ESC European Heart Journal - Cardiovascular Pharmacotherapy (2026) **00**, 1–13
https://doi.org/10.1093/ehjcvp/pvag031

ORIGINAL ARTICLE

Effectiveness and safety of sodium-glucose cotransporter-2 inhibitor initiation in sacubitril-valsartan users with heart failure: a population-based cohort study

Che-Yuan Wu[1,2], Baiju R. Shah [3,4,5], Justin A. Ezekowitz [6,7], Abhinav Sharma [8,9], Tianru Wang[5], C. Fangyun Wu[5], Peter P. Liu[10], Jodi D. Edwards[10,11,12,*†], and Walter Swardfager [1,2,13,*†]

[1]Department of Pharmacology and Toxicology, University of Toronto, 777 Bay Street, Toronto, Ontario M5G 2R3, Canada; [2]Dr. Sandra Black Centre for Brain Resilience and Recovery, Hurvitz Brain Sciences Program, Sunnybrook Research Institute, 2075 Bayview Avenue, Toronto, Ontario M4N 3M5, Canada; [3]Division of Endocrinology, Department of Medicine, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Toronto, Ontario M4N 3M5, Canada; [4]Department of Medicine, Temerty Faculty of Medicine, University of Toronto, 6 Queen's Park Crescent West, Toronto, Ontario M5S 3H2, Canada; [5]ICES, 2075 Bayview Avenue, Toronto, Ontario M4N 3M5, Canada; [6]Mazankowski Alberta Heart Institute, University of Alberta, 11220 83 Avenue, Edmonton, Alberta T6G 2B7, Canada; [7]Canadian VIGOUR Centre, University of Alberta, 4-120 Katz Group Centre for Pharmacy and Health Research, Edmonton, Alberta T6G 2E1, Canada; [8]Division of Cardiology, McGill University Health Centre, McGill University, 1001 Boulevard Décarie, Montreal, Quebec H4A 3J1, Canada; [9]DREAM-CV Lab, McGill University Health Centre, McGill University, 1001 Boulevard Décarie, Montreal, Quebec H4A 3J1, Canada; [10]University of Ottawa Heart Institute, University of Ottawa, 40 Ruskin Street, Ottawa, Ontario K1Y 4W7, Canada; [11]School of Epidemiology and Public Health, University of Ottawa, 600 Peter Morand Crescent, Ottawa, Ontario K1G 5Z3, Canada; [12]ICES uOttawa, 1053 Carlind Avenue, Ottawa, Ontario K1Y 4E9, Canada; and [13]KITE University Health Network Toronto Rehabilitation Institute, 347 Rumsey Road, Toronto, Ontario M4G 1R7, Canada

Received 31 January 2026; revised 5 April 2026; accepted 30 April 2026; online publish-ahead-of-print 7 May 2026

Aims Large-scale real-world evidence regarding outcomes of sodium-glucose cotransporter-2 inhibitors (SGLT2i) initiation added to sacubitril-valsartan is currently limited. We aim to investigate effectiveness and safety of SGLT2i initiation among older sacubitril-valsartan users with heart failure in routine clinical practice.

Methods and results This prevalent new-user cohort study used linkable administrative data in Ontario, Canada, to emulate a target trial. In sacubitril-valsartan users with heart failure aged ≥66 years, SGLT2i initiators were matched on time-conditional propensity scores to non-initiators (October 2019 to June 2024). The primary effectiveness outcome was a composite of hospitalization for heart failure (HHF) or all-cause mortality. We also studied safety outcomes, including acute kidney injury (AKI), genital infection, urinary tract infection (UTI), falls, hospitalization for hypotension, diabetic ketoacidosis, and hypoglycaemia. Among 5000 matched pairs, SGLT2i initiation was associated with lower HHF or all-cause mortality [hazard ratio (HR) 0.71, 95% confidence interval 0.64–0.78; 1-year absolute risk: 13.9% vs. 19.2%]. Sodium-glucose cotransporter-2 inhibitor initiation was associated with a higher genital infection risk (2.36, 1.58–3.51; 1.8% vs. 0.7%) but not with higher rates of falls, hospitalization for hypotension, or UTI. Diabetic ketoacidosis was uncommon among SGLT2i users with diabetes as were hypoglycaemic events among SGLT2i users without diabetes. Sodium-glucose cotransporter-2 inhibitor initiation showed lower AKI among those with diabetes (0.78, 0.66–0.94) but not among those without diabetes (1.01, 0.66–0.94; HR homogeneity: $P = 0.035$).

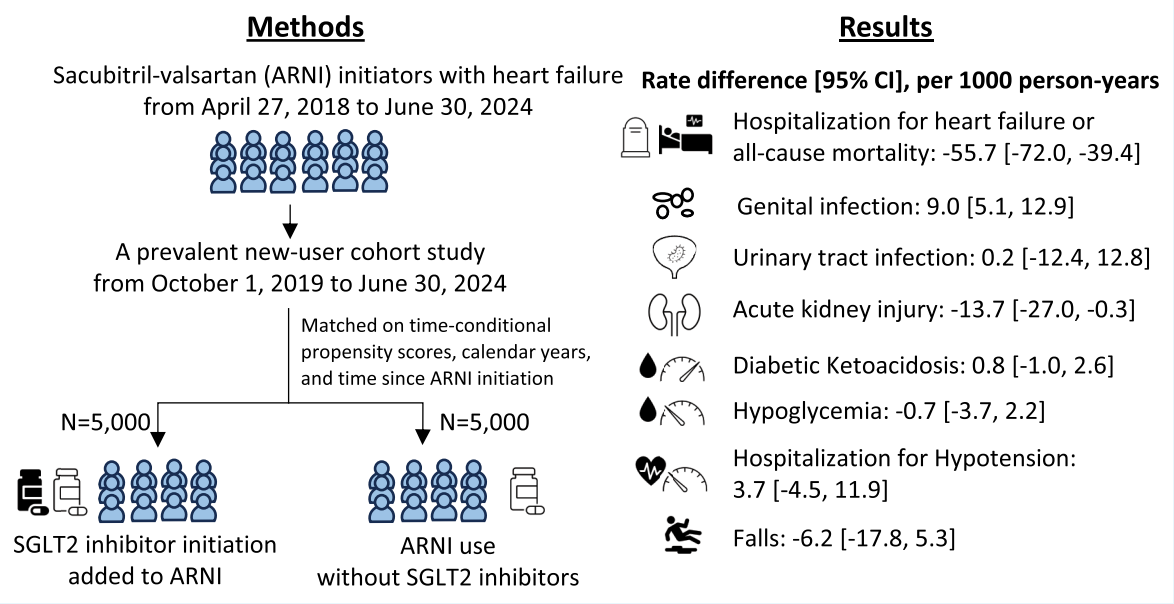
Conclusion This observational real-world evidence study supports effectiveness of SGLT2i among older sacubitril-valsartan users with heart failure, and suggests no increase in the safety outcomes studied, except genital infection.

*Corresponding authors. Tel: 416-480-6100, Fax: 416-480-4552, Email: w.swardfager@utoronto.ca (WS); Tel: 416-696-7000, Email: jedwards@ottawaheart.ca (JDE)
†These authors contributed equally to this work.

© The Author(s) 2026. Published by Oxford University Press on behalf of European Society of Cardiology.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (https://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact reprints@oup.com for reprints and translation rights for reprints. All other permissions can be obtained through our RightsLink service via the Permissions link on the article page on our site—for further information please contact journals.permissions@oup.com.

Downloaded from https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvag031/8672705 by guest on 11 June 2026

Graphical abstract



Keywords Sodium-glucose cotransporter 2 inhibitors • Angiotensin receptor-neprilysin inhibitor • Heart failure • Comparative effectiveness • Safety

Introduction

Sacubitril-valsartan is an angiotensin receptor-neprilysin inhibitor (ARNI), which has been shown to reduce hospitalization for heart failure (HHF) and mortality in people with heart failure with reduced ejection fraction (HFrEF).[1] The efficacy of ARNI is less certain in heart failure with mildly reduced or preserved ejection fraction (HFmrEF or HFpEF).[2] For HFrEF, Canadian guidelines have recommended ARNI as the first-line therapy,[3] and multiple guidelines have recommended combination of ARNI, beta-blockers, mineralocorticoid receptor antagonists (MRAs), and sodium-glucose cotransporter-2 (SGLT2) inhibitors.[3–5]

Sodium-glucose cotransporter-2 inhibitors are first approved for type 2 diabetes treatment and recently approved for heart failure treatment. In placebo-controlled trials of people with heart failure, SGLT2 inhibitors reduce worsening heart failure regardless of diabetes status and ejection fraction.[6–12] Real-world evidence studies have recapitulated the effectiveness of SGLT2 inhibitor initiation in heart failure with diabetes,[13–16] indicating that experimental findings may be generalized to routine clinical practice; however, most robust real-world evidence studies focused on either heart failure with diabetes[13–16] or acute heart failure.[15,16] To our knowledge, large-scale real-world evidence with robust methodology in broad heart failure populations regardless of diabetes status has been limited.[17] In a rigorous cohort study,[17] SGLT2 inhibitor initiation was associated with lower all-cause mortality but not with lower HHF in a broad HFrEF population, inconsistent with experimental evidence.[7,8] Also, pharmacovigilance studies using voluntary safety report data detected signals for potential acute kidney injury (AKI) risk with combination of ARNI and SGLT2 inhibitors.[18,19]

While ARNI is increasingly used in heart failure,[20] data on the efficacy and safety of SGLT2 inhibitor initiation added to ARNI in heart failure regardless of diabetes have been limited to small subgroup analyses of the DAPA-HF and EMPEROR-Reduced trials.[21–23] Large-scale evidence assessing the effectiveness and safety of this combination in routine clinical practice is needed.

To provide real-world evidence complementary to experimental data,[21–23] the present study investigates the effectiveness and safety of SGLT2 inhibitor initiation added to ARNI in older adults with heart failure regardless of diabetes status, using administrative datasets in Ontario, Canada.

Methods

Data source

This population-based, retrospective cohort study used linkable administrative datasets in Ontario, Canada. The datasets (see Supplementary material online, *Table S1*) were linked using unique encoded identifiers and analysed at ICES. The use of the data is authorized under section 45 of Ontario's Personal Health Information Protection Act and does not require review by a Research Ethics Board.

Ontario residents of any age are eligible for the Ontario Health Insurance Plan (OHIP), but only those aged ≥65 years are universally eligible for the Ontario Drug Benefit (ODB) program.

Population selection

The study selected ARNI dispensations from 27 April 2017 (i.e. the formulary listing date) to 30 June 2024. Angiotensin receptor-neprilysin inhibitor initiation was defined as no ARNI dispensing in the past year, and therefore we only included those with first

Downloaded from https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvag031/8672705 by guest on 11 June 2026

ARNI dispensing at the age ≥66 years from 27 April 2018 to 30 June 2024, and those with continuous eligibility in the past year. To identify heart failure patients, ARNI initiators without heart failure diagnoses from hospital admissions or OHIP physician claims before or at ARNI initiation were excluded.

Angiotensin receptor-neprilysin inhibitor is more likely to be prescribed in HFrEF,[3–5] and HFrEF diagnosis accounts for approximately half of the heart failure patients.[24,25] Reimbursement of ARNI use by the ODB is limited to people with documented HFrEF and New York Heart Association (NYHA) Class II or III. Thus, most ARNI users were anticipated to be HFrEF cases in our study; however, ejection fraction measures or diagnostic codes for classifying heart failure were not available in the study, nor a within a population subset to extrapolate, validate, or quantify the HFrEF prevalence.

Supplementary material online, *Figure S1* graphically summarizes the study design. The present study used a prevalent new-user cohort design[26] to emulate a hypothetical pragmatic trial[27] comparing initiation vs. no initiation of SGLT2 inhibitors among prevalent or new users of ARNI with heart failure (see Supplementary material online, *Table S2*). All ARNI dispensations from first identified initiation were potential cohort entries, and eligibility criteria were consistently applied to each ARNI dispensation. As the exposures, cohort creation, and eligibility criteria followed a target trial emulation framework, immortal time bias and baseline selection bias were minimized.[27] The first trial of SGLT2 inhibitors in heart failure was published in September 2019;[7] thus, the cohort entry period started from 1 October 2019 to 30 June 2024.

For individuals re-initiating ARNI, dispensations from re-initiation were not used for potential cohort entries. To identify initiators vs. non-initiators of SGLT2 inhibitors, we excluded those without continuous eligibility in the past year of cohort entry and those dispensed SGLT2 inhibitors at any time before cohort entry. To minimize false positives in identifying combination therapy initiators, those dispensed both ARNI and an SGLT2 inhibitor on the same date were considered as combination therapy initiators. To reduce the likelihood of violating the positivity assumption, we excluded those with diabetic ketoacidosis (DKA), dialysis, or latest estimated glomerular filtration rate (eGFR) < 20 mL/min/1.73 m^2 in the past year. We also excluded those dispensed ARNI with angiotensin-converting enzyme inhibitors or another angiotensin receptor blocker on the same date at cohort entry. Supplementary material online, *Table S3* lists details on exclusion criteria.

Exposures

Sodium-glucose cotransporter-2 inhibitors covered by ODB are canagliflozin, dapagliflozin, and empagliflozin. As canagliflozin is not indicated for heart failure treatment, canagliflozin initiators were excluded. Initiators of multiple SGLT2 inhibitors were also excluded. Sacubitril-valsartan is the only ARNI in the market.

Follow-up

The primary analysis emulated a per-protocol analysis, comparing outcomes of continuous use of SGLT2 inhibitors vs. no initiation of SGLT2 inhibitors among baseline ARNI users. The primary analysis did not consider ARNI discontinuation as treatment deviation.

Individuals were followed until the outcome of interest, death, SGLT2 inhibitor dispensing among baseline non-initiators, SGLT2 inhibitor discontinuation among baseline initiators, end of OHIP coverage, or 30 November 2024 (i.e. end of study period), whichever occurred first. Discontinuation was defined as no subsequent dispensing during the days of supply plus a 30-day grace period.

Per-protocol analysis was chosen over intention-to-treat analysis to minimize exposure misclassification, especially exposure misclassification due to staggered dispensations or rapid guideline-directed medical therapy initiation among baseline non-initiators.

Outcome definitions

The primary effectiveness outcome was a composite of HHF or all-cause mortality. Hospitalization for heart failure was defined as inpatient admissions with the diagnosis recorded as the most responsible diagnosis.[28] Restricting acute cardiovascular events to the most responsible diagnosis was shown to improve the positive predictive value (PPV).[29] Secondary effectiveness outcomes were all-cause mortality and HHF separately.

We also examined safety outcomes potentially linked to dapagliflozin or empagliflozin, including AKI, DKA, falls, hospitalization for hypotension, hypoglycaemia, genital infection, and urinary tract infection (UTI).

Acute kidney injury was defined as the diagnosis recorded as a significant diagnosis present at an inpatient admission, which was shown to have 99.2% specificity and 81.6% PPV when the AKI Network Stage 1 or greater was the referent.[30] Diabetic ketoacidosis and hypoglycaemia were defined based on one diagnostic code from inpatient admissions or emergency visits at any position. Diabetic ketoacidosis codes from inpatient admissions showed 99.6% specificity and 67.0% PPV.[31] Hypoglycaemia codes were shown to have 94.0% PPV among hypoglycaemia cases in inpatient stays or emergency visits.[32]

Falls, genital infection, UTI, and hospitalization for hypotension were defined using previously used algorithms.[33,34] Hospitalization for hypotension was defined as hypotension recorded as a significant diagnosis present at an inpatient admission.[34] Falls were defined as one diagnostic code from inpatient admissions or emergency visits at any position. Genital infection and UTI were defined as one diagnostic code in any settings. Detailed definitions of each outcome are summarized in Supplementary material online, *Table S4*.

Statistical analysis

Creation of exposure sets was based on time since ARNI initiation and calendar years (see Supplementary material online, *Figure S2*). Eligible ARNI dispensations were first classified into new and prevalent ARNI use. New ARNI use with or without concurrent SGLT2 inhibitor initiation in the same calendar year were considered in the same exposure set. For prevalent ARNI use, the exposure sets were created by dividing time since ARNI initiation into 30-day intervals,[35] and then further stratified by calendar years. Angiotensin receptor-neprilysin inhibitor dispensations with or without SGLT2 inhibitor initiation on the same date was identified within each exposure set. When an individual had multiple ARNI dispensations eligible for the comparator within an exposure set, we randomly selected one as the potential cohort entry for that exposure set.

Propensity scores were estimated using a logistic regression model in stacked exposure sets, conditional on exposure sets and 118 covariates listed in Supplementary material online, *Table S5*, including demographics, prescribing speciality, disease-related variables, healthcare utilization, recent hospitalization (all-cause hospitalization and HHF), eGFR stages, comorbidities, procedures, and concurrent medications. This modelling approach estimates propensity scores, rather than pseudo-probabilities from conditional logistic regression.[36] Restricted cubic splines with 4 percentile knots were used to model continuous covariates. The models were fitted separately for new and prevalent users of ARNI. For the positivity assumption, exposure sets without eligible SGLT2 inhibitor initiators were excluded from propensity score estimation, and exposure sets with no propensity scores overlap between groups were excluded. Within an exposure set, unique individuals were 1:1 matched on propensity scores with a caliper of 0.1 times the standard deviation of propensity scores.[36] Individuals selected for matching in one exposure set could still enter a subsequent exposure set when eligible (i.e. matching with replacement), which was suggested to be unbiased and more efficient than matching without replacement across exposure sets.[36]

Follow-up started from the date of ARNI dispensing in the corresponding exposure sets. Cause-specific hazard ratios (HRs) and the 95% confidence intervals (CIs) were estimated using Cox regression. Absolute rates and incidence rate differences (IRDs) per 1000

Downloaded from https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvag031/8672705 by guest on 11 June 2026

person-years were estimated using Poisson regression. Robust variance estimation was used in regression models to yield conservative standard errors that account for within-subject non-independence.[37] The Aalen-Johansen estimator with death as a competing risk[38] was used to visualize cumulative incidence functions (CIFs) and calculate absolute risks. Analyses were conducted in SAS v9.4 (SAS Institute, Cary, NC, USA).

Subgroup analysis

Subgroup analyses by new vs. prevalent use of ARNI, age >75 vs. ≤75 years, sex, MRA use, diabetes, atrial fibrillation, HHF in the past year, and eGFR ≥60 vs. <60 mL/min/1.73 m^2 were performed. Molecule-specific analyses for dapagliflozin and empagliflozin were also performed, and switching from one to another SGLT2 inhibitor was considered as an additional censoring endpoint. For each subgroup analysis, propensity scores calculation and matching were re-performed. The Wald test for homogeneity with a 5% significance level was used to test whether the estimates significantly differed between subgroups.

Supporting analysis

First, SGLT2 inhibitors might be initiated in hospitals, but inpatient prescription data were unavailable. To more accurately select initiators, we excluded those discharged from hospitals in the past week. Second, to explore the potential for reverse causality due to existing infection, we excluded those diagnosed with UTI or dispensed antibiotics for UTI and those diagnosed with genital infection or dispensed antifungals in the past 90 days. Third, inverse probability of censoring weighting for selection bias due to treatment-related time-varying confounding was applied to examine the robustness to informative censoring caused by treatment deviation (see Supplementary material online, *Methods S1*). Fourth, to estimate effects of continuous combination of ARNI and SGLT2 inhibitors vs. continuous ARNI without SGLT2 inhibitors, we further censored at ARNI discontinuation, and a separate analysis included censoring weights to further adjust for selection bias over time (see Supplementary material online, *Methods S1*). Fifth, to explore the role of ARNI adherence in the primary analysis, ARNI discontinuation as an outcome was studied. Sixth, alternative outcome definitions for AKI and UTI were explored (see Supplementary material online, *Table S4*). Seventh, to examine the robustness to residual confounding, ischaemic stroke as a negative control outcome was examined (see Supplementary material online, *Methods S2*).[14,39] Eighth, colorectal cancer screening as another negative control outcome was examined to explore potential bias due to differential healthcare contact. Ninth, for safety outcomes revealing significantly higher risk with SGLT2 inhibitors, quantitative bias analyses (see Supplementary material online, *Methods S3*) were performed to explore the impact of non-differential misclassification on risk estimates.[40] Tenth, another quantitative bias analysis for unmeasured confounding was conducted using the rule-out approach.[41]

Results

Population characteristics

The cohort study analysed 5000 matched pairs of SGLT2 inhibitor initiators and non-initiators (*Figure 1*). Among matched SGLT2 inhibitor initiators, 67% used empagliflozin (see Supplementary material online, *Table S6*). All covariates (see Supplementary material online, *Table S7*) showed standardized mean differences (SMDs) < 0.1 after matching, and highlighted baseline characteristics are shown in *Table 1*. The propensity score distributions are depicted in Supplementary material online, *Figure S4*. Reasons for end of follow-up by exposure groups are summarized in Supplementary material online, *Table S8*.

Effectiveness outcomes

The crude analyses are reported in Supplementary material online, *Table S9*. The estimates for effectiveness are summarized in *Table 2*, the CIFs are illustrated in *Figure 2*, and the absolute risks are summarized in Supplementary material online, *Table S10*.

Among older ARNI users with heart failure, SGLT2 inhibitor initiation was associated with lower HHF or all-cause mortality [IRD (95% CI): −55.7 (−72.0, −39.4); 1-year absolute risk: 13.9% vs. 19.2%]. When individual effectiveness outcomes were analysed, the IRDs for HHF and all-cause mortality were −28.1 (95% CI: −39.4, −16.7) and −40.3 (95% CI: −52.7, −27.8), respectively.

Safety outcomes

Crude estimates are reported in Supplementary material online, *Table S11*. The estimates for safety outcomes are summarized in *Table 3*, the CIFs are illustrated in Supplementary material online, *Figures S5–S11*, and the absolute risks are summarized in Supplementary material online, *Table S12*.

Sodium-glucose cotransporter-2 inhibitor initiation was not significantly associated with higher rates of DKA, hypoglycaemia, falls, hospitalization for hypotension, and UTI. However, SGLT2 inhibitor initiation was associated with a higher genital infection rate [IRD (95% CI): 9.0 (5.1, 12.9); 1-year absolute risk: 1.8% vs. 0.7%]. Sodium-glucose cotransporter-2 inhibitor initiation overall showed an IRD of −13.7 (95% CI: −27.0, −0.3) for AKI.

Subgroup analysis

The subgroup analyses are reported in Supplementary material online, *Figures S11–S20*. There were no significant differences in effectiveness between empagliflozin and dapagliflozin or between diabetes status (*Figure 3*). Females vs. males showed significantly greater absolute increase [IRD (95% CI): 17.3 (7.5, 27.1) vs. 5.7 (2.2, 9.1), homogeneity: $P = 0.028$] in genital infection but numerically smaller reduction in the effectiveness endpoint [IRD (95% CI): −31.8 (−60.2, −3.5) vs. −65.8 (−86.2, −45.4), homogeneity: $P = 0.056$]. Acute kidney injury reduction was observed in people with diabetes [IRD (95% CI): −35.7 (−61.0, −10.3)] but not observed in people without diabetes [IRD (95% CI): 2.0 (−13.2, 17.1), homogeneity: $P = 0.013$]. Incident DKA was rare among SGLT2 inhibitor initiators with diabetes (absolute rate: 4.5). Hypoglycaemic events were rare (absolute rate: 4.3) but numerically higher in SGLT2 inhibitor initiators without diabetes [IRD (95% CI): 1.7 (−1.0, 4.5)].

Supporting analysis

Results were comparable when those recently discharged were excluded (see Supplementary material online, *Table S13*). Similar estimates were seen when individuals with recent diagnostic codes of genital infection or UTI or individuals recently dispensed antibiotics or antibiotics for UTI were excluded (see Supplementary material online, *Table S14*). In analyses with censoring weighting for SGLT2 inhibitors (see Supplementary material online, *Table S15*) or in analyses that considered ARNI discontinuation as an additional endpoint (see Supplementary material online, *Tables S16* and *S17*), although smaller all-cause mortality reduction was observed, results for safety outcomes were similar. The HRs for the alternative AKI and UTI definitions were 0.85 (95% CI: 0.64–1.13) and 0.88 (95% CI: 0.72–1.08), respectively (see Supplementary material online, *Table S18*).

Downloaded from https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvag031/8672705 by guest on 11 June 2026

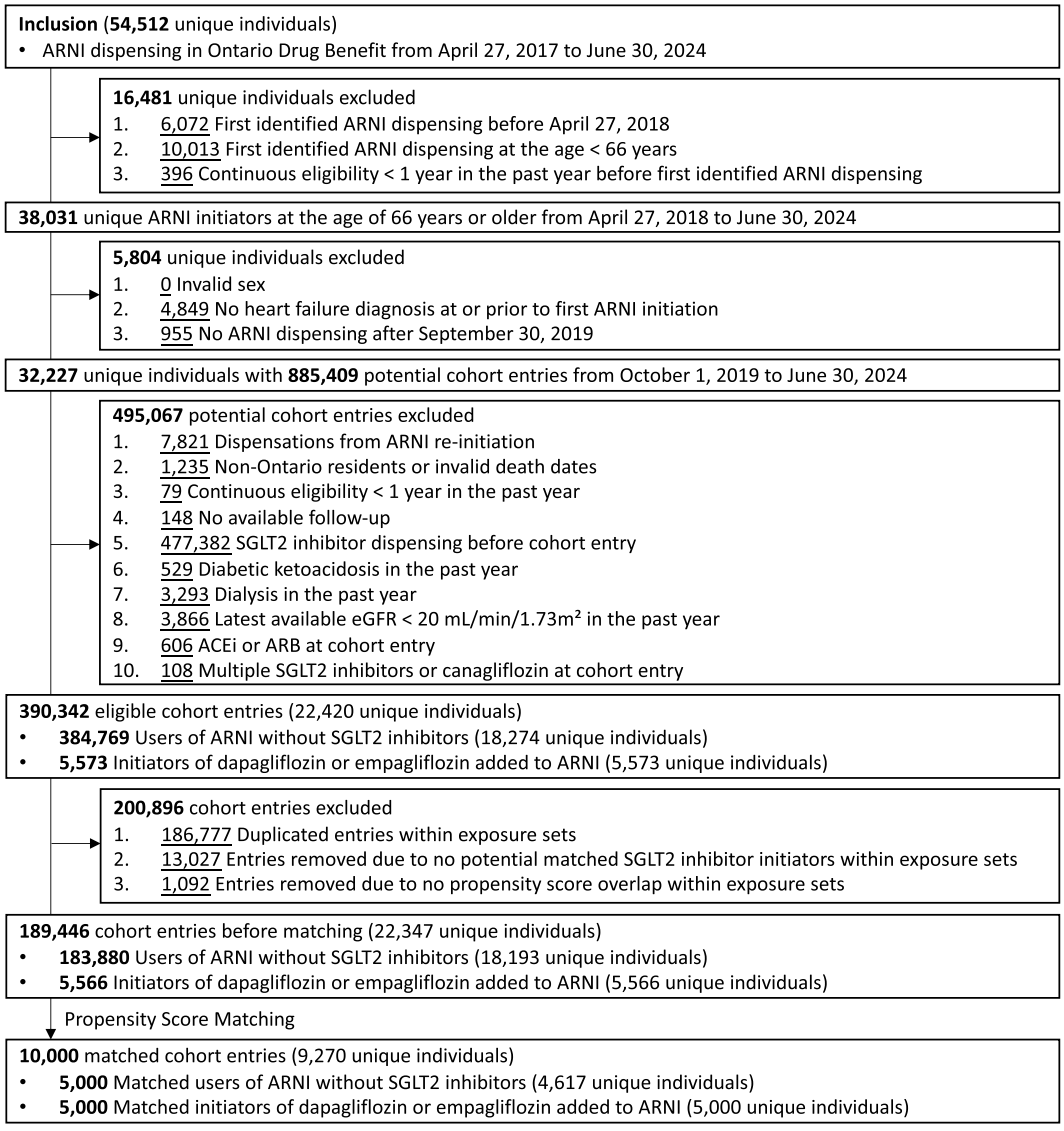


Figure 1 Cohort flow diagram. Among 9270 unique individuals, 8585 (92.6%) entered the study only once as either sodium-glucose cotransporter-2 inhibitor initiators or non-initiators, and the maximum number of cohort entry was 4 (interquartile range: 1-1). Among 5000 unique sodium-glucose cotransporter-2 inhibitor initiators, only 347 (6.9%) previously entered the study as non-initiators.

Sensitivity analyses sorted by outcomes were presented in Supplementary material online, *Figures S21–S30*.

Ischaemic stroke as a negative control outcome showed an HR of 1.04 (95% CI: 0.68–1.58) (see Supplementary material online, *Table S18*). Colorectal cancer screening as another negative control outcome showed an HR of 1.19 (95% CI: 0.81–1.75) (see Supplementary material online, *Table S18*).

Sodium-glucose cotransporter-2 inhibitor initiators were less likely to discontinue ARNI [HR (95% CI): 0.81 (0.76–0.87); 1-year absolute risk: 32.5% vs. 38.1%], suggesting ARNI adherence might partly account for the observed effectiveness with SGLT2 inhibitors (see Supplementary material online, *Tables S19* and *S20*).

In the quantitative bias analysis, the corrected absolute difference in genital infection did not exceed the observed difference in effectiveness unless assuming extremely low sensitivity (see Supplementary material online, *Figure S31*). According to the quantitative bias analysis, moderate to large unmeasured confounding would be needed to nullify the observed effectiveness (see Supplementary material online, *Figure S32*).

Discussion

In this real-world evidence study, SGLT2 inhibitor initiation was associated with lower HHF or all-cause mortality among older ARNI users with heart failure. No significant increase in the rates of falls, hospitalization for hypotension, or UTI was seen with SGLT2 inhibitor initiation. Diabetic ketoacidosis was rare among those with diabetes, and hypoglycaemic events were rare among those without diabetes. Nonetheless, genital infection was significantly higher in the SGLT2 inhibitor group, and AKI

Downloaded from https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvag031/8672705 by guest on 11 June 2026

Table 1 Highlighted baseline characteristics by sodium-glucose cotransporter-2 inhibitor initiation among angiotensin receptor-neprilysin inhibitor users

	Before matching			After matching		
Characteristics[a]	Initiators (*N* = 5566)[b]	Non-initiators (*N* = 183 880)[b]	SMD	Initiators (*N* = 5000)[b]	Non-initiators (*N* = 5000)[b]	SMD
Age, years, mean (SD)	77.08 (7.20)	79.14 (7.45)	−0.28	77.25 (7.23)	77.34 (7.29)	−0.01
Male	66.87% (3722)	63.72% (117 166)	0.07	66.64% (3332)	67.34% (3367)	−0.01
Days since ARNI initiation, median (IQR)	0 [0–10]	386 [116–758]	0.00	0 [0–14]	0 [0–14]	0.00
Concurrent ARNI initiation	74.36% (4139)	8.03% (14 774)	1.82	73.98% (3699)	73.98% (3699)	0.00
Rurality						
Rural	11.52% (641)	12.67% (23 295)	−0.04	11.62% (581)	11.56% (578)	0.00
Urban	88.23% (4911)	87.09% (160 146)	0.03	88.14% (4407)	88.22% (4411)	0.00
Missing	0.25% (14)	0.24% (439)	0.00	0.24% (12)	0.22% (11)	0.00
Duration of heart failure, years, median (IQR)	0.99 [0.05–7.82]	4.39 [1.68–10.61]	−0.31	1.24 [0.06–8.13]	1.24 [0.07–8.37]	0.00
ARNI dose at cohort entry						
Low	64.98% (3617)	56.21% (103 362)	0.18	64.80% (3240)	65.60% (3280)	−0.02
Medium	27.94% (1555)	29.91% (54 995)	−0.04	27.92% (1396)	27.12% (1356)	0.02
High	7.08% (394)	13.88% (25 523)	−0.22	7.28% (364)	7.28% (364)	0.00
Discharge from hospitalization in the past week	37.35% (2079)	2.77% (5097)	0.96	30.92% (1546)	30.52% (1526)	0.01
Discharge from hospitalized heart failure in the past week	20.86% (1161)	1.17% (2154)	0.66	16.56% (828)	16.16% (808)	0.01
eGFR, mL/min/1.73 m^2						
≥90	10.91% (607)	6.84% (12 581)	0.14	10.86% (543)	10.94% (547)	0.00
60–90	46.16% (2569)	38.07% (70 009)	0.16	46.18% (2309)	46.18% (2309)	0.00
45–60	24.06% (1339)	25.61% (47 091)	−0.04	23.90% (1195)	23.06% (1153)	0.02
30–45	13.01% (724)	17.94% (32 981)	−0.14	13.02% (651)	13.84% (692)	−0.02
<30	2.44% (136)	4.58% (8422)	−0.12	2.50% (125)	2.64% (132)	−0.01
Missing	3.43% (191)	6.96% (12 796)	−0.16	3.54% (177)	3.34% (167)	0.01
Comorbidities[c]						
Acute kidney injury	19.49% (1085)	20.62% (37 922)	−0.03	19.16% (958)	19.04% (952)	0.00
Anaemia	19.39% (1079)	21.38% (39 313)	−0.05	19.54% (977)	19.42% (971)	0.00
Angina	25.78% (1435)	27.14% (49 905)	−0.03	25.50% (1275)	26.08% (1304)	−0.01
Atrial fibrillation	46.35% (2580)	48.26% (88 743)	−0.04	45.60% (2280)	46.50% (2325)	−0.02
Coronary atherosclerosis	49.95% (2780)	54.11% (99 493)	−0.08	50.02% (2501)	50.44% (2522)	−0.01
Diabetes	37.28% (2075)	33.20% (61 047)	0.09	35.58% (1779)	35.90% (1795)	−0.01
Diabetic ketoacidosis	1–5	0.15% (268)	NA	1–5	1–5	NA
Fall	14.25% (793)	18.25% (33 565)	−0.11	14.50% (725)	14.70% (735)	−0.01
Genital infection	2.32% (129)	2.70% (4969)	−0.02	2.48% (124)	2.46% (123)	0.00
Hypertension	73.01% (4064)	69.20% (127 242)	0.08	72.16% (3608)	72.76% (3638)	−0.01

Continued

Downloaded from https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvag031/8672705 by guest on 11 June 2026

Table 1 *Continued*

Characteristics[a]	Before matching			After matching		
	Initiators (*N* = 5566)[b]	Non-initiators (*N* = 183 880)[b]	SMD	Initiators (*N* = 5000)[b]	Non-initiators (*N* = 5000)[b]	SMD
Hypoglycaemia	1.02% (57)	0.95% (1739)	0.01	0.92% (46)	0.92% (46)	0.00
Hypotension	6.13% (341)	7.87% (14 473)	−0.07	6.00% (300)	6.60% (330)	−0.02
Myocardial infarction	22.76% (1267)	18.57% (34 155)	0.10	21.52% (1076)	21.88% (1094)	−0.01
Stroke	9.36% (521)	10.03% (18 452)	−0.02	9.30% (465)	9.02% (451)	0.01
Urinary tract infection	15.83% (881)	19.81% (36 423)	−0.10	16.20% (810)	16.42% (821)	−0.01
Procedures[c]						
Coronary angiography	37.53% (2089)	33.59% (61 757)	0.08	36.04% (1802)	36.46% (1823)	−0.01
Coronary artery bypass graft	3.41% (190)	3.09% (5674)	0.02	3.58% (179)	4.06% (203)	−0.03
Implantable defibrillator	10.89% (606)	18.87% (34 702)	−0.23	11.02% (551)	10.76% (538)	0.01
Pacemaker	16.58% (923)	25.23% (46 401)	−0.21	17.00% (850)	16.50% (825)	0.01
Percutaneous coronary intervention	12.16% (677)	10.10% (18 570)	0.07	11.42% (571)	11.36% (568)	0.00
Medications[d]						
ACE inhibitors	35.20% (1959)	13.70% (25 195)	0.52	35.40% (1770)	36.10% (1805)	−0.01
Angiotensin II receptor blockers	21.49% (1196)	7.53% (13 849)	0.40	21.86% (1093)	21.34% (1067)	0.01
Antibiotics	36.22% (2016)	33.90% (62 338)	0.05	36.44% (1822)	36.54% (1827)	0.00
Anticoagulants	52.08% (2899)	56.26% (103 452)	−0.08	51.94% (2597)	52.18% (2609)	0.00
Antifungals	5.46% (304)	6.80% (12 503)	−0.06	5.48% (274)	5.80% (290)	−0.01
Antiplatelets	19.76% (1100)	15.20% (27 955)	0.12	18.86% (943)	18.54% (927)	0.01
Beta blockers	88.20% (4909)	88.17% (162 134)	0.00	87.72% (4386)	87.52% (4376)	0.01
Calcium channel blockers	26.39% (1469)	14.86% (27 328)	0.29	26.06% (1303)	26.74% (1337)	−0.02
Digoxin	9.50% (529)	11.12% (20 452)	−0.05	9.18% (459)	9.62% (481)	−0.02
Hydralazine	1.69% (94)	1.25% (2304)	0.04	1.66% (83)	1.62% (81)	0.00
Insulin	4.99% (278)	5.28% (9704)	−0.01	4.60% (230)	4.90% (245)	−0.01
Ivabradine	1.28% (71)	1.93% (3547)	−0.05	1.16% (58)	1.16% (58)	0.00
Loop diuretics	64.70% (3601)	62.43% (114 788)	0.05	63.66% (3183)	65.52% (3276)	−0.04
Metformin	19.15% (1066)	13.85% (25 475)	0.14	17.54% (877)	17.60% (880)	0.00
Mineralocorticoid receptor antagonists	60.03% (3341)	47.34% (87 040)	0.26	56.16% (2808)	56.20% (2810)	0.00
Nitrate vasodilators	16.98% (945)	11.94% (21 951)	0.14	16.18% (809)	16.38% (819)	−0.01
Statin	74.83% (4165)	76.34% (140 380)	−0.04	74.52% (3726)	74.12% (3706)	0.01
Thiazides	13.62% (758)	5.50% (10 113)	0.28	13.14% (657)	13.40% (670)	−0.01

SD, standard deviation; SMD, standardized mean difference; IQR, interquartile range.
[a]Categorical variables are reported as proportion (count). Full baseline characteristics are reported in the supplementary material.
[b]In a prevalent new-user cohort, a unique individual could enter the study more than once. Therefore, *N* represents the number of cohort entries, rather than unique individuals.
[c]Three-year lookback window.
[d]One hundred and eighty day lookback window.

Downloaded from https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvag031/8672705 by guest on 11 June 2026

Table 2 Associations between sodium-glucose cotransporter-2 inhibitor initiation and effectiveness outcomes among angiotensin receptor-neprilysin inhibitor users

	N	Events	Person-years[a]	Rates (95% CI)[b]	IRD (95% CI)[b]	HR (95% CI)
Hospitalization for heart failure or all-cause mortality						
Initiators	5000	773	5805.85	133.1 (123.5, 142.8)	−55.7 (−72.0, −39.4)	0.71 (0.64, 0.78)
Non-initiators	5000	992	5253.00	188.8 (175.7, 202.0)	0.0 (Reference)	1.00 (Reference)
Hospitalization for heart failure						
Initiators	5000	382	5805.85	65.8 (59.1, 72.5)	−28.1 (−39.4, −16.7)	0.70 (0.61, 0.81)
Non-initiators	5000	493	5253.00	93.9 (84.7, 103.0)	0.0 (Reference)	1.00 (Reference)
All-cause mortality						
Initiators	5000	500	6053.39	82.6 (75.3, 89.9)	−40.3 (−52.7, −27.8)	0.67 (0.59, 0.76)
Non-initiators	5000	677	5510.65	122.9 (112.7, 133.0)	0.0 (Reference)	1.00 (Reference)

CI, confidence interval; IRD, incidence rate difference; HR, hazard ratio.
[a]Total person-years on treatment.
[b]Per 1000 person-years.

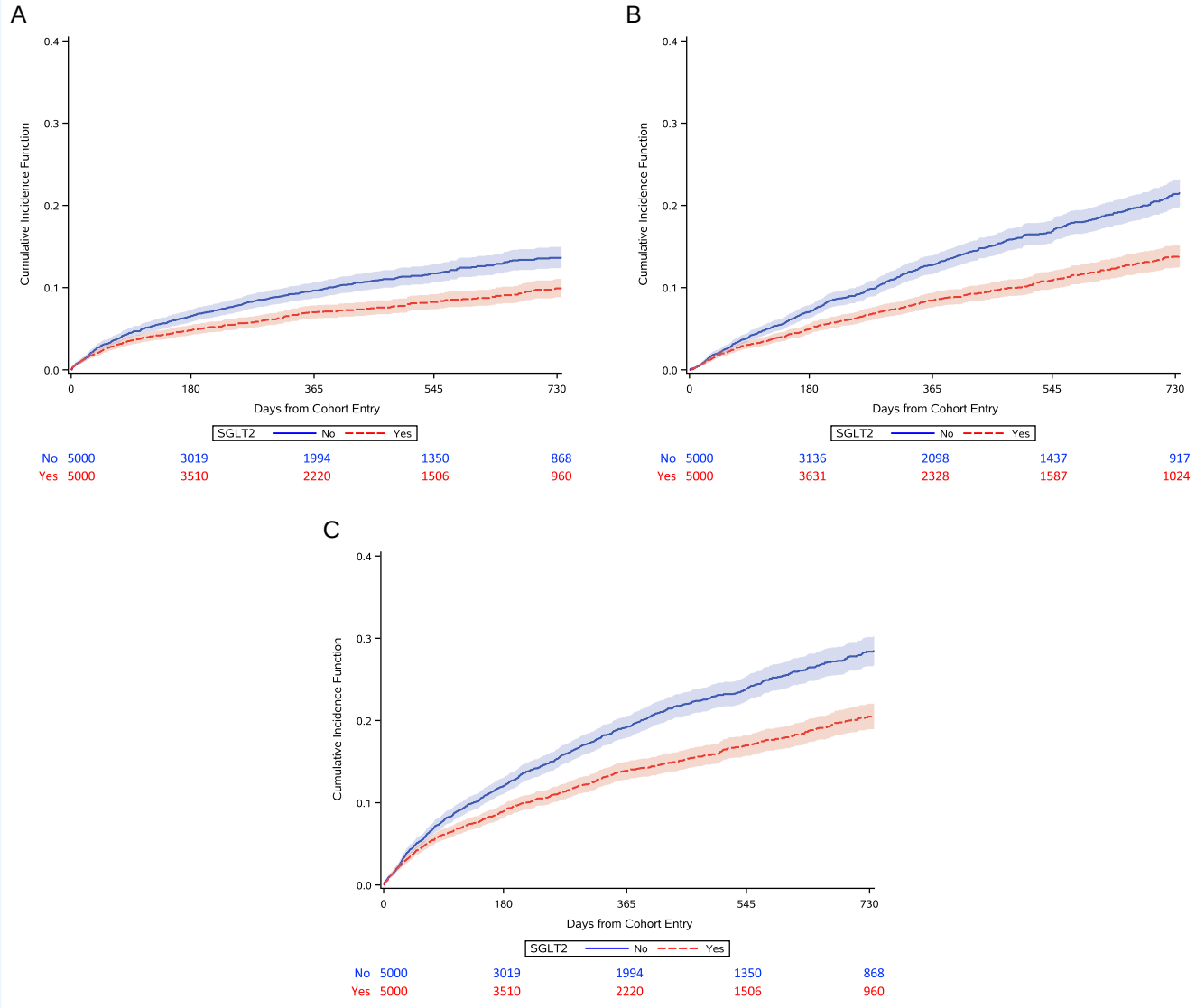


Figure 2 Cumulative incidences of (*A*) hospitalization for heart failure, (*B*) all-cause mortality, and (*C*) the composite effectiveness outcome by sodium-glucose cotransporter-2 inhibitor initiation.

Downloaded from https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvag031/8672705 by guest on 11 June 2026

Table 3 Associations between sodium-glucose cotransporter-2 inhibitor initiation and safety outcomes among angiotensin receptor-neprilysin inhibitor users

	N	Events	Person-years[a]	Rates (95% CI)[b]	IRD (95% CI)[b]	HR (95% CI)
Acute kidney injury						
Initiators	5000	592	5754.90	102.9 (94.4, 111.3)	−13.7 (−27.0, −0.3)	0.89 (0.79, 1.002)
Non-initiators	5000	598	5131.82	116.5 (106.2, 126.9)	0.0 (Reference)	1.00 (Reference)
Diabetic ketoacidosis						
Initiators	5000	16	6050.95	2.6 (1.3, 3.9)	0.8 (−1.0, 2.6)	1.42 (0.61, 3.26)
Non-initiators	5000	10	5503.85	1.8 (0.6, 3.1)	0.0 (Reference)	1.00 (Reference)
Falls						
Initiators	5000	469	5700.02	82.3 (74.8, 89.8)	−6.2 (−17.8, 5.3)	0.93 (0.81, 1.06)
Non-initiators	5000	452	5106.16	88.5 (79.7, 97.4)	0.0 (Reference)	1.00 (Reference)
Genital infection						
Initiators	5000	93	5965.70	15.6 (12.4, 18.8)	9.0 (5.1, 12.9)	2.36 (1.58, 3.51)
Non-initiators	5000	36	5467.93	6.6 (4.3, 8.9)	0.0 (Reference)	1.00 (Reference)
Hospitalization for hypotension						
Initiators	5000	277	5899.29	47.0 (41.4, 52.5)	3.7 (−4.5, 11.9)	1.10 (0.92, 1.31)
Non-initiators	5000	231	5344.08	43.2 (37.2, 49.2)	0.0 (Reference)	1.00 (Reference)
Hypoglycaemia						
Initiators	5000	34	6036.90	5.6 (3.7, 7.5)	−0.7 (−3.7, 2.2)	0.86 (0.53, 1.41)
Non-initiators	5000	35	5489.55	6.4 (4.1, 8.7)	0.0 (Reference)	1.00 (Reference)
Urinary tract infection						
Initiators	5000	561	5675.66	98.8 (90.5, 107.2)	0.2 (−12.4, 12.8)	1.01 (0.89, 1.14)
Non-initiators	5000	501	5078.15	98.7 (89.2, 108.1)	0.0 (Reference)	1.00 [Reference)

CI, confidence interval; IRD, incidence rate difference; HR, hazard ratio.
[a]Total person-years on treatment.
[b]Per 1000 person-years.

Downloaded from https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvag031/8672705 by guest on 11 June 2026

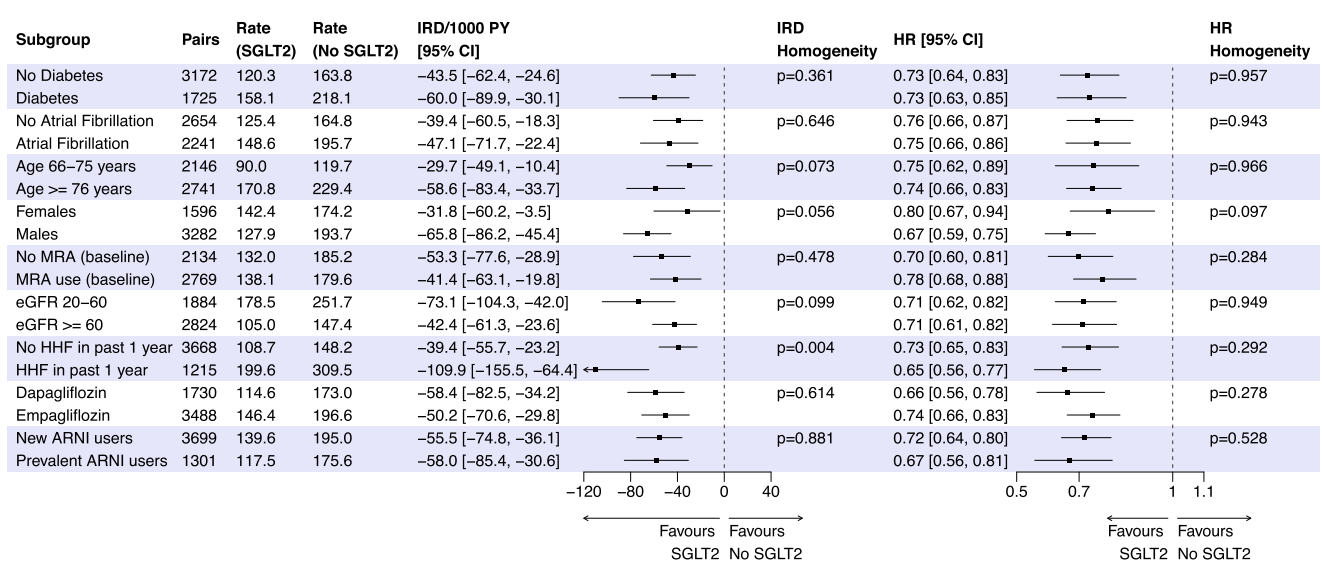


Figure 3 Subgroup analysis for hospitalization for heart failure or all-cause mortality. CI, confidence interval; IRD, incidence rate difference; PY, person-years; HR, hazard ratio; MRA, mineralocorticoid receptor antagonists; eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure.

reduction with SGLT2 inhibitors was specific to those with diabetes.

The present study provides large-scale evidence that supports the effectiveness of SGLT2 inhibitors among ARNI users with heart failure in routine clinical practice, complementary to small subgroup analyses of the DAPA-HF and EMPEROR-Reduced trials.[21–23] In line with the DAPA-HF and EMPEROR-Reduced trials [HR (95% CI): 0.64 (0.41–1.02) and 0.61 (0.42–0.90), respectively],[21,22] we demonstrated lower HHF associated with SGLT2 inhibitor initiation among ARNI users with heart failure [HR (95% CI): 0.70 (0.61–0.81)]. Estimates for all-cause mortality with SGLT2 inhibitor initiation among ARNI users were imprecise in the DAPA-HF and EMPEROR-Reduced trials [HR (95% CI): 0.91 (0.52–1.57) and 0.73 (0.47–1.13), respectively],[21,22] possibly caused by a low event count. In our study, all-cause mortality was significantly lower [HR (95% CI): 0.67 (0.59–0.76)] with dapagliflozin or empagliflozin. Larger samples may yield more stable point estimates with greater precision. According to the sensitivity analysis with censoring weights, although time-varying confounding might have partly overestimated the observed reduction in all-cause mortality, the observed effectiveness is likely robust to time-varying confounding.

A meta-analysis of randomized trials[42] yielded a modest relative risk increase in UTI and hypotension with SGLT2 inhibitors in heart failure, but the pooled estimate was mainly driven by the EMPEROR-Preserved trial.[10] We did not identify a significantly higher risk of UTI with SGLT2 inhibitors. Although ARNI use elevates baseline hypotension risk,[1,2] the relative risk increase in hospitalization for hypotension with SGLT2 inhibitors was small without statistical significance in our study, implying that the relative risk might not be amplified by background ARNI use. As hospitalization for hypotension only represents a subset of hypotensive events, the true absolute hypotension risk would be greater than that observed here; nonetheless, the influence of non-differential outcome misclassification on the point estimate of the relative risk is expected to be minimal with high outcome specificity.[40]

While the absolute genital infection risk was also likely underestimated due to limited sensitivity, the quantitative bias analysis correcting absolute risk underestimation suggests that the effectiveness likely still outweighs the risk of genital infection, unless there was extreme underdiagnosis. Notably, females vs. males showed smaller effectiveness but greater absolute genital infection risk in our study. Smaller relative and absolute effectiveness estimates among females might have partly resulted from a higher prevalence of HFmrEF or HFpEF, as unmeasured confounding could be more influential if the unmeasured confounder was more prevalent. However, females could still present a poorer risk-benefit ratio because of greater absolute genital infection risk.

Disproportionality analyses detected a greater odds of AKI with combination of ARNI and SGLT2 inhibitors,[18,19] prompting the need for validation with rigorous studies. The present study concludes that SGLT2 inhibitor initiation among ARNI users with heart failure is not associated with increased AKI risk, even in the subgroups of baseline MRA use and renal insufficiency. Despite potential residual confounding in our subgroup analysis, diabetes was found to be a potential effect modifier for AKI, and AKI reduction with SGLT2 inhibitors among ARNI users was seen only in the subgroup of diabetes. Sodium-glucose cotransporter-2 inhibitors contribute to afferent vasoconstriction and efferent vasodilation, whereas ARNI contributes to afferent vasodilation.[43] Concurrent ARNI use might modify the renal effects of SGLT2 inhibitors.[43] Glucose-lowering effects might mainly mediate the observed AKI reduction among ARNI users with diabetes. Diabetes and ARNI use as possible effect modifiers for this relationship warrants further investigation. In the EMPEROR-Reduced trial stratified by diabetes status, AKI rates appeared comparable between empagliflozin and placebo in HFrEF with diabetes,[44] whereas the AKI rate appeared lower among empagliflozin users without diabetes. Furthermore, real-world evidence studies may continue to investigate different renal outcomes[45] and hyperkalaemia risk with SGLT2 inhibitors, as well as in subgroups by diabetes, eGFR or MRA use.[46,47]

Downloaded from https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvag031/8672705 by guest on 11 June 2026

Limitations

First, unavailable ejection fraction data limited the ability to clearly define an HFrEF population, estimate and validate the prevalence of HFrEF in this study, and identify subgroups by ejection fraction. The observed proportion of males was lower than the what might be expected in HFrEF,[7,8] which could be consistent with HFmrEF or HFpEF being not uncommon in this study. Heart failure severity could not be characterized because data on B-type natriuretic peptide measures, NYHA class, and ejection fraction measures were unavailable. These unmeasured variables, as well as other unmeasured variables such as blood pressure measures, could limit external validity and introduce residual confounding. Second, residual selection bias due to unmeasured time-varying confounders could exist in supporting analyses with inverse probability of censoring weighting. Third, the safety outcomes might not have high sensitivity, and events not resulting in physician visits could not be detected. Non-differential outcome misclassification could have underestimated the estimates, especially absolute measures. Fourth, cardiovascular mortality could not be ascertained because causes of mortality were unavailable. As the OHIP database does not have corresponding diagnostic codes for hypotension or hypoglycaemia, symptomatic cases in an outpatient setting could not be captured. Lastly, selecting combination therapy initiators based on same-day dispensations precludes combination therapy initiators dispensed the medications on separate dates.

Conclusions

This study supports effectiveness of SGLT2 inhibitor initiation added to ARNI in older adults with heart failure regardless of diabetes status in routine clinical practice. There was no significant increase in the study safety events, except genital infection. Sodium-glucose cotransporter-2 inhibitor initiation was not associated with higher AKI, but reduction in AKI was observed only in the diabetes subgroup. Further studies are needed to validate whether the findings are robust to unmeasured confounding and replicable.

Supplementary material

Supplementary material is available at *European Heart Journal—Cardiovascular Pharmacotherapy* online.

Acknowledgements

This study was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health (MOH) and the Ministry of Long-Term Care (MLTC). As a prescribed entity under Ontario's privacy legislation, ICES is authorized to collect and use health care data for the purposes of health system analysis, evaluation and decision support. Secure access to these data is governed by policies and procedures that are approved by the Information and Privacy Commissioner of Ontario. This document used data adapted from the Statistics Canada Postal Code^{OM} Conversion File, which is based on data licenced from Canada Post Corporation, and/or data adapted from the Ontario Ministry of Health Postal Code Conversion File, which contains data copied under licence from ©Canada Post Corporation and Statistics Canada. We thank IQVIA Solutions Canada Inc. for use of their Drug Information File. Parts of this material are based on data and/or information compiled and provided by the Ontario Ministry of Health and CIHI. The analyses, conclusions, opinions and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred. This Project has been made possible by the Canada Brain Research Fund (CBRF), an innovative arrangement between the Government of Canada (through Health Canada) and Brain Canada Foundation, and Heart and Stroke Foundation of Canada. To date, Health Canada has invested over $130 million through the CBRF which has been matched by Brain Canada Foundation and its donors and partners. The views expressed herein do not necessarily represent the views of the Minister of Health or the Government of Canada.

Author contributions

Conceptualization: C.-Y.W., B.R.S., J.A.E., and W.S. Study design: C.-Y.W., B.R.S., J.A.E., A.S., C.F.W., J.D.E., and W.S. Interpretation of data: Everyone. Drafting of the manuscript: C.-Y.W. Critical review of the manuscript: Everyone. Statistical analysis: C.-Y.W., T.W., and C.F.W. Supervision: B.R.S., J.D.E., and W.S. Funding acquisition: A.S., P.P.L., J.D.E., and W.S.

Funding

C.-Y.W. receives financial support from the Canadian Institutes of Health Research (Doctoral Research Award: Canadian Graduate Scholarships; 202111FBD-47623-75801). W.S. is supported by the Canada Research Chairs Program (award number: CRC-2024-00213), the Ontario Ministry of Colleges and Universities (award number: ER21-16-146), and the Dr. Sandra Black Centre for Brain Resilience and Recovery. C.-Y.W., W.S., A.S., J.D.E., and P.P.L. receive financial support from Heart-Brain Connection BHRIITE IMPACT Award from Heart & Stroke Foundation, Brain Canada, and from the Brain-Heart Interconnectome Canada First Research Excellence Fund Program from the Canadian federal government.

Conflict of interest: The authors declare no conflict of interest. All funders for the present project and other unrelated projects did not influence the conduct, interpretation, and reporting of the present study.

Data availability

The dataset from this study is held securely in coded form at ICES (formerly, Institute for Clinical Evaluative Sciences). While data sharing agreements prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS. The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

References

1. McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;**371**:993–1004.
2. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, van Veldhuisen DJ, Zannad F, Zile MR, Desai AS, Claggett B, Jhund PS, Boytsov SA, Comin-Colet J, Cleland J, Düngen H-D, Goncalvesova E, Katova T, Kerr Saraiva JF, Lelonek M, Merkely B, Senni M, Shah SJ, Zhou J, Rizkala AR,

Downloaded from https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvag031/8672705 by guest on 11 June 2026

Gong J, Shi VC, Lefkowitz MP; PARAGON-HF Investigators and Committees. Angiotensin–neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med* 2019;**381**:1609–1620.
3. McDonald M, Virani S, Chan M, Ducharme A, Ezekowitz JA, Giannetti N, Heckman GA, Howlett JG, Koshman SL, Lepage S, Mielniczuk L, Moe GW, O'Meara E, Swiggum E, Toma M, Zieroth S, Anderson K, Bray SA, Clarke B, Cohen-Solal A, D'Astous M, Davis M, De S, Grant ADM, Grzeslo A, Heshka J, Keen S, Kouz S, Lee D, Masoudi FA, McKelvie R, Parent M-C, Poon S, Rajda M, Sharma A, Siatecki K, Storm K, Sussex B, Van Spall H, Yip AMC. CCS/CHFS heart failure guidelines update: defining a new pharmacologic standard of care for heart failure with reduced ejection fraction. *Can J Cardiol* 2021;**37**:531–546.
4. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Kathrine Skibelund A; ESC Scientific Document Group. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;**42**:3599–3726.
5. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, Fang JC, Fedson SE, Fonarow GC, Hayek SS, Hernandez AF, Khazanie P, Kittleson MM, Lee CS, Link MS, Milano CA, Nnacheta LC, Sandhu AT, Stevenson LW, Vardeny O, Vest AR, Yancy CW. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2022;**145**:e895–e1032.
6. Vaduganathan M, Docherty KF, Claggett BL, Jhund PS, De Boer RA, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, Shah SJ, Desai AS, McMurray JJV, Solomon SD. SGLT2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials. *Lancet* 2022;**400**:757–767.
7. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohlávek J, Böhm M, Chiang C-E, Chopra VK, de Boer RA, Desai AS, Diez M, Drozdz J, Dukát A, Ge J, Howlett JG, Katova T, Kitakaze M, Ljungman CEA, Merkely B, Nicolau JC, O'Meara E, Petrie MC, Vinh PN, Schou M, Tereshchenko S, Verma S, Held C, DeMets DL, Docherty KF, Jhund PS, Bengtsson O, Sjöstrand M, Langkilde A-M. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019;**381**:1995–2008.
8. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M, Jamal W, Kimura K, Schnee J, Zeller C, Cotton D, Bocchi E, Böhm M, Choi D-J, Chopra V, Chuquiure E, Giannetti N, Janssens S, Zhang J, Gonzalez Juanatey JR, Kaul S, Brunner-La Rocca H-P, Merkely B, Nicholls SJ, Perrone S, Pina I, Ponikowski P, Sattar N, Senni M, Seronde M-F, Spinar J, Squire I, Taddei S, Wanner C, Zannad F. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020;**383**:1413–1424.
9. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, Shah SJ, Desai AS, Jhund PS, Belohlavek J, Chiang C-E, Borleffs CJW, Comin-Colet J, Dobreanu D, Drozdz J, Fang JC, Alcocer-Gamba MA, Al Habeeb W, Han Y, Cabrera Honorio JW, Janssens SP, Katova T, Kitakaze M, Merkely B, O'Meara E, Saraiva JFK, Tereshchenko SN, Thierer J, Vaduganathan M, Vardeny O, Verma S, Pham VN, Wilderäng U, Zaozerska N, Bachus E, Lindholm D, Petersson M, Langkilde AM. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med* 2022;**387**:1089–1098.
10. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, Brunner–La Rocca H-P, Choi D-J, Chopra V, Chuquiure-Valenzuela E, Giannetti N, Gomez-Mesa JE, Janssens S, Januzzi JL, Gonzalez-Juanatey JR, Merkely B, Nicholls SJ, Perrone SV, Piña IL, Ponikowski P, Senni M, Sim D, Spinar J, Squire I, Taddei S, Tsutsui H, Verma S, Vinereanu D, Zhang J, Carson P, Lam CSP, Marx N, Zeller C, Sattar N, Jamal W, Schnaidt S, Schnee JM, Brueckmann M, Pocock SJ, Zannad F, Packer M. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med* 2021;**385**:1451–1461.
11. Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, Lewis JB, Riddle MC, Voors AA, Metra M, Lund LH, Komajda M, Testani JM, Wilcox CS, Ponikowski P, Lopes RD, Verma S, Lapuerta P, Pitt B. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med* 2021;**384**:117–128.
12. Voors AA, Angermann CE, Teerlink JR, Collins SP, Kosiborod M, Biegus J, Ferreira JP, Nassif ME, Psotka MA, Tromp J, Borleffs CJW, Ma C, Comin-Colet J, Fu M, Janssens SP, Kiss RG, Mentz RJ, Sakata Y, Schirmer H, Schou M, Schulze PC, Spinarova L, Volterrani M, Wranicz JK, Zeymer U, Zieroth S, Brueckmann M, Blatchford JP, Salsali A, Ponikowski P. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. *Nat Med* 2022;**28**:568–574.
13. Gonzalez J, Bates BA, Setoguchi S, Gerhard T, Dave CV. Cardiovascular outcomes with SGLT2 inhibitors versus DPP4 inhibitors and GLP-1 receptor agonists in patients with heart failure with reduced and preserved ejection fraction. *Cardiovasc Diabetol* 2023;**22**:54.
14. Fu EL, Patorno E, Everett BM, Vaduganathan M, Solomon SD, Levin R, Schneeweiss S, Desai RJ. Sodium-glucose cotransporter 2 inhibitors vs. sitagliptin in heart failure and type 2 diabetes: an observational cohort study. *Eur Heart J* 2023;**44**:2216–2230.
15. Wu C-Y, Shah BR, Sharma A, Sheng Y, Liu PP, Kopp A, Saskin R, Edwards JD, Swardfager W. Timing of sodium–glucose cotransporter 2 inhibitor initiation and post-discharge outcomes in acute heart failure with diabetes: a population-based cohort study. *Eur J Heart Fail* 2025;**27**:307–316.
16. Park S, Jeong HE, Lee H, You SC, Shin J-Y. Association of sodium-glucose cotransporter 2 inhibitors with post-discharge outcomes in patients with acute heart failure with type 2 diabetes: a cohort study. *Cardiovasc Diabetol* 2023;**22**:191.
17. Svanström H, Mkoma GF, Hviid A, Pasternak B. SGLT-2 inhibitors and mortality among patients with heart failure with reduced ejection fraction: linked database study. *BMJ* 2024;**387**:e080925.
18. Zhao S, He R, Mei M, Yu M, Yang Z, Tian C, Zhang P, Li R. Drug interaction of SGLT2Is and ARNI on acute kidney injury: a real-world pharmacovigilance analysis through the FAERS. *J Cardiovasc Pharmacol* 2025;**85**:44–53.
19. Chen C, Wu B, Zhang C, Xu T. Angiotensin receptor-neprilysin inhibitor and sodium-dependent glucose cotransporter-2 inhibitor-associated renal injury: a pharmacovigilance study. *Expert Opin Drug Saf* 2023;**22**:259–266.
20. Ozaki AF, Krumholz HM, Mody FV, Jackevicius CA. National trends in the use of sacubitril/valsartan. *J Card Fail* 2021;**27**:839–847.
21. Solomon SD, Jhund PS, Claggett BL, Dewan P, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Inzucchi SE, Desai AS, Bengtsson O, Lindholm D, Sjostrand M, Langkilde AM, McMurray JJV. Effect of dapagliflozin in patients with HFrEF treated with sacubitril/valsartan: the DAPA-HF trial. *JACC Heart Fail* 2020;**8**:811–818.
22. Packer M, Anker SD, Butler J, Filippatos G, Ferreira JP, Pocock SJ, Rocca H-PB-L, Janssens S, Tsutsui H, Zhang J, Brueckmann M, Jamal W, Cotton D, Iwata T, Schnee J, Zannad F. Influence of neprilysin inhibition on the efficacy and safety of empagliflozin in patients with chronic heart failure and a reduced ejection fraction: the EMPEROR-Reduced trial. *Eur Heart J* 2021;**42**:671–680.
23. Zannad F, Ferreira JP, Pocock SJ, Anker SD, Butler J, Filippatos G, Brueckmann M, Ofstad AP, Pfarr E, Jamal W, Packer M. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. *Lancet* 2020;**396**:819–829.
24. Gupta M, Bell A, Padarath M, Ngui D, Ezekowitz J. Physician perspectives on the diagnosis and management of heart failure with preserved ejection fraction. *CJC Open* 2021;**3**:361–366.
25. Khan MS, Shahid I, Bennis A, Rakisheva A, Metra M, Butler J. Global epidemiology of heart failure. *Nat Rev Cardiol* 2024;**21**:717–734.
26. Suissa S, Moodie EEM, Dell'Aniello S. Prevalent new-user cohort designs for comparative drug effect studies by time-conditional propensity scores: prevalent new-user designs. *Pharmacoepidemiol Drug Saf* 2017;**26**:459–468.
27. Cashin AG, Hansford HJ, Hernán MA, Swanson SA, Lee H, Jones MD, Dahabreh IJ, Dickerman BA, Egger M, Garcia-Albeniz X, Golub RM, Islam N, Lodi S, Moreno-Betancur M, Pearson S-A, Schneeweiss S, Sharp MK, Sterne JAC, Stuart EA, McAuley JH. Transparent reporting of observational studies emulating a target trial—the TARGET statement. *JAMA* 2025;**334**:1084.
28. Filion KB, Lix LM, Yu OHY, Dell'Aniello S, Douros A, Shah BR, St-Jean A, Fisher A, Tremblay E, Bugden SC, Alessi-Severini S, Ronksley PE, Hu N, Dormuth CR, Ernst P, Suissa S. Sodium glucose cotransporter 2 inhibitors and risk of major adverse cardiovascular events: multi-database retrospective cohort study. *BMJ* 2020;**370**:m3342.
29. Austin PC, Daly PA, Tu JV. A multicenter study of the coding accuracy of hospital discharge administrative data for patients admitted to cardiac care units in Ontario. *Am Heart J* 2002;**144**:290–296.
30. Hwang YJ, Shariff SZ, Gandhi S, Wald R, Clark E, Fleet JL, Garg AX. Validity of the *International Classification of Diseases, Tenth Revision* code for acute kidney injury in elderly patients at presentation to the emergency department and at hospital admission. *BMJ Open* 2012;**2**:e001821.
31. Hodzic-Santor B, Colacci M, Raissi A, Ray P, Verma AA, Razak F, MacFadden DR, Biering-Sørensen T, Skaarup KG, Sarma S, Fralick M. Validation of the diagnostic accuracy levels of international classification of diseases, 10th revision codes for diabetic ketoacidosis: a multicentre, cross-sectional study of adults. *Can J Diabetes* 2024;**48**:227–232.
32. Hodge MC, Dixon S, Garg AX, Clemens KK. Validation of an international statistical classification of diseases and related health problems 10th revision

Downloaded from https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvag031/8672705 by guest on 11 June 2026

coding algorithm for hospital encounters with hypoglycemia. *Can J Diabetes* 2017;**41**:322–328.
33. Wu C-Y, Sharma A, Edwards JD, Liu PP, Kapral MK, Herrmann N, Wu CF, Podolsky S, Swardfager W, Shah BR. Cardiovascular effectiveness and safety of SGLT2 inhibitors vs DPP4 inhibitors by dementia status: a cohort study of older adults with diabetes. *Diabetologia* 2026;**69**:386–398.
34. Wright AJ, Gomes T, Mamdani MM, Horn JR, Juurlink DN. The risk of hypotension following co-prescription of macrolide antibiotics and calcium-channel blockers. *Can Med Assoc J* 2011;**183**:303–307.
35. Simms-Williams N, Treves N, Yin H, Lu S, Yu O, Pradhan R, Renoux C, Suissa S, Azoulay L. Effect of combination treatment with glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors on incidence of cardiovascular and serious renal events: population based cohort study. *BMJ* 2024;**385**:e078242.
36. Webster-Clark M, Mavros P, Garry EM, Stürmer T, Shmuel S, Young J, Girman C. Alternative analytic and matching approaches for the prevalent new-user design: a simulation study. *Pharmacoepidemiol Drug Saf* 2022;**31**:796–803.
37. Limozin JM, Seaman SR, Su L. Inference procedures in sequential trial emulation with survival outcomes: comparing confidence intervals based on the sandwich variance estimator, bootstrap and jackknife. *Stat Methods Med Res* 2025;**34**:2011–2033.
38. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. *Circulation* 2016;**133**:601–609.
39. Lipsitch M, Tchetgen Tchetgen E, Cohen T. Negative controls: a tool for detecting confounding and bias in observational studies. *Epidemiology* 2010;**21**:383–388.
40. Lash TL, Fox MP, Fink AK. *Applying Quantitative Bias Analysis to Epidemiologic Data*. New York, NY: Springer; 2009.
41. Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. *Pharmacoepidemiol Drug Saf* 2006;**15**:291–303.
42. Younes AM, Salem M, Maraey A, Nomigolzar S, Sewell K, Khalil M, Elzanaty A, Saeyeldin A, Dar M. Safety outcomes of SGLT2i in the heart failure trials: a systematic review and meta-analysis. *Int J Cardiol* 2022;**366**:51–56.
43. De La Espriella R, Bayés-Genís A, Morillas H, Bravo R, Vidal V, Núñez E, Santas E, Miñana G, Sanchis J, Fácila L, Torres F, Górriz JL, Valle A, Núñez J. Renal function dynamics following co-administration of sacubitril/valsartan and empagliflozin in patients with heart failure and type 2 diabetes. *ESC Heart Fail* 2020;**7**:3792–3800.
44. Anker SD, Butler J, Filippatos G, Khan MS, Marx N, Lam CSP, Schnaidt S, Ofstad AP, Brueckmann M, Jamal W, Bocchi EA, Ponikowski P, Perrone SV, Januzzi JL, Verma S, Böhm M, Ferreira JP, Pocock SJ, Zannad F, Packer M. Effect of empagliflozin on cardiovascular and renal outcomes in patients with heart failure by baseline diabetes status: results from the EMPEROR-reduced trial. *Circulation* 2021;**143**:337–349.
45. Svanström H, Mkoma GF, Hviid A, Pasternak B. SGLT2 inhibitors and serious renal events among patients with heart failure with reduced ejection fraction. *JACC Heart Fail* 2025;**13**:102522.
46. Razaghizad A, Ni J, Marques P, Mavrakanas TA, Tsoukas MA, Possik E, Huynh T, Edwards JD, Liu P, Swardfager W, Baroz F, Ferreira JP, Sharma A. Cardiovascular phenotypes in type 2 diabetes: latent class analysis of the CANVAS Program and CREDENCE trial. *Diabetes Obes Metab* 2024;**26**:5025–5035.
47. Marques P, Blydt-Hansen M, Takano T, Ferreira JP, Tsoukas MA, Sharma A, Mavrakanas TA. Systematic review on the management of diuretic resistance in acute heart failure across the spectrum of kidney disease. *Cardiorenal Med* 2025;**15**:462–483.

Downloaded from https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvag031/8672705 by guest on 11 June 2026