr

Seoul National University

Research Article

Keywords: Sodium–glucose cotransporter 2 inhibitors, Acute kidney injury, Type 2 diabetes mellitus, Sulfonylureas, Renal safety, Real-world evidence, Cohort study, Propensity score matching, Drug utilization, Korean National Health Insurance Service

Posted Date: July 3rd, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10097416/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background: Evidence on the short-term renal safety of sodium-glucose cotransporter-2 inhibitors (SGLT2i) in Asian populations is limited. In this study, we evaluated whether SGLT2i initiation as metformin-based second-line therapy is associated with a lower 180-day risk of acute kidney injury (AKI) compared with sulfonylureas (SUs), and whether this association varies by baseline cardiorenal status.

Methods: We used Korean National Health Insurance Service claims data from 2013 to 2022 to conduct a nationwide retrospective cohort study. Eligible adults with type 2 diabetes mellitus who newly initiated either an SGLT2i or an SU as add-on therapy to metformin were included. After exact matching on the diagnosis-to-treatment interval, we performed 1:1 propensity score matching. The primary outcome was incident AKI within 180 days, identified using validated claims algorithms; biopsy-confirmed acute interstitial nephritis was a secondary outcome. Stratified Cox proportional hazards models estimated adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs). Additional analyses examined variation by heart failure (HF), chronic kidney disease (CKD), cumulative exposure, and individual agents, with sensitivity analyses to test robustness.

Results: After matching, 125,832 SGLT2i initiators were compared with 125,832 SU initiators. SGLT2i initiation was associated with a lower 180-day AKI risk than SU initiation (aHR: 0.63, 95% CI: 0.55–0.72). This association was observed in patients with and without HF, with no interaction by HF status. In contrast, CKD modified the association: the lower AKI risk was pronounced in patients without CKD but attenuated and not statistically significant in those with pre-existing CKD. Ingredient-specific estimates were directionally consistent, although less precise for infrequently used agents. Biopsy-confirmed AIN was rare, yielding imprecise estimates. Sensitivity analyses supported the primary findings.

Conclusions: In this large East Asian real-world cohort, SGLT2i initiation as metformin-based second-line therapy was associated with lower 180-day AKI risk than SU initiation. This association persisted in patients with HF, but was attenuated primarily among those with pre-existing CKD. These findings support the comparative short-term renal safety of SGLT2i and underscore the importance of distinguishing HF from CKD when interpreting early renal risk.

Research Insights

What is currently known about this topic?	• SGLT2 inhibitors improve major cardiorenal outcomes in type 2 diabetes. • Prior studies suggest neutral or reduced AKI risk, but estimates vary by comparator. • Evidence from Asian routine second-line treatment settings remains limited.
What is the key research question?	• Is SGLT2i initiation associated with lower 180-day AKI risk than SU initiation in metformin-treated T2DM?
What is new?	• Compared with SU use, metformin-based second-line SGLT2i use is associated with lower 180-day AKI risk. • This lower AKI risk persists in HF but is attenuated in pre-existing CKD. • Ingredient-specific and sensitivity analyses support consistent findings.
How might this study influence clinical practice?	• Baseline cardiorenal status may inform early renal risk assessment.

Background

Sodium–glucose cotransporter 2 inhibitors (SGLT2i) have emerged as a key class of antihyperglycemic agents that reduce blood glucose by increasing urinary glucose excretion. Beyond glycemic control, they have drawn attention for cardiovascular and renal protection, with large randomized controlled trials (RCTs) demonstrating reductions in major adverse cardiovascular events and slower chronic kidney disease (CKD) progression [1–3]. Accordingly, current international guidelines recommend SGLT2i for patients with type 2 diabetes mellitus (T2DM) and established cardiovascular disease, heart failure (HF), or diabetic kidney disease (DKD), irrespective of glycemic status [4].

With accumulating evidence and guideline support, SGLT2i use has expanded beyond glucose lowering in T2DM to cardiorenal protection in patients with CKD or HF, including those without diabetes [5–8]. As these agents are used in broader patient populations, rare but serious renal adverse events, particularly acute kidney injury (AKI) and acute interstitial nephritis (AIN), have become increasingly relevant. In East Asia, real-world SGLT2i use has increased markedly [9], whereas post-marketing renal safety profiles remain incompletely characterized.

AKI is a clinically significant complication linked to both short- and long-term morbidity. In patients with T2DM, AKI risk is amplified by comorbid CKD and HF and by exposure to nephrotoxic medications. Even a single AKI episode may accelerate progression to end-stage kidney disease (ESKD) [10–12]. AIN, also known as tubulointerstitial nephritis (TIN), is a rare but serious drug-induced form of AKI that requires histological confirmation and can cause irreversible kidney damage if missed [13]. Given the consequences of AKI and the diagnostic challenges of AIN, real-world pharmacovigilance is essential.

Renal benefits of SGLT2i have been consistently reported in landmark cardiovascular and renal outcome RCTs, including EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58, CREDENCE, DAPA-CKD, and EMPA-KIDNEY [1–3, 5, 6, 14]. However, these trials often enrolled select populations and were not designed primarily to assess short-term AKI or biopsy-confirmed AIN in routine second-line diabetes care. Observational studies have generally reported neutral or lower AKI risk with SGLT2i, but estimates vary by population, comparator, and clinical setting [15, 16]. Meanwhile, pharmacovigilance databases, post-marketing case reports, and regulatory communications continue to identify AKI and TIN as rare but clinically relevant renal safety concerns [17–21]. Thus, evidence remains limited on the comparative short-term AKI risk of SGLT2i versus SUs as metformin-based second-line therapy, particularly in East Asian patients with heterogeneous baseline cardiorenal status.

To address this evidence gap, we compared 180-day AKI risk between SGLT2i and SU initiators receiving metformin-based second-line therapy in routine clinical practice. We further examined whether this association differed by baseline cardiorenal status and assessed biopsy-confirmed AIN, individual SGLT2i agents, and cumulative SGLT2i exposure.

Methods

Study design and data source

We conducted a retrospective cohort study using Korean National Health Insurance Service (NHIS) claims data from January 1, 2013, to December 31, 2022. The NHIS is a universal, single-payer system covering approximately 97% of the Korean population and includes administrative claims on demographics, ICD-10-coded diagnoses, procedures, and prescriptions. These features support real-world pharmacoepidemiologic research [22].

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and was approved by the Institutional Review Board of the Korea Institute of Drug Safety and Risk Management (IRB No. 2023-2). Informed consent was waived because the analysis used de-identified administrative data, with all personal identifiers removed before analysis.

Study population

We identified adults aged ≥ 18 years with T2DM (ICD-10 codes E11–E14) [23] who newly initiated an SGLT2i or SU as add-on therapy to metformin between January 2016 and June 2022. Restricting the cohort to metformin-based second-line therapy was intended to improve comparability across treatment stages. A 3-year washout period for prior use of either study drug class was applied to identify new users.

We excluded individuals with prior AKI, acute pyelonephritis, or TIN, as well as those with advanced CKD, dialysis dependence, or prior renal replacement therapy or kidney transplantation. Other major exclusion

criteria are summarized in Fig. 1, and operational definitions and code lists are provided in Additional file 1 (Tables S1 and S2). Given that all eligible individuals in the nationwide database were included, no formal sample size calculation was performed.

Exposure assessment

Exposure was defined as initiation of an SGLT2i (Anatomical Therapeutic Chemical [ATC] code: A10BK) or SU (ATC code: A10BB) with metformin; the index date was the first prescription date for the regimen. SGLT2i exposure was assessed at the class and ingredient levels. In class-level analyses, all SGLT2i initiators were grouped and compared with SU initiators. In ingredient-specific analyses, patients were classified by exclusive use of dapagliflozin, empagliflozin, ipragliflozin, or ertugliflozin during follow-up; those who switched agents or received more than one SGLT2i were excluded.

To examine whether AKI risk varied by cumulative exposure, patients were classified by cumulative defined daily dose (cDDD) during the 180-day follow-up. The cDDD was calculated by summing the World Health Organization-defined daily doses (DDD) for all dispensed SGLT2i prescriptions during follow-up [24, 25].

Outcomes

The primary outcome was incident AKI, identified by ICD-10 code N17, which has acceptable validity in administrative claims data [26]. To assess short-term renal safety after treatment initiation and improve temporal specificity, we considered only the first AKI diagnosis within 180 days of the index date. Follow-up began on the index date and continued until AKI, 180 days after the index date, death, NHIS disenrollment, or the end of the study, whichever occurred first.

The secondary outcome was AIN, defined as an AIN-related ICD-10 diagnosis accompanied by a renal biopsy procedure code within the same clinical episode to improve specificity [27]. As some regulatory and coding sources refer to the same entity as acute TIN, we applied AIN throughout this article. Detailed diagnosis and procedure codes are provided in Additional file 1 (Table S1).

Covariates

Baseline covariates included age, sex, income quintile, index year, the Elixhauser Comorbidity Index (ECI) [28], comorbidities, and concomitant medications assessed during 3 years before the index date. Comorbidities included CKD, HF, hypertension, dyslipidemia, and other clinically relevant conditions. Concomitant medications included nonsteroidal anti-inflammatory drugs (NSAIDs), diuretics, angiotensin-converting enzyme inhibitors (ACEis), angiotensin II receptor blockers (ARBs), and other drugs potentially associated with renal outcomes. To reduce misclassification due to transient exposure, most concomitant medications were defined as prescriptions lasting at least 7 consecutive days during

the 3-year baseline period. Covariates were prespecified based on clinical relevance and existing evidence (Table 1) [29–31].

Table 1
Baseline characteristics of the study population in the final matched cohort

Variable	Patients, No (%)		
	SGLT2i group (N = 125832)	SU group (N = 125832)	SMD
Sex			
Male	84031 (66.78)	84205 (66.92)	0.00
Female	41801 (33.22)	41627 (33.08)	0.00
Age at entry			
Mean(SD)	51.98 (11.89)	53.03 (11.88)	-0.09
18–44	30921 (24.57)	30051 (23.88)	0.02
45–64	76636 (60.9)	77110 (61.28)	-0.01
65–79	16946 (13.47)	17343 (13.78)	-0.01
≥ 80	1329 (1.06)	1328 (1.06)	0.00
Index year			
2016	15324 (12.18)	15234 (12.11)	0.00
2017	19413 (15.43)	19352 (15.38)	0.00
2018	20818 (16.54)	20729 (16.47)	0.00
2019	21882 (17.39)	21990 (17.48)	0.00
2020	20845 (16.57)	21262 (16.9)	-0.01
2021	19758 (15.7)	19592 (15.57)	0.00
2022	7792 (6.19)	7673 (6.1)	0.00
Income level			
Low	33674 (26.76)	33835 (26.89)	0.00
Moderate	47131 (37.46)	47205 (37.51)	0.00
High	45027 (35.78)	44792 (35.6)	0.00
ECI Score			
Mean(SD)	3.69 (2.31)	3.68 (2.36)	0.01
0	7891 (6.27)	7347 (5.84)	0.02

Variable	Patients, No (%)		
	SGLT2i group (N = 125832)	SU group (N = 125832)	SMD
1–2	34563 (27.47)	33900 (26.94)	0.01
3–4	44068 (35.02)	44554 (35.41)	-0.01
≥ 5	39310 (31.24)	40031 (31.81)	-0.01
Comorbidity			
CKD	3297 (2.62)	3301 (2.62)	0.00
Unspecified kidney failure	1538 (1.22)	1293 (1.03)	0.02
HF	9787 (7.78)	6041 (4.8)	0.12
Hypertension	57930 (46.04)	52286 (41.55)	0.09
Dyslipidemia	99992 (79.46)	93350 (74.19)	0.13
Autoimmune disease	9368 (7.44)	10101 (8.03)	-0.02
Viral infection	13608 (10.81)	13045 (10.37)	0.01
Bacterial infection	1094 (0.87)	995 (0.79)	0.01
Sepsis	568 (0.45)	588 (0.47)	0.00
Rhabdomyolysis	1016 (0.81)	776 (0.62)	0.02
Cardiac arrhythmias	6669 (5.3)	5329 (4.24)	0.05
Glomerular diseases	7801 (6.2)	6818 (5.42)	0.03
Gout/Hyperuricemia	22954 (18.24)	20752 (16.49)	0.05
Comedication			
NSAIDs	112996 (89.8)	111567 (88.66)	0.04
Radio-contrast agents	33446 (26.58)	28842 (22.92)	0.08
Thiazide diuretics	12532 (9.96)	12478 (9.92)	0.00
Loop diuretics	4026 (3.2)	3337 (2.65)	0.03
MRA	39 (0.03)	60 (0.05)	0.01
ACE inhibitors	1989 (1.58)	650 (0.52)	0.03
ARB	43761 (34.78)	36722 (29.18)	0.12
CCB	36555 (29.05)	33395 (26.54)	0.06

Variable	Patients, No (%)		
	SGLT2i group (N = 125832)	SU group (N = 125832)	SMD
Beta-blockers	6836 (5.43)	6704 (5.33)	0.00
Other antihypertensives	505 (0.4)	538 (0.43)	0.01
Immunosuppressants	1128 (0.9)	1286 (1.02)	-0.01
Antibiotics	102596 (81.53)	102245 (81.26)	0.01
Antivirals	5270 (4.19)	5361 (4.26)	0.00
Antifungal agents	11 (0.00)	34 (0.01)	-0.01
Class III Antiarrhythmics	58 (0.05)	16 (0.01)	0.02
Adrenergic agents	9054 (7.2)	8139 (6.47)	0.03
HMG-CoA reductase inhibitors	67957 (54.01)	58142 (46.21)	0.16
Fibrates	12475 (9.91)	12052 (9.58)	0.01
Xanthine oxidase inhibitors	4348 (3.46)	3474 (2.76)	0.04
Bisphosphonates	2636 (2.09)	3276 (2.60)	-0.03
Antiplatelet agents	9665 (7.68)	5310 (4.22)	0.15
H2-receptor antagonists	90944 (72.27)	90942 (72.27)	0.00
PPI	63988 (50.85)	58844 (46.76)	0.08
Antidepressants	48352 (38.43)	49039 (38.97)	-0.01
Anticonvulsants	14572 (11.58)	15964 (12.69)	-0.03
Benzodiazepines	46878 (37.25)	47549 (37.79)	-0.01
Carbonic anhydrase inhibitors	550 (0.44)	571 (0.45)	0.00

Note: Data are presented as n (%) unless otherwise indicated. Continuous variables are presented as mean (SD).

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; CKD, chronic kidney disease; ECI, Elixhauser Comorbidity Index; HF, heart failure; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; MRA, mineralocorticoid receptor antagonist; NSAIDs, non-steroidal anti-inflammatory drugs; PPI, proton pump inhibitor; SD, standard deviation; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SMD, standardized mean difference; SU, sulfonylurea.

Statistical analysis

To reduce confounding and improve comparability in disease stage, we used two-step matching. First, patients were matched on the interval from the first T2DM diagnosis to the initiation of second-line therapy. Second, 1:1 propensity score matching (PSM) was performed using greedy nearest-neighbor matching with a caliper of 0.2 standard deviations (SDs) of the logit of the propensity score [32–36]. Covariate balance was evaluated using absolute standardized mean differences (SMDs), with values < 0.1 indicating acceptable balance.

The primary analysis compared time to first AKI between SGLT2i and SU initiators in the propensity score-matched cohort using stratified Cox proportional hazards models, with matched pair as the stratification variable. This accounted for matching by allowing each pair to have its own baseline hazard. Given that modest residual imbalance remained for several covariates, adjusted models additionally included these variables. Adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) were estimated. The proportional hazards assumption was assessed using Schoenfeld residuals and log–log plots. Cumulative incidence was displayed as 1 minus the Kaplan–Meier estimate, and group differences were evaluated with the log-rank test.

Subgroup analyses were conducted by age, sex, HF, CKD, hypertension, and dyslipidemia. Effect heterogeneity was assessed using interaction terms and interpreted with caution, given the multiple subgroup comparisons. Ingredient-specific associations were examined using separate adjusted Cox models restricted to exclusive users of a single SGLT2i agent during follow-up, with SU initiators as the reference. As an exploratory supplementary analysis, cumulative SGLT2i exposure was categorized as < 90, 90–179, 180–209, and ≥ 210 cDDD. A P for trend was estimated by modeling ordered cDDD categories as an ordinal term. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA), with a two-sided α of 0.05.

Sensitivity analyses

We conducted prespecified sensitivity analyses to assess robustness. First, inverse probability of treatment weighting (IPTW) was applied to the exact-matched cohort before PSM to assess consistency using an alternative approach to confounding adjustment [37, 38]. Second, to reduce potential protopathic bias and early outcome misclassification, a 7-day lag period was applied after the index date; person-time accrued from day 8, and events within the first 7 days were not counted [39]. Third, follow-up was restricted to 3 months after initiation to assess temporal stability. Fourth, prespecified self-controlled risk interval (SCRI) analyses were conducted separately among SGLT2i and SU initiators to assess within-person temporal variation in AKI incidence, comparing days 1–30 and 31–90 with days 91–180 as the reference. Day 0 was excluded, and follow-up was censored at the first AKI event. Except for the SCRI analyses, which used conditional Poisson regression with a log person-time offset, the time-to-AKI sensitivity analyses used Cox-based models. Finally, E-values quantified the minimum strength of unmeasured confounding required to explain the observed association [40].

Results

Baseline characteristics after matching

After applying the eligibility criteria, we identified 403,088 adults with T2DM who initiated an SGLT2i or SU as add-on therapy to metformin. Exact matching on the diagnosis-to-treatment interval followed by 1:1 propensity score matching yielded a final matched cohort of 251,664 individuals: 125,832 SGLT2i initiators and 125,832 SU initiators (Fig. 1). Baseline characteristics were generally comparable between groups, although modest residual imbalances remained for HF, dyslipidemia, selected antihypertensive and lipid-lowering medications, and antiplatelet agents (Table 1). These variables were retained in the multivariable models. Propensity score overlap improved between treatment groups after matching (Additional file 1: Figure S2).

Association between SGLT2i initiation and acute kidney injury

During follow-up, AKI was less frequent among SGLT2i initiators than SU initiators (365 vs. 552 events), with incidence rates of 5.90 (95% CI: 5.30–6.51) and 8.95 (95% CI: 8.21–9.70) per 1,000 person-years, respectively. In stratified multivariable Cox proportional hazards models, SGLT2i initiation was associated with lower AKI risk than SU initiation (aHR: 0.63, 95% CI: 0.55–0.72; P < 0.001; Table 2). Cumulative incidence curves showed early and sustained separation between treatment groups over 180 days (Fig. 2). Schoenfeld residuals and log–log plots showed no major violation of the proportional hazards assumption (Additional file 1: Figure S3).

Table 2
Association between SGLT2i use and risk of AKI

Group(N)	Follow-up Mean (SD), days	AKI events (n)	Incidence rate (per 1000 PY, 95% CI)	Adjusted HR (95% CI)	p-value
SU (125,832)	179.23 (9.98)	552	8.95 (8.21–9.70)	Reference	–
SGLT2i (125,832)	179.55 (7.56)	365	5.90 (5.30–6.51)	0.63 (0.55–0.72)	< 0.001

Note: HRs compare SGLT2i initiators with SU initiators as the reference group and were estimated using Cox proportional hazards models stratified by matched pair and additionally adjusted for covariates with residual imbalance after matching, including heart failure, dyslipidemia, angiotensin II receptor blocker use, HMG-CoA reductase inhibitor use, and antiplatelet agent use.

Abbreviations: AKI, acute kidney injury; CI, confidence interval; HR, hazard ratio; PY, person-years; SD, standard deviation; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SU, sulfonylurea.

Subgroup analyses according to baseline cardiorenal status

Prespecified subgroup analyses showed generally consistent associations across most strata, with the clearest heterogeneity by baseline CKD status. SGLT2i initiation was associated with lower AKI risk in patients with HF (aHR: 0.55, 95% CI: 0.39–0.78; P = 0.002) and without HF (aHR: 0.64, 95% CI: 0.55–0.74; P < 0.001), with no evidence of interaction by HF status (P for interaction = 0.609). In contrast, the association differed by CKD status. Among individuals without CKD, SGLT2i initiation was associated with substantially lower AKI risk (aHR: 0.50, 95% CI: 0.42–0.60; P < 0.001), whereas no significant association was observed in those with pre-existing CKD (aHR: 0.94, 95% CI: 0.77–1.15; P = 0.541; P for interaction < 0.001).

Associations were otherwise broadly similar across prespecified strata. Lower AKI risk with SGLT2i initiation was observed among individuals with and without hypertension or dyslipidemia, in both age groups, and in both sexes, with no statistically significant interactions. Subgroup-specific estimates and interaction P values are provided in Additional file 1 (Table S3), with subgroup patterns summarized in Fig. 3. Cumulative incidence curves by baseline HF and CKD status are shown in Fig. 4.

Ingredient-specific analysis

Ingredient-specific analyses showed broadly similar associations across individual SGLT2i agents. Compared with SU initiators, aHRs for AKI were 0.66 (95% CI: 0.56–0.77) for dapagliflozin, 0.80 (95% CI: 0.73–0.88) for empagliflozin, 0.80 (95% CI: 0.68–0.96) for ipragliflozin, and 0.50 (95% CI: 0.26–0.96) for ertugliflozin. Associations were directionally consistent, although estimates for less frequently used agents were less precise (Table 3; Additional file 1: Figure S4).

Table 3
Ingredient-specific associations with AKI compared with SUs

Group (N)	Follow-up Mean (SD), days	AKI events (n)	Incidence rate (per 1000 PY, 95% CI)	Adjusted HR (95% CI)	p-value
SU (125,832)	179.23 (9.98)	552	8.95 (8.21–9.70)	Reference	–
SGLT2i					
Dapagliflozin (68,505)	179.54 (7.67)	208	6.18 (5.37–7.08)	0.66 (0.56–0.77)	< 0.001
Empagliflozin (47,577)	179.54 (7.67)	142	6.07 (5.11–7.16)	0.80 (0.73–0.88)	< 0.001
Ipragliflozin (4,681)	179.75 (5.64)	13	5.64 (3.00–9.65)	0.80 (0.68–0.96)	0.015
Ertugliflozin (1,788)	179.96 (1.69)	2	2.27 (0.27–8.20)	0.50 (0.26–0.96)	0.038

Note: HRs compare initiators of each SGLT2i ingredient with SU initiators as the reference group. Analyses were restricted to patients exposed to a single SGLT2i ingredient during follow-up. Models were adjusted for the same covariates as the primary analysis.

Abbreviations: AKI, acute kidney injury; CI, confidence interval; HR, hazard ratio; PY, person-years; SD, standard deviation; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SU, sulfonylurea.

Additional analyses

Biopsy-confirmed AIN was rare during follow-up, yielding imprecise estimates that were directionally consistent with the primary AKI analysis (Additional file 1: Table S4). Exploratory analyses stratified by cumulative SGLT2i exposure showed variation across cDDD categories, with lower estimates in the two highest cDDD categories (Additional file 1: Table S5 and Figure S5). Given the accrued cumulative exposure during follow-up, these cDDD findings should be interpreted as hypothesis-generating.

Sensitivity analyses

Sensitivity analyses supported the robustness of the primary findings. In the IPTW analysis, SGLT2i initiation remained associated with a lower risk of AKI. Applying a 7-day lag period yielded an aHR of 0.66 (95% CI: 0.58–0.76), suggesting that the association was not driven solely by very early events. Similar estimates were observed when follow-up was restricted to 3 months (Additional file 1: Table S6).

In the prespecified SCRI analyses, within-person incidence rate ratios (IRRs) were higher during the early post-initiation intervals than during the reference period (days 91–180) in both treatment groups. Among SGLT2i initiators, IRRs were 2.03 (95% CI: 1.56–2.64) for days 1–30 and 1.47 (95% CI: 1.16–1.87) for

days 31–90. The corresponding IRRs among SU initiators were 2.73 (95% CI: 2.23–3.34) and 1.36 (95% CI: 1.11–1.67), respectively (Additional file 1: Table S7). E-value estimates are presented in Additional file 1 (Table S8).

Discussion

In this nationwide cohort study of adults with T2DM initiating metformin-based second-line therapy, SGLT2i initiation was associated with a lower 180-day AKI risk than SU initiation. The principal finding was that this association differed by baseline cardiorenal status. Lower AKI risk persisted in patients with HF, with no statistical interaction by HF status, but was attenuated and no longer significant in those with pre-existing CKD. Ingredient-specific estimates were directionally consistent, while biopsy-confirmed AIN was rare and yielded imprecise supplementary estimates. These results align with prior evidence suggesting renal benefits or lower risks of renal events with SGLT2i therapy [1–3, 5, 6, 14, 41].

Landmark cardiovascular and renal outcome trials have shown that SGLT2i slow CKD progression and reduce serious renal outcomes; however, they were not designed primarily to assess short-term AKI or biopsy-confirmed AIN in routine second-line diabetes care [1, 5, 6, 14]. Observational studies have reported heterogeneous estimates, from neutral associations to modest AKI risk reductions [15, 16, 42, 43], and a pooled analysis of nine cohorts estimated an HR of 0.61 [44]. Scandinavian and Taiwanese cohorts also reported substantially lower risks of renal events with SGLT2i than with DPP-4 inhibitors [45, 46]. However, these studies differed in their comparators, treatment stages, and populations. By anchoring both groups to metformin-based second-line therapy and aligning the diagnosis-to-treatment interval, our study provides evidence from a clinically comparable treatment decision point.

The active-comparator design is central to interpreting these findings. We selected SUs as they remain a relevant second-line glucose-lowering option after metformin in routine diabetes care [47], whereas guidelines increasingly prioritize SGLT2i for patients with cardiorenal comorbidities [48]. Although DPP-4 inhibitors are also relevant comparators and have been used in prior real-world studies of SGLT2i-related renal outcomes [49], the SU comparator reflects a distinct second-line treatment choice and enables assessment of short-term renal safety relative to an alternative therapy without established cardiorenal protective indications. The subgroup findings further clarify early renal safety by baseline cardiorenal status. Lower AKI risk with SGLT2i initiation was preserved among patients with HF, with no statistical interaction by HF status. This is clinically relevant because patients with HF may be vulnerable to renal hypoperfusion due to venous congestion, reduced cardiac output, diuretic use, and acute volume shifts [50–52]. Despite these concerns, we found no excess early AKI signal in patients with HF, supporting the comparative short-term renal safety of SGLT2i versus SUs in this subgroup.

In contrast, CKD appeared to be the principal modifier: the inverse association was pronounced in patients without CKD but attenuated and not significant in those with pre-existing CKD. This attenuation may reflect reduced nephron reserve, impaired autoregulation, lower filtered glucose load, higher baseline AKI susceptibility, and residual differences in CKD severity not fully captured in claims data [50,

53]. Associations were otherwise broadly consistent across hypertension, dyslipidemia, age, and sex strata, with no significant interactions. These subgroup findings should be interpreted cautiously as hypothesis-generating. Overall, HF and CKD should not be treated as a single cardiorenal phenotype when interpreting short-term AKI risk after SGLT2i initiation.

Additional analyses contextualized the primary findings. Biopsy-confirmed AIN was rare, yielding imprecise estimates despite use of a diagnostic-procedural definition to improve specificity [27]. This analysis should be considered exploratory and does not exclude a rare AIN risk. Exploratory analyses by cumulative SGLT2i exposure showed variation across cDDD categories. As cumulative exposure accrued during follow-up, these findings may reflect treatment persistence, selective survival, or clinical stability rather than a definitive dose–response relationship.

Multiple complementary sensitivity analyses supported the primary findings. The association persisted in IPTW, restricted-follow-up, and 7-day-lag analyses, suggesting that results were not sensitive to analytic approach, follow-up duration, or very early events. The prespecified SCRI analyses showed higher AKI incidence during the earlier than later post-initiation intervals within both treatment groups. Because these analyses were conducted separately by treatment group, they characterize within-person temporal patterns rather than provide a formal between-group comparison. E-value estimates further suggested that relatively strong unmeasured confounding would be required to fully explain the association. Together, these analyses support the consistency of the observed short-term renal safety association, although residual bias cannot be excluded.

Several design features strengthen the study's internal validity and clinical relevance. First, the metformin-anchored, active-comparator design restricted comparisons to patients initiating second-line glucose-lowering therapy, improving treatment-stage comparability and reducing confounding by indication [4, 54]. Second, exact matching on the interval from diabetes diagnosis to treatment initiation, followed by 1:1 PSM, reduced temporal and clinical confounding and improved baseline comparability. Third, nationwide claims data enabled large-scale outcome ascertainment and clinically relevant subgroup analyses, particularly by baseline cardiorenal status, in an East Asian population. Fourth, cumulative exposure and ingredient-specific analyses extended the assessment beyond the overall class-level comparison. Finally, multiple cohort-based sensitivity analyses supported the consistency of the comparative association, while treatment-specific within-person analyses characterized temporal patterns of AKI after initiation.

Notwithstanding these strengths, certain limitations should also be considered. First, AKI was identified using diagnosis codes rather than laboratory-based KDIGO criteria. This likely captured clinically recognized AKI but may have missed milder, uncoded episodes, and AKI severity, creatinine trajectory, and recovery could not be assessed. Second, key clinical variables, including estimated glomerular filtration rate, albuminuria, and glycemic control, were unavailable in claims data. Metformin anchoring, temporal matching, detailed covariate adjustment, and IPTW were used to reduce residual confounding. Nevertheless, treatment selection bias related to cardiorenal indications for SGLT2i may persist,

particularly because HF severity, renal function, albuminuria, glycemic control, and volume status were unavailable. Third, drug exposure was inferred from dispensing records rather than confirmed intake, which may have caused exposure misclassification. However, the active-comparator new-user design, short follow-up, and consistent findings across the cohort-based sensitivity analyses reduce concern that this limitation fully explains the primary association.

Clinically, these findings may inform the selection between SGLT2i and SUs for appropriate candidates who require second-line therapy after metformin, particularly when early renal safety is a major consideration. The observed heterogeneity by HF and CKD status suggests that baseline cardiorenal status may help contextualize early renal risk after SGLT2i initiation in routine care. Although these findings should be interpreted alongside the established long-term cardiorenal benefits of SGLT2i, they support early renal monitoring in patients with established cardiorenal disease, particularly given ongoing regulatory attention to renal safety outcomes [18–21]. Taken together, our findings extend current evidence by showing that the short-term renal safety profile of SGLT2i in routine second-line diabetes care may differ by baseline cardiorenal status.

Conclusions

In this nationwide real-world cohort of Korean adults with T2DM, SGLT2i initiation as second-line therapy was associated with lower AKI risk than SU initiation. This association persisted in patients with HF but was attenuated primarily in those with pre-existing CKD, suggesting that HF and CKD should be considered separately when interpreting early renal risk after treatment initiation. Ingredient-specific and sensitivity analyses support the main findings, although estimates vary across cumulative exposure categories. Biopsy-confirmed AIN was rare but directionally consistent. Overall, these findings clarify the short-term renal safety of SGLT2i initiation in routine clinical practice and highlight the importance of baseline cardiorenal status.

Abbreviations

AIN
acute interstitial nephritis
AKI
acute kidney injury
aHR
adjusted hazard ratio
ATC
Anatomical Therapeutic Chemical
ACEi
angiotensin-converting enzyme inhibitor
ARB
angiotensin II receptor blocker

CCB
calcium channel blocker
CI
confidence interval
CKD
chronic kidney disease
cDDD
cumulative defined daily dose
DDD
defined daily dose
DKD
diabetic kidney disease
ECI
Elixhauser Comorbidity Index
EMA
European Medicines Agency
ESKD
end-stage kidney disease
HF
heart failure
HR
hazard ratio
ICD-10
International Classification of Diseases, 10th Revision
IPTW
inverse probability of treatment weighting
IRB
Institutional Review Board
IRR
incidence rate ratio
KDIGO
Kidney Disease:Improving Global Outcomes
KIDS
Korea Institute of Drug Safety and Risk Management
NHIS
National Health Insurance Service
NPRA
National Pharmaceutical Regulatory Agency
NSAID
nonsteroidal anti-inflammatory drug

PS
propensity score
PPI
proton pump inhibitor
PSM
propensity score matching
PY
person-years
RCT
randomized controlled trial
SCRI
self-controlled risk interval
SGLT2i
sodium–glucose cotransporter-2 inhibitor
SMD
standardized mean difference
STROBE
Strengthening the Reporting of Observational Studies in Epidemiology
SU
sulfonylurea
T2DM
type 2 diabetes mellitus
TIN
tubulointerstitial nephritis.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of the Korea Institute of Drug Safety and Risk Management (IRB No. 2023-2). The requirement for informed consent was waived by the Institutional Review Board because the study used de-identified administrative claims data.

Consent for publication

Not applicable.

Availability of data and materials

The datasets analyzed during the current study are derived from the Korean NHIS claims database and are not publicly available due to data use restrictions. Access to NHIS data requires approval from the

data owner and an institutional review process; qualified researchers may apply through the NHIS data access portal. Aggregated summary tables supporting the findings are provided in the Additional file 1.

Competing interests

The authors declare no competing interests.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Authors' contributions

EJN conceived and designed the study, curated the data, performed the statistical analyses, interpreted the results, and drafted the manuscript. HRY assisted with data processing and statistical analysis and contributed to the interpretation of findings. SHW and BGK supervised the study, provided critical revisions for important intellectual content, and approved the final version for submission. EJN is the guarantor of the work and accepts responsibility for the integrity of the data and the accuracy of the analysis.

Acknowledgements

We thank the data custodians and administrative staff of the Korea Institute of Drug Safety and Risk Management (KIDS) for their support in data access and governance. We also appreciate the constructive comments from our colleagues during manuscript preparation.

References

1. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015;373:2117–28. https://doi.org/10.1056/NEJMoa1504720
2. Neal B, Perkovic V, Mahaffey KW, Zeeuw D de, Fulcher G, Erondu N, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2017;377:644–57. https://doi.org/10.1056/NEJMoa1611925
3. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019;380:347–57. https://doi.org/10.1056/NEJMoa1812389
4. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int. 2022;102:S1–127. https://doi.org/10.1016/j.kint.2022.06.008

5. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou F-F, et al. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2020;383:1436–46. https://doi.org/10.1056/NEJMoa2024816
6. The EMPA-KIDNEY Collaborative Group. Empagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2023;388:117–27. https://doi.org/10.1056/NEJMoa2204233
7. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019;381:1995–2008. https://doi.org/10.1056/nejmoa1911303
8. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020;383:1413–24. https://doi.org/10.1056/NEJMoa2022190
9. Ha KH, Shin S, Na E, Kim DJ. Trends in prescribing sodium-glucose cotransporter 2 inhibitors for individuals with type 2 diabetes with and without cardiovascular-renal disease in South Korea, 2015–2021. J Diabetes Investig. 2025;16:215–24. https://doi.org/10.1111/jdi.14363
10. Kellum JA, Romagnani P, Ashuntantang G, Ronco C, Zarbock A. Acute kidney injury. Nat Rev Dis Primers. Nature Publishing Group; 2021;7:52. https://doi.org/10.1038/s41572-021-00284-z
11. Lewington AJP, Cerdá J, Mehta RL. Raising awareness of acute kidney injury: a global perspective of a silent killer. Kidney Int. 2013;84:457–67. https://doi.org/10.1038/ki.2013.153
12. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney Int. 2012;81:442–8. https://doi.org/10.1038/ki.2011.379
13. Praga M, González E. Acute interstitial nephritis. Kidney Int. 2010;77:956–61. https://doi.org/10.1038/ki.2010.89
14. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med. 2019;380:2295–306. https://doi.org/10.1056/NEJMoa1811744
15. Zhuo M, Paik JM, Wexler DJ, Bonventre JV, Kim SC, Patorno E. SGLT2 Inhibitors and the Risk of Acute Kidney Injury in Older Adults With Type 2 Diabetes. Am J Kidney Dis. 2022;79:858-867.e1. https://doi.org/10.1053/j.ajkd.2021.09.015
16. Iskander C, Cherney DZ, Clemens KK, Dixon SN, Harel Z, Jeyakumar N, et al. Use of sodium–glucose cotransporter-2 inhibitors and risk of acute kidney injury in older adults with diabetes: a population-based cohort study. CMAJ. 2020;192:E351–60. https://doi.org/10.1503/cmaj.191283
17. Yu T, Xiao J, Li M, Cheng SQ, Cai R, Huang L, et al. Risk of acute renal failure associated with combined use of SGLT2 inhibitors and potentially nephrotoxic drugs: an epidemiological surveillance study based on the FDA adverse event reporting system (FAERS). Expert Opin Drug Saf. 2025;1–12. https://doi.org/10.1080/14740338.2025.2471529
18. FDA Drug Safety Communication: FDA strengthens kidney warnings for diabetes medicines canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR). 2016.

https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-strengthens-kidney-warnings-diabetes-medicines-canagliflozin. Accessed 30 July 2025

19. Health Canada. Summary Safety Review – Sodium Glucose Cotransporter 2 (SGLT2) Inhibitors INVOKANA (canagliflozin) and FORXIGA (dapagliflozin) – Evaluation of a Potential Risk of Acute Kidney Injury. 2015 Oct. https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/safety-reviews/summary-safety-review-sodium-glucose-cotransporter-2-sglt2-inhibitors-invokana-canagliflozin-forxiga-dapagliflozin-risk-acute-kidney-injury.html. Accessed 30 July 2025
20. European Medicines Agency. Jardiance: EPAR – Procedural steps taken and scientific information after authorisation. https://www.ema.europa.eu/en/documents/procedural-steps-after/jardiance-epar-procedural-steps-taken-scientific-information-after-authorisation-archive_en.pdf. Accessed 30 July 2025
21. NPRA. Empagliflozin: Risk of Tubulointerstitial Nephritis. 2022. https://www.npra.gov.my/index.php/my/industry-news-announcements/more-recent-updates/435-english/safety-alerts-main/safety-alerts-2022/1527362-empagliflozin-risk-of-tubulointerstitial-nephritis.html. Accessed 30 July 2025
22. Cheol Seong S, Kim Y-Y, Khang Y-H, Heon Park J, Kang H-J, Lee H, et al. Data Resource Profile: The National Health Information Database of the National Health Insurance Service in South Korea. Int J Epidemiol. 2017;46:799-800. https://doi.org/10.1093/ije/dyw253
23. Baek JH, Park Y-M, Han KD, Moon MK, Choi JH, Ko S-H. Comparison of Operational Definition of Type 2 Diabetes Mellitus Based on Data from Korean National Health Insurance Service and Korea National Health and Nutrition Examination Survey. Diabetes Metab J. 2023;47:201–10. https://doi.org/10.4093/dmj.2022.0375
24. The ATC/DDD Methodology. https://www.who.int/tools/atc-ddd-toolkit/methodology. Accessed 30 July 2025
25. Wertheimer AI. The defined daily dose system (DDD) for drug utilization review. Hosp Pharm. 1986;21:233–4, 239–41, 258.
26. Tomlinson LA, Riding AM, Payne RA, Abel GA, Tomson CR, Wilkinson IB, et al. The accuracy of diagnostic coding for acute kidney injury in England - a single centre study. BMC Nephrol. 2013;14:58. https://doi.org/10.1186/1471-2369-14-58
27. Moledina DG, Eadon MT, Calderon F, Yamamoto Y, Shaw M, Perazella MA, et al. Development and external validation of a diagnostic model for biopsy-proven acute interstitial nephritis using electronic health record data. Nephrol Dial Transplant. 2021;37:2214–22. https://doi.org/10.1093/ndt/gfab346
28. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity Measures for Use with Administrative Data. Med Care. 1998;36:8-27. https://doi.org/10.1097/00005650-199801000-00004
29. Garcia G, Pacchini VR, Zamoner W, Balbi AL, Ponce D. Drug-induced acute kidney injury: a cohort study on incidence, identification of pathophysiological mechanisms, and prognostic factors. Front

Med (Lausanne). 2024;11:1459170. https://doi.org/10.3389/fmed.2024.1459170

30. Takeuchi T, Rahman AKMF, Ghazi L, Moe OW, Toto RD, Siew ED, et al. Epidemiological risk factors for acute kidney injury outcomes in hospitalized adult patients: a multicenter cohort study. Clin Kidney J. 2025;18. https://doi.org/10.1093/ckj/sfae426
31. Perazella MA, Rosner MH. Drug-Induced Acute Kidney Injury. Clin J Am Soc Nephrol. 2022;17:1220–33. https://doi.org/10.2215/CJN.11290821
32. Suissa S. Immeasurable Time Bias in Observational Studies of Drug Effects on Mortality. Am J Epidemiol. 2008;168:329–35. https://doi.org/10.1093/aje/kwn135
33. Parsons LS. Reducing bias in a propensity score matched-pair sample using greedy matching techniques. Twenty-Sixth Annual SAS Users Group International Conference. SAS Institute Inc.; 2001.
34. Seeger JD, Williams PL, Walker AM. An application of propensity score matching using claims data. Pharmacoepidemol Drug Saf. 2005;14:465–76. https://doi.org/10.1002/pds.1062
35. Yang C-Y, Kuo S, Lai EC-C, Ou H-T. Three-step matching algorithm to enhance between-group comparability and minimize confounding in comparative effectiveness studies. Sci Rep. 2022;12:214. https://doi.org/10.1038/s41598-021-04014-z
36. Inzucchi SE, Tunceli K, Qiu Y, Rajpathak S, Brodovicz KG, Engel SS, et al. Progression to insulin therapy among patients with type 2 diabetes treated with sitagliptin or sulphonylurea plus metformin dual therapy. Diabetes Obes Metab. 2015;17:956–64. https://doi.org/10.1111/dom.12489
37. Robins JM, Hernán MÁ, Brumback B. Marginal Structural Models and Causal Inference in Epidemiology. Epidemiology. 2000;11:550.
38. Chesnaye NC, Stel VS, Tripepi G, Dekker FW, Fu EL, Zoccali C, et al. An introduction to inverse probability of treatment weighting in observational research. Clin Kidney J. 2022;15:14–20. https://doi.org/10.1093/ckj/sfab158
39. Tamim H, Monfared AAT, LeLorier J. Application of lag-time into exposure definitions to control for protopathic bias. Pharmacoepidemiol Drug Saf. 2007;16:250–8. https://doi.org/10.1002/pds.1360
40. VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. Ann Intern Med. 2017;167:268–74. https://doi.org/10.7326/M16-2607
41. Neuen BL, Fletcher RA, Anker SD, Bhatt DL, Butler J, Cherney DZI, et al. SGLT2 Inhibitors and Kidney Outcomes by Glomerular Filtration Rate and Albuminuria: A Meta-Analysis. JAMA. 2026;335:233-244. https://doi.org/10.1001/jama.2025.20834
42. Rampersad C, Kraut E, Whitlock RH, Komenda P, Woo V, Rigatto C, et al. Acute Kidney Injury Events in Patients With Type 2 Diabetes Using SGLT2 Inhibitors Versus Other Glucose-Lowering Drugs: A Retrospective Cohort Study. Am J Kidney Dis. 2020;76:471-479.e1. https://doi.org/10.1053/j.ajkd.2020.03.019
43. Nadkarni GN, Ferrandino R, Chang A, Surapaneni A, Chauhan K, Poojary P, et al. Acute Kidney Injury in Patients on SGLT2 Inhibitors: A Propensity-Matched Analysis. Diabetes Care. 2017;40:1479–85.

https://doi.org/10.2337/dc17-1011

44. Delanaye P, Scheen AJ. Epidemiology of acute kidney injury adverse events with SGLT2 inhibitors: A meta-analysis of observational cohort studies. Diabetes Epidemiol Manag. 2021;3:100021. https://doi.org/10.1016/j.deman.2021.100021
45. Pasternak B, Wintzell V, Melbye M, Eliasson B, Svensson A-M, Franzén S, et al. Use of sodium-glucose co-transporter 2 inhibitors and risk of serious renal events: Scandinavian cohort study. BMJ. 2020;369:m1186. https://doi.org/10.1136/bmj.m1186
46. Chung M-C, Hung P-H, Hsiao P-J, Wu L-Y, Chang C-H, Hsiao K-Y, et al. Sodium-Glucose Transport Protein 2 Inhibitor Use for Type 2 Diabetes and the Incidence of Acute Kidney Injury in Taiwan. JAMA Netw Open. 2023;6:e230453. https://doi.org/10.1001/jamanetworkopen.2023.0453
47. Kang S, Kang SM, Choi JH, Ko S-H, Koo BK, Kwon H-S, et al. 2025 Clinical Practice Guidelines for Diabetes Management in Korea: Recommendation of the Korean Diabetes Association. Diabetes Metab J. Korean Diabetes Association; 2025;49:582–783. https://doi.org/10.4093/dmj.2025.0469
48. American Diabetes Association Professional Practice Committee for Diabetes*. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2026. Diabetes Care. 2025;49:S183–215. https://doi.org/10.2337/dc26-S009
49. Chang J, Kim C, Choi H, Park RW, Lee S. Renal and Safety Outcomes of SGLT2 Inhibitors in Patients with Type 2 Diabetes: A Nationwide Observational Cohort Study. J Clin Med. 2025;14:3349. https://doi.org/10.3390/jcm14103349
50. Vallon V, Thomson SC. Targeting renal glucose reabsorption to treat hyperglycaemia: the pleiotropic effects of SGLT2 inhibition. Diabetologia. 2017;60:215–25. https://doi.org/10.1007/s00125-016-4157-3
51. Heerspink HJL, Perkins BA, Fitchett DH, Husain M, Cherney DZI. Sodium Glucose Cotransporter 2 Inhibitors in the Treatment of Diabetes Mellitus: Cardiovascular and Kidney Effects, Potential Mechanisms, and Clinical Applications. Circulation. 2016;134:752–72. https://doi.org/10.1161/CIRCULATIONAHA.116.021887
52. Leoncini G, Russo E, Bussalino E, Barnini C, Viazzi F, Pontremoli R. SGLT2is and Renal Protection: From Biological Mechanisms to Real-World Clinical Benefits. Int J Mol Sci. 2021;22:4441. https://doi.org/10.3390/ijms22094441
53. Thomas MC, Cherney DZI. The actions of SGLT2 inhibitors on metabolism, renal function and blood pressure. Diabetologia. 2018;61:2098–107. https://doi.org/10.1007/s00125-018-4669-0
54. Navaneethan SD, Zoungas S, Caramori ML, Chan JCN, Heerspink HJL, Hurst C, et al. Diabetes Management in Chronic Kidney Disease: Synopsis of the KDIGO 2022 Clinical Practice Guideline Update. Ann Intern Med. 2023;176:381–7. https://doi.org/10.7326/M22-2904

Figures

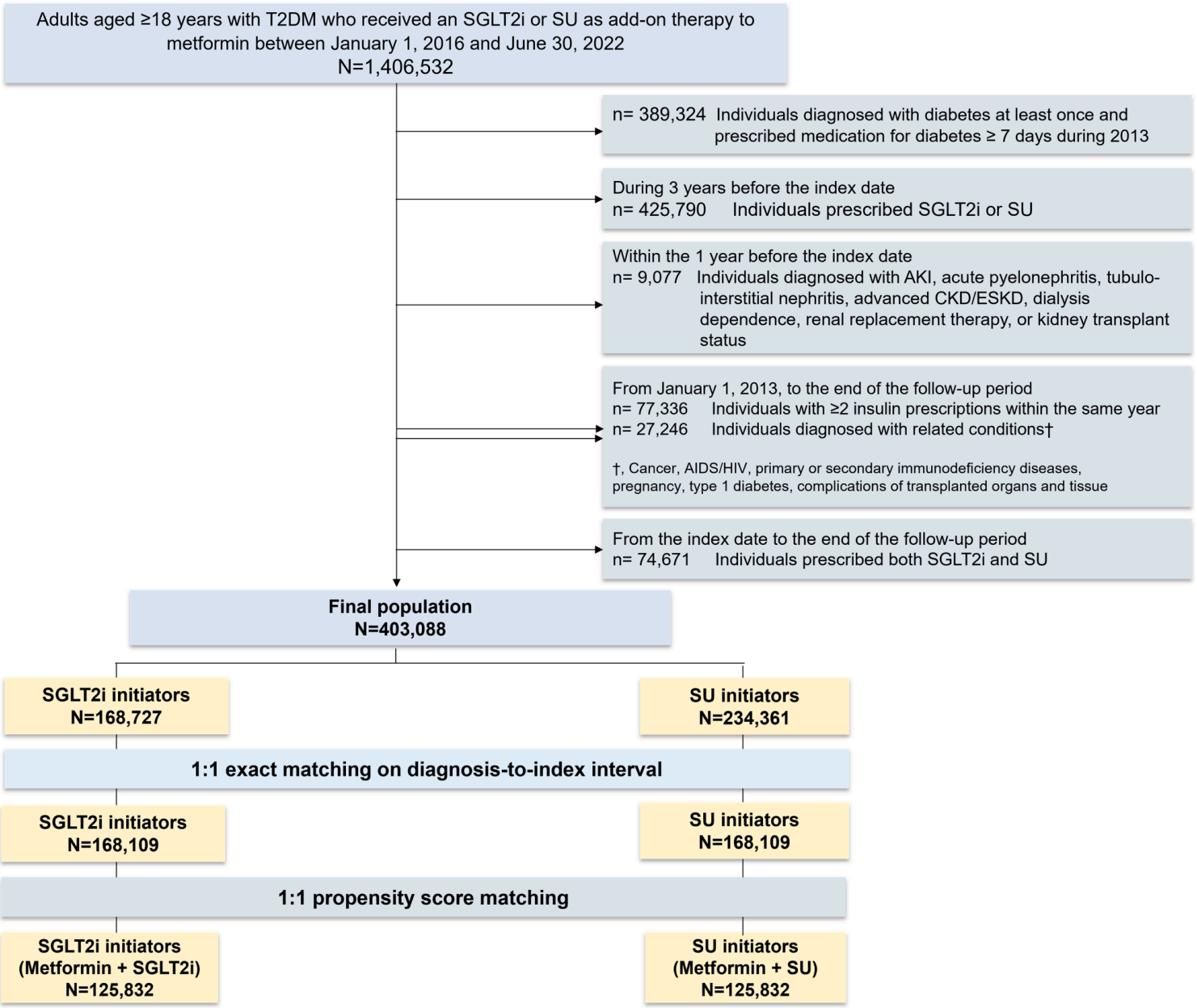


Figure 1

Study cohort selection and matching using exact matching followed by 1:1 PSM

Flow diagram of cohort selection. Exact matching on the interval from first T2DM diagnosis to treatment initiation was followed by 1:1 propensity score matching.

Abbreviations: NHIS, National Health Insurance Service; PSM, propensity score matching; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SU, sulfonylurea; T2DM, type 2 diabetes mellitus.

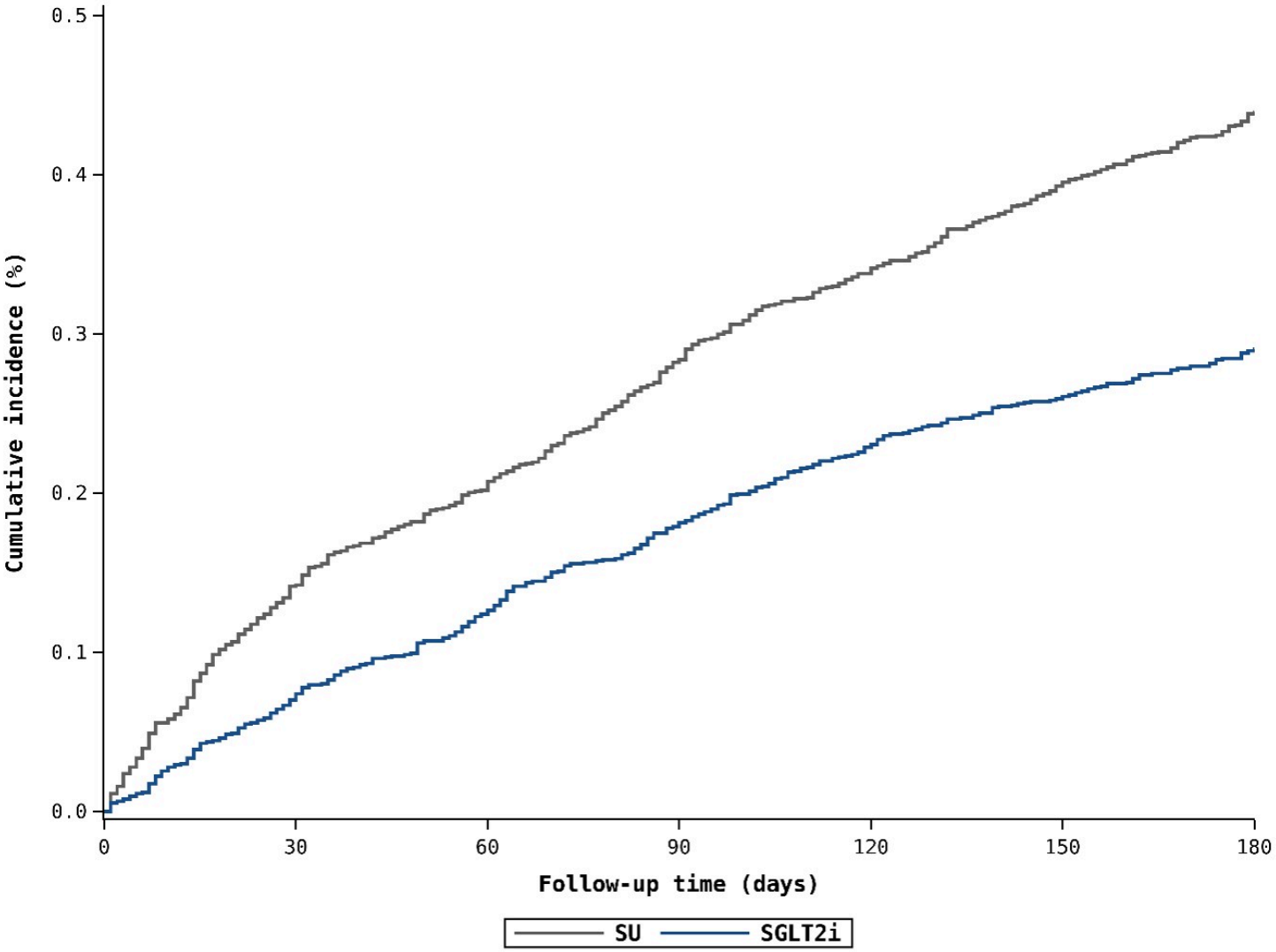


Figure 2

Cumulative incidence of AKI by SGLT2i versus SU

Cumulative incidence of acute kidney injury among SGLT2i and SU initiators in the propensity score-matched cohort over 180 days.

Abbreviations: AKI, acute kidney injury; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SU, sulfonylurea.

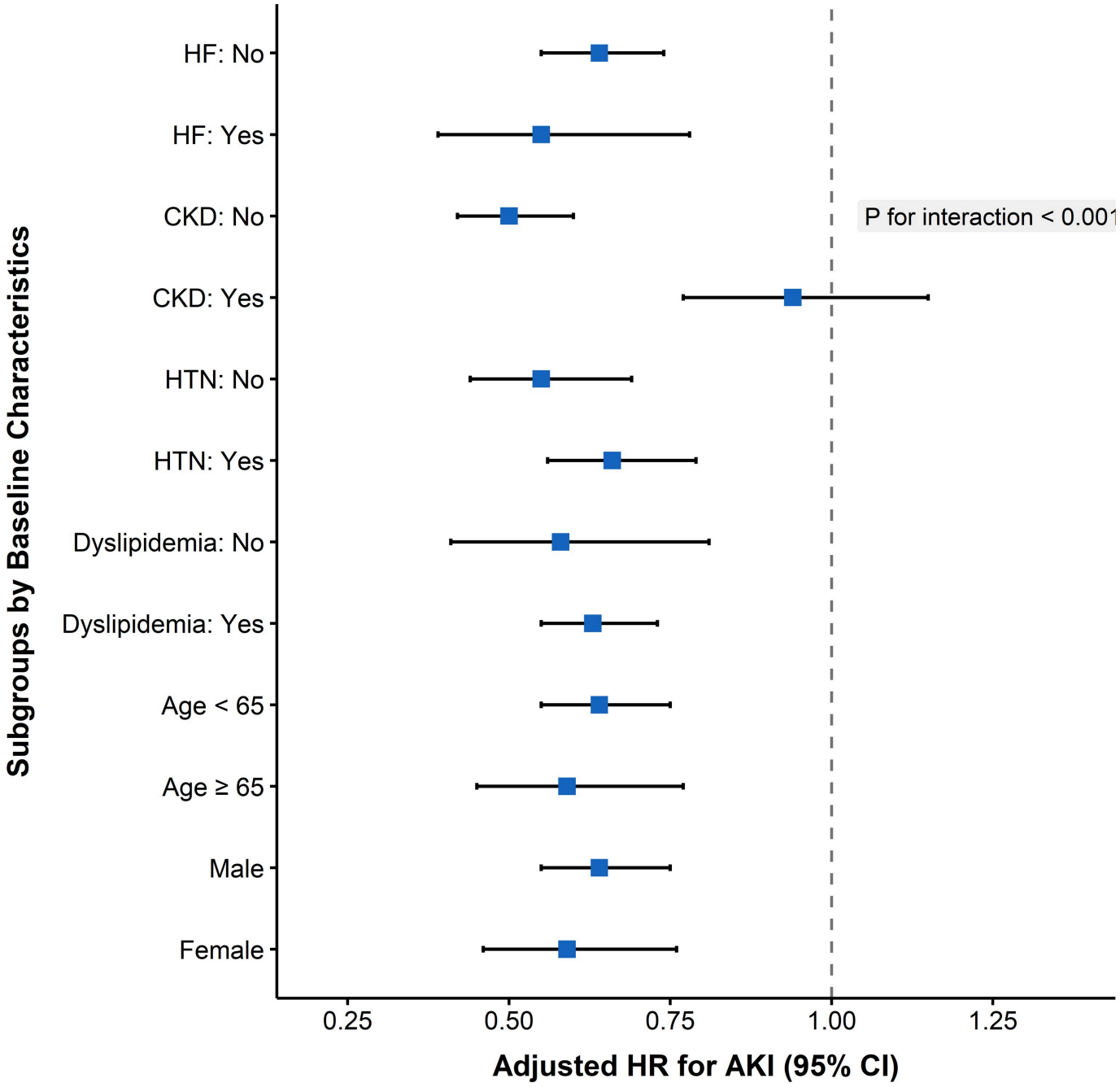


Figure 3

Subgroup-specific adjusted hazard ratios for AKI by SGLT2i exposure

Adjusted HRs for acute kidney injury comparing SGLT2i initiators with SU initiators across prespecified subgroups. Points and horizontal bars represent HRs and 95% CIs.

Abbreviations: AKI, acute kidney injury; CI, confidence interval; CKD, chronic kidney disease; HF, heart failure; HR, hazard ratio; HTN, hypertension; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SU, sulfonylurea.

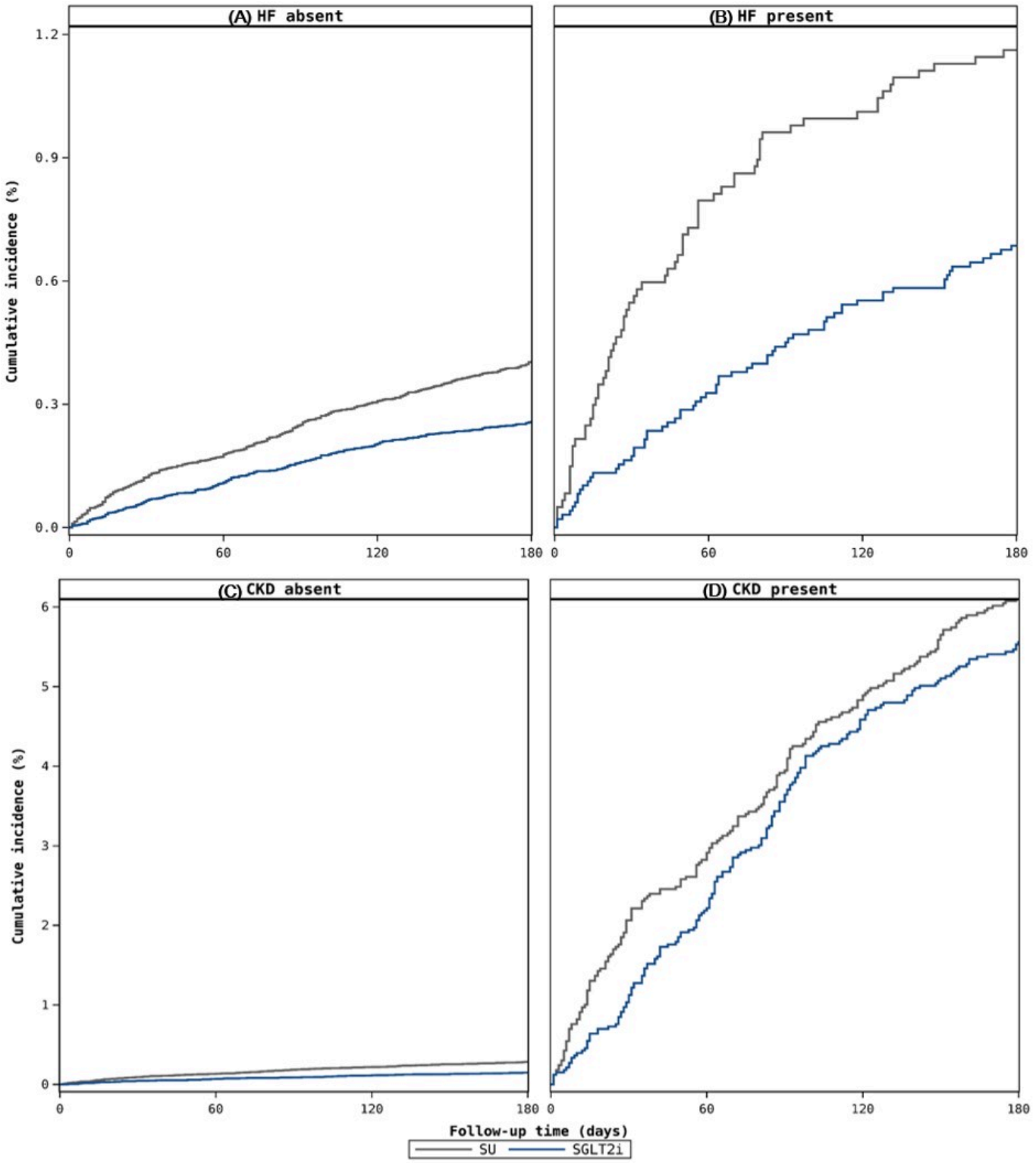


Figure 4

Cumulative incidence of acute kidney injury according to heart failure and chronic kidney disease status

Cumulative incidence of acute kidney injury among SGLT2i and SU initiators according to baseline HF and CKD status over 180 days.

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; HF, heart failure; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SU, sulfonylurea.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile1.docx
- Graphicalabstract.jpg