

ORIGINAL ARTICLE

Temporal risk patterns of severe hypovolemia associated with sodium-glucose cotransporter-2 inhibitors in patients with type 2 diabetes mellitus: A self-controlled case series study

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Abstract

Aims: We aimed to investigate the temporal risk patterns of severe hypovolemia induced by sodium-glucose cotransporter-2 inhibitors (SGLT2i) in patients with type 2 diabetes mellitus.

Materials and Methods: We conducted a self-controlled case series using claims data from Japan. Patients who were prescribed SGLT2i for treating type 2 diabetes mellitus and experienced severe hypovolemia were enrolled. The primary analysis evaluated the adjusted incidence rate ratios (IRRs) of exposure risk periods (Days 1 to 30, Days 31 to 90, Days 91 to 180 and Days ≥ 181) with their corresponding 95% confidence intervals (CIs), calculated using a multivariable conditional Poisson regression model, relative to that of the unexposed control period.

Results: A total of 1200 new users of SGLT2i with 1334 severe hypovolemia events were included. The median follow-up and treatment periods were 3.66 and 2.53 years, respectively. The cohort was predominantly male (78.4%) with a median age of 54.1 years. A higher risk of severe hypovolemia associated with SGLT2i was observed particularly in the first 30 days (adjusted IRR 7.39, 95% CI 6.09–8.96) of treatment initiation. Secondary analyses highlighted the first 22 to 28 days (adjusted IRR 15.24, 95% CI 11.92–19.48) of treatment as the highest risk period for severe hypovolemia.

Conclusions: SGLT2i use in patients with type 2 diabetes mellitus was associated with a higher risk of severe hypovolemia, particularly within the first 30 days of treatment initiation, with the highest risk observed during 22 to 28 days.

KEYWORDS

hypovolemia, observational study, sodium-glucose cotransporter-2 inhibitors, temporal risk pattern, type 2 diabetes mellitus

1 | INTRODUCTION

Type 2 diabetes mellitus is a serious public health concern with a considerable impact on human health and healthcare expenditures.¹ Its prevalence has dramatically increased in recent years. In 2021,

approximately 529 million people worldwide were living with diabetes, with a global age-standardized total diabetes prevalence of 6.1%.¹ Diabetes represents a substantial burden on the healthcare system, with global health expenditures reaching US\$966 billion in 2021, a figure projected to exceed \$1054 billion by 2045.¹

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have demonstrated promising therapeutic effects by lowering blood glucose levels through the inhibition of glucose reabsorption in the kidneys.² In addition to lowering blood glucose and preventing cardiovascular death, heart failure and kidney disease progression,³ SGLT2i reduces hepatic fat content^{3,4} and fibrosis in the liver.³ However, the potential adverse event of hypovolemia cannot be overlooked.^{2,5,6} Clinical studies have reported a significant increase in urine volume and urinary sodium excretion after SGLT2i treatment,^{7,8} which is attributed to osmotic diuresis and natriuretic effects.⁹ Clinical practice guidelines have highlighted the risk of hypovolemia in patients treated with SGLT2i.^{2,5,6} These guidelines caution about the potential adverse effects of reduced fluid volume due to the diuretic effects of SGLT2i and recommends regular monitoring of patients for symptoms, such as hypotension, changes in weight and volume status.^{2,5,6} Pooled data from randomized controlled trials (RCTs) of SGLT2i, as reported in the US package inserts, indicated increased rates of hypovolemia-related events (0.3 to 4.4%) than in placebo groups (0% to 1.5%).⁶ Furthermore, meta-analyses demonstrated that SGLT2i treatment increases the risk of hypovolemia in patients with type 2 diabetes mellitus than placebo.^{10–12}

Considering the aforementioned benefits of SGLT2i, specific elucidation of the timing and duration of increased hypovolemia risk induced by the initiation of SGLT2i would be crucial for optimizing the use of this treatment, as adverse reactions of hypovolemia can lead to or be associated with life-threatening conditions, such as diabetic ketoacidosis, symptomatic hypotension and acute kidney injury.^{2,5,6,13} However, no clinical evidence has been provided regarding the timing yet. Therefore, we aimed to conduct a self-controlled case series (SCCS) study to evaluate the temporal risk patterns of severe hypovolemia over SGLT2i-exposure periods (Days 1–30, 31–90, 91–180 and ≥ 181) compared to that during an unexposed period in patients with type 2 diabetes mellitus.

2 | MATERIALS AND METHODS

2.1 | Data source

We used claims data from the Japan Medical Data Center (JMDC Co., Ltd., Japan) claims database.¹⁴ It is a large nationwide database of health insurance claims that has collected receipts (inpatient, outpatient and pharmacy) and medical check-up data from health associations since January 2005. As of March 2024, the cumulative dataset includes approximately 19 million insured individuals, primarily company employees and their family members. An encrypted personal identifier is used to link claims data from different hospitals, clinics and pharmacies unless the individual moves to another insurance provider. This enables the tracking of medical information across various healthcare facilities within the same health insurance system, making it widely used for epidemiological studies in Japan.^{4,15}

2.2 | Self-controlled case series study design

We adopted the SCCS design^{16,17} for this study. We selected patients who experienced both SGLT2i treatment and severe hypovolemia events, and compared the risk of severe hypovolemia events bidirectionally during the follow-up period using different time windows, with and without SGLT2i exposure. The SCCS design evaluates different time windows (i.e., lengths of time) for the same individual¹⁶ and determines whether triggering effects exist during the exposure period, whereas a cohort study assesses whether cumulative effects are greater in exposed patients than in unexposed patients.^{18,19} A major strength of the SCCS design is its ability to minimize confounding by implicitly controlling for both measured and unmeasured time-invariant confounding factors, since each case acts as its own control.^{16,17,19} Originally developed for vaccine safety evaluations, the SCCS design has been applied in various contexts, particularly where precise information on the size of the at-risk population is unavailable or identification of an appropriate comparison group is challenging, for instance, in studies on the adverse effects of drug treatments.¹⁷

2.3 | Patients

Cases were identified as patients who received at least one prescription of SGLT2i, had at least one claim with a diagnosis of type 2 diabetes mellitus within 180 days before the index date (defined as the date of the first SGLT2i prescription) and experienced an incidence of severe hypovolemia during the observation period (from 1 April 2012 to 31 December 2023). The observation period began on 1 April 2012, since claims records in the national health insurance reimbursement scheme in Japan did not include information on dates before 31 March 2012.²⁰ The study included new users of SGLT2i who had at least 180 days of continuous enrollment and no recorded use of SGLT2i before the index date. We applied a new user design in which the effects associated with treatment duration could be assessed.²¹

Hypovolemia was diagnosed based on the International Classification of Diseases 10th revision (ICD-10) codes from previous observational studies.^{22,23} However, no observational study has validated the diagnosis of hypovolemia yet. We considered defining the study outcome to minimize the risk of misclassification. Severe hypovolemia was defined as a hospitalized case of hypovolemia associated with the ICD-10 code E86 (volume depletion) or Standard Disease Code 8835370 (hypovolemia shock) in conjunction with specific hypovolemia treatments (Table S1). The hypovolemia events were excluded if patients were hospitalized within 30 days before or after these events and if the following medical conditions, which are not clearly associated with the pharmacological effects of SGLT2i but are potential contributors to hypovolemia,²⁴ were presented: trauma or burns, infectious diseases, non-infective enteritis and colitis. A second or subsequent event of severe hypovolemia was classified as a recurrence if it occurred more than 7 days after the previous event.²⁵ Patients with type 1 diabetes mellitus, gestational diabetes or

secondary diabetes within 180 days before or on the index date were excluded. Definitions of the diseases and medications used in this study are detailed in Table S1. The follow-up started either 180 days before the first type 2 diabetes mellitus diagnosis or on 1 April 2012, whichever occurred later, and continued until treatment discontinuation, end of the database enrollment (including death) or end of the study period (31 December 2023), whichever occurred first. The current study was approved by the Institutional Review Board of Kyoto University (application number: R4527). The requirement for individual consent was waived because the study used anonymized data.

2.4 | Exposure

The exposure risk periods were categorized as Days 1–30, 31–90, 91–180 and ≥ 181 after the index date, based on references regarding the diuretic effects observed in clinical pharmacological studies⁹ and hypovolemia events reported in the long-term extension safety study of canagliflozin.²⁶ We incorporated a 30-day grace period²⁷ and extended the exposure effect window to 30 days after the expiration of the last prescription. To minimize the impact of the occurrence of an event on subsequent exposures, two consecutive pre-exposure periods were defined as Days 30–16 and Days 15–1 before the index date to evaluate whether a recent event of severe hypovolemia affected the likelihood of the SGLT2i prescription.^{17,19} The remaining period was defined as the unexposed control period. The study scheme delineating the index date, follow-up period, control period and pre-exposure and exposure periods is shown in Figure S1.

2.5 | Statistical analysis

The baseline characteristics of patients for whom SGLT2i treatment was initiated were summarized. Categorical variables were reported as percentages and continuous variables were reported as medians with interquartile ranges. To evaluate the association between exposure to SGLT2i and the risk of severe hypovolemia, we used a multi-variable conditional Poisson regression model to calculate the adjusted incidence rate ratios (IRRs) and their corresponding 95% confidence intervals (CIs) in the pre-exposure and exposure risk periods compared to that in the unexposed control period in the primary analysis. The time-varying covariates were adjusted for the outcome of severe hypovolemia, including age, renal dysfunction defined by estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² and prescription of diuretics (Table S1), which are considered risk factors for hypovolemia.^{2,11,13,28} The eGFR values were calculated using medical check-up data in the database.

We performed secondary analyses to evaluate the impact of different risk window lengths on the study outcomes²⁹ and identified the period with the highest risk of severe hypovolemia. The following short exposure periods were defined during the first 3 months after the index date: (1) Days 1–15, 16–30, 31–60, and 61–90 after the

index date; and (2) Days 1–7, 8–14, 15–21, 22–28, 29–42, 43–56, 57–70, and 71–84 after the index date.

Subgroup analyses were performed as a tertiary analysis to assess factors by season and calendar year of the first SGLT2i prescription as described in Appendix S1.

Sensitivity analyses were performed to assess the robustness of the findings as described in Appendix S1.

All analyses were performed via complete case approach using R, version 4.4.0., including the SCCS package.

3 | RESULTS

We identified 1200 new users of SGLT2i with a type 2 diabetes mellitus diagnosis, as shown in Figure 1, and summarized their baseline characteristics in Table 1. The enrolled patients experienced 1334 severe hypovolemia events. The median follow-up and treatment periods were 3.66 and 2.53 years, respectively. The cohort was predominantly male (78.4%) with a median age of 54.1 years. The enrolled patients commonly had dyslipidemia (65.8%) and hypertension (62.5%). Glucose-lowering medications other than SGLT2i (81.8%), antihypertensive agents (59.1%) and antidyslipidemic agents (51.6%) were commonly prescribed. The timing of the first SGLT2i prescription was consistent across all seasons: spring (24.8%), summer (24.2%), autumn (27.0%) and winter (24.0%). The number of prescriptions initiated was higher in 2018–2020 (39.3%) and 2021–2023 (39.3%) than in 2014–2017 (21.3%).

3.1 | Primary analysis

The number of severe hypovolemia events, follow-up periods and adjusted incidence rate ratios are presented in Table 2. A higher risk of severe hypovolemia was observed during SGLT2i treatment, particularly in the first 30 days (Days 1 to 30: adjusted IRR 7.39, 95% CI 6.09–8.96; Days 31 to 90: adjusted IRR 1.99, 95% CI 1.56–2.54; Days 91 to 180: adjusted IRR 1.56, 95% CI 1.22–2.00; Days ≥ 181 : adjusted IRR 1.36, 95% CI 1.13–1.63) after the initiation of SGLT2i treatment compared to the unexposed control period. Figures 2 and S2 indicate a higher incidence of severe hypovolemia in the first 30 days, with a peak around days 21 to 25, compared to other periods before or after SGLT2i treatment initiation.

3.2 | Secondary analysis

In the secondary analysis with shorter exposure periods during the first 3 months after the index date, the risk of severe hypovolemia was the highest during Days 22 to 28 (adjusted IRR 15.24, 95% CI 11.92–19.48), followed by Days 15 to 21 (adjusted IRR 7.60, 95% CI 5.53–10.45), after the initiation of SGLT2i treatment. A higher risk of severe hypovolemia was observed throughout the SGLT2i

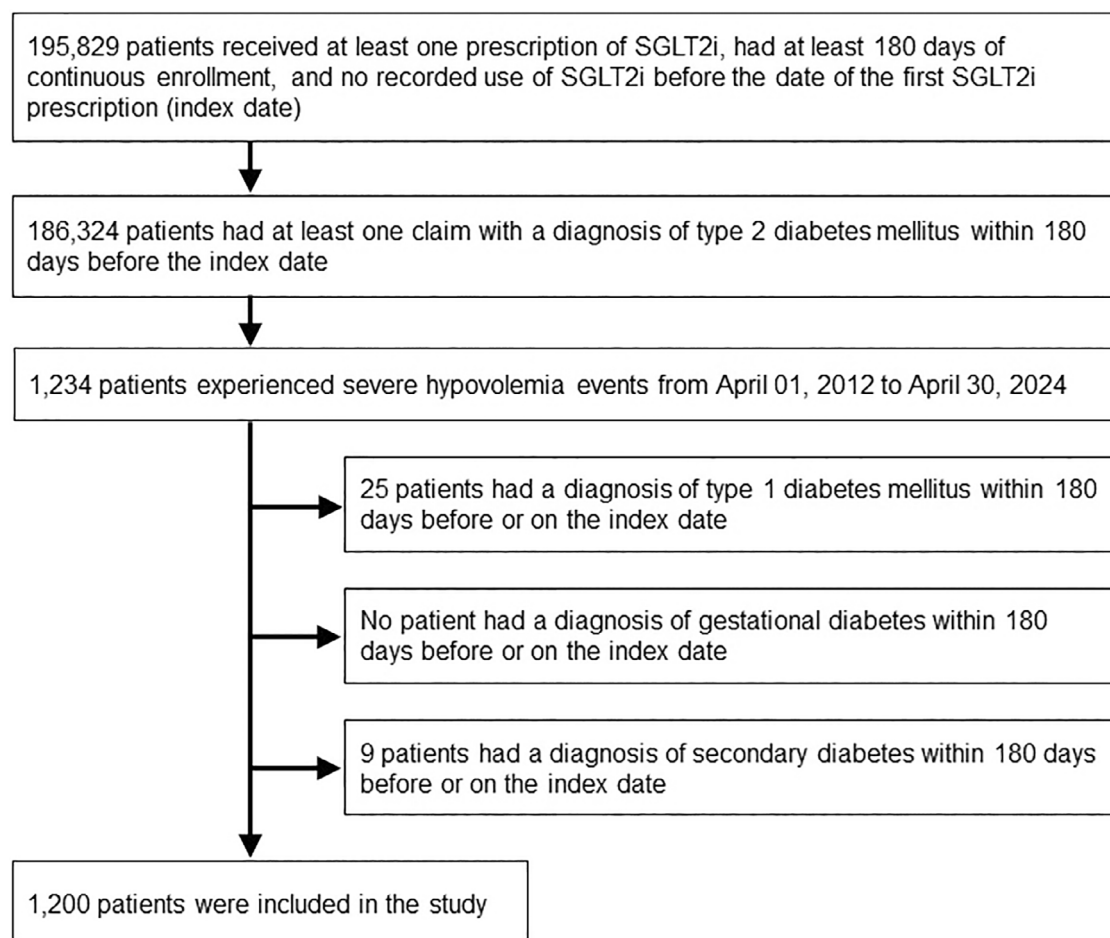


FIGURE 1 Patient and study flow diagram. SGLT2i, sodium-glucose cotransporter-2 inhibitors.

exposure period compared to the unexposed control period, as shown in Figure 3.

3.3 | Tertiary analysis

Tertiary analysis results are illustrated in Figures S3 and S4. The subgroup analyses showed a higher risk of severe hypovolemia during SGLT2i treatment across all seasons, particularly in the first 30 days (spring: adjusted IRR 6.20, 95% CI 4.19–9.18; summer: adjusted IRR 6.64, 95% CI 4.57–9.64; autumn: adjusted IRR 11.90, 95% CI 8.11–17.45; winter: adjusted IRR 5.87, 95% CI 3.87–8.91) of SGLT2i initiation. Similar trends of higher risk of severe hypovolemia were observed across all calendar year periods (in the first 30 days after SGLT2i treatment initiation, 2014–2017: adjusted IRR 3.52, 95% CI 1.92–6.43; 2018–2020: adjusted IRR 8.03, 95% CI 5.77–11.17; 2021–2023: adjusted IRR 8.40, 95% CI 6.44–10.95).

3.4 | Sensitivity analysis

Our findings were consistent across all sensitivity analyses, as presented in Figures S5–S8, such as excluding second or subsequent

events, restricting severe hypovolemia events, excluding patients with a single prescription or those who died within 90 days after severe hypovolemia events, excluding patients with a history of severe hypovolemia, and including post-SGLT2i treatment period in control period, and modifying the pre-exposure periods.

4 | DISCUSSION

4.1 | Study findings and scientific background

In this SCCS of patients with type 2 diabetes mellitus, we found that SGLT2i treatment is associated with a higher risk of severe hypovolemia, particularly during the first 30 days of treatment initiation. Our study identified the first 22 to 28 days after the initiation of SGLT2i treatment to be the period with the highest risk for severe hypovolemia in patients with type 2 diabetes mellitus. Similar trends were observed across all seasons (spring, summer, autumn and winter) and calendar year periods (2014–2017, 2018–2020 and 2021–2023) during SGLT2i treatment. The findings were robust across all sensitivity analyses.

SGLT2i have a unique mechanism of action; they increase glucosuria, which is associated with osmotic diuresis and natriuresis,

TABLE 1 Patient baseline characteristics.

Baseline characteristics	Study population <i>n</i> = 1200
Sex, male, <i>n</i> (%)	941 (78.4)
Age, year, median (IQR)	54.1 (47.4–61.1)
Follow-up period, year, median (IQR)	3.66 (2.08–5.74)
Treatment period, year, median (IQR)	2.53 (1.01–4.76)
Numbers of hypovolemia events	1334
History of severe hypovolemia, <i>n</i> (%)	171 (14.3)
Comorbidities, <i>n</i> (%)	
Diabetic nephropathy	79 (6.6)
Diabetic retinopathy	26 (2.2)
Diabetic neuropathy	16 (1.3)
Hypertension	750 (62.5)
Dyslipidemia	789 (65.8)
Obesity	40 (3.3)
Renal diseases	72 (6.0)
Depression	96 (8.0)
Nausea and vomiting	97 (8.1)
Comedications, <i>n</i> (%)	
Glucose-lowering medications	981 (81.8)
Insulins	378 (31.5)
Sulfonylureas	207 (17.2)
Glucagon-like peptide-1 receptor agonists	52 (4.3)
Dipeptidyl peptidase-4 inhibitors	685 (57.1)
Antihypertensive agents	709 (59.1)
Renin-angiotensin-aldosterone system inhibitors	523 (43.6)
Antidyslipidemic agents	619 (51.6)
Diuretics	169 (14.1)
Non-steroidal anti-inflammatory drugs	350 (29.2)
Antiarrhythmic agents	29 (2.4)
Antidepressants	86 (7.2)
Season of the first prescription, <i>n</i> (%)	
Spring (March to May)	298 (24.8)
Summer (Jun to August)	290 (24.2)
Autumn (September to November)	324 (27.0)
Winter (December to February)	288 (24.0)
Calendar year of the first prescription, <i>n</i> (%)	
2014–2017	256 (21.3)
2018–2020	472 (39.3)
2021–2023	472 (39.3)

Note: History of severe hypovolemia, comorbidity or comedication at baseline was defined as at least one diagnosis, regardless of inpatient or outpatient, or prescription within 180 days before or on the index date. Abbreviation: IQR, interquartile ranges.

although the latter appears mostly transient.⁹ Some investigators have reported significant increase in urine volume and sodium excretion during SGLT2i treatment.^{7,8} Eickhoff et al. indicated that 10 mg

dapagliflozin, when combined with renin-angiotensin-aldosterone system inhibitors, exerted osmotic and natriuretic effects in patients with type 2 diabetes mellitus and albuminuria. However, compensatory mechanisms were activated within 6–12 weeks to retain sodium and water.³⁰ Masuda et al. reported that dapagliflozin increased urine volume (18.7%), urinary Na excretion (43.0%) and urinary Cl excretion (39.2%) on Day 2 compared to baseline, but the parameters returned to baseline levels on Day 7.³¹ Bode et al. published a long-term safety study on canagliflozin in patients with type 2 diabetes mellitus over 104 weeks.²⁶ In this study, more adverse events of hypovolemia were reported with 100 mg canagliflozin (5.4%, *n* = 241) and 300 mg canagliflozin (5.9%, *n* = 236) than with placebo (1.7%, *n* = 237), and most of these events were observed within the first 26 weeks of canagliflozin treatment. Two meta-analyses demonstrated an increased risk of hypovolemia upon SGLT2i treatment (Mukai et al.¹⁰ RR 1.12, 95% CI 0.48–2.61; Rong et al.¹¹ RR 1.12, 95% CI 1.02–1.22), regardless of whether the effect was substantial. Pooled data from SGLT2i RCTs indicated increased rates of hypovolemia-related events (0.3 to 4.4%) than in placebo groups (0 to 1.5%), as reported in the US package inserts.⁶ Clinical practice guidelines have highlighted the risk of hypovolemia in patients treated with SGLT2i.^{2,5,6} These guidelines caution against the potential adverse effects of SGLT2i treatment on hypovolemia and emphasize that the volume status of patients should be assessed and corrected as appropriate before treatment initiation.^{2,5,6} They also advise that physicians regularly monitor symptoms (e.g., hypotension), changes in weight and volume status, and provide appropriate interventions such as hydration and medications.^{2,5,6}

Collectively, the findings supported the hypothesis that SGLT2i may lead to hypovolemia, particularly shortly after initiating treatment in patients with type 2 diabetes mellitus, owing to the pharmacological effects of osmotic diuresis and natriuresis. However, detailed data on the risks or event rates associated with SGLT2i treatment periods have not yet been published. Clarifying the timing and duration of increased risk following the initiation of SGLT2i treatment would be clinically meaningful.

4.2 | Interpretation of our findings

To the best of our knowledge, this is the first study to investigate the association between SGLT2i use and the risk of severe hypovolemia during the treatment period. Our study provided clinically informative insights into the higher risks associated with different periods of SGLT2i exposure, suggesting that caution is required during the early phase of treatment, especially within the first 30 days. Given that SGLT2i is one of the most commonly used classes of medications for type 2 diabetes mellitus, knowing the risk period for common adverse reactions, such as hypovolemia, would be beneficial for optimizing SGLT2i usage.

Our secondary analyses highlighted the period within the first 22 to 28 days after the index date as having the highest risk of severe hypovolemia. The histogram of the observed severe hypovolemia events, shown in Figure 2, indicated a peak around the first 21 to 25 days, supporting our findings from the SCCS analyses. Although

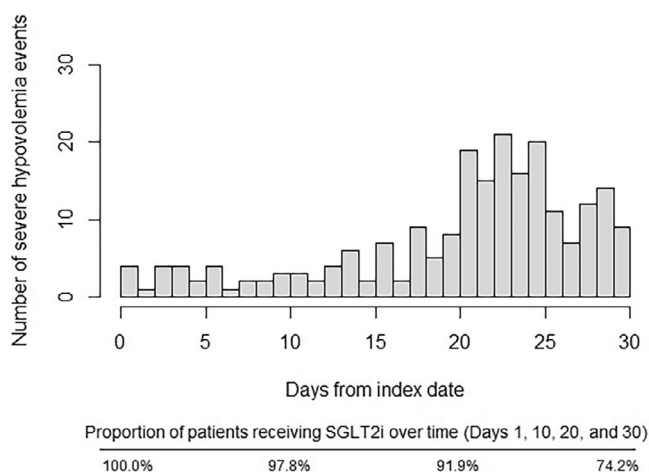
TABLE 2 Primary analysis: Association between sodium-glucose cotransporter-2 inhibitors exposure and an incident of severe hypovolemia.

Evaluation period	Number of patients	Number of patients with events	Number of events	Patient-years	Adjusted IRR ^a (95% CI)
Control period	1200	208	227	959	1.00 [Reference]
Pre-exposure period					
Days 30 to 16	1200	15	15	49	1.12 (0.66–1.89)
Days 15 to 1	1200	17	17	49	1.27 (0.78–2.08)
Exposure period					
Days 1 to 30	1200	214	219	99	7.39 (6.09–8.96)
Days 31 to 90	1157	90	99	207	1.99 (1.56–2.54)
Days 91 to 180	1091	94	99	292	1.56 (1.22–2.00)
Days ≥181	1024	594	658	3483	1.36 (1.13–1.63)

Note: Follow-up period includes SGLT2i treatment period with the grace period (exposure period) and non-SGLT2i treatment period (control period and pre-exposure period), as illustrated in Supplementary Figure S1.

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; SGLT2i, sodium-glucose cotransporter-2 inhibitors.

^aThe model was adjusted by time-varying covariates, including age, renal dysfunction defined by estimated glomerular filtration rate <60 mL/min/1.73 m² and prescription of diuretics.

**FIGURE 2** Number of severe hypovolemia events by day from the index date, ranging from Days 1 to 30. SGLT2i, sodium-glucose cotransporter-2 inhibitors.

some clinical studies have reported different results, suggesting that osmotic diuresis and natriuresis associated with SGLT2i treatment were maintained or attenuated within 12 weeks,⁹ our study suggested that many patients may still experience the pharmacological effects for at least 30 days after the initiation of SGLT2i treatment, leading to a higher risk of severe hypovolemia as a clinical outcome.

Our tertiary analyses of the seasonal subgroups suggested that caution is necessary for severe hypovolemia across all seasons when initiating SGLT2i treatment. Tanaka et al. investigated the seasonal hydration status in an elderly population and found that subjects were more dehydrated in spring, showing the highest levels of plasma osmolality, than in summer, although the seasonal differences were considered clinically mild.³² Although our study did not provide a definitive explanation, the highest risk of severe hypovolemia was observed in patients initiating SGLT2i treatment during autumn. While there may be a common perception that hypovolemia frequently occurs during

the hot and humid summer months, our findings emphasized the importance of monitoring severe hypovolemia across all seasons. Furthermore, our calendar-year subgroup analyses indicated that the risk of severe hypovolemia persisted for more than a decade after the first SGLT2i was launched and clinical guidelines on managing hypovolemia were introduced.^{2,5,6} As noted by the World Health Organization and other medical associations,^{33,34} global warming is accelerating and exposing more people to extreme heat worldwide. This environmental factor further underscores the need for heightened vigilance and proactive measures to manage severe hypovolemia during SGLT2i treatment.

4.3 | Strengths

We employed the SCCS design to leverage its strength for analysing relative risks across different exposure periods,¹⁶ because we aimed to investigate the temporal risk patterns of severe hypovolemia induced by SGLT2i treatment compared with non-SGLT2i exposure. Our study provided clinically informative insights into the higher risks of severe hypovolemia by SGLT2i, particularly highlighting the critical periods when caution should be exercised during treatment. Besides, the SCCS design implicitly adjusted for both measured and unmeasured time-invariant confounders, thereby reducing the likelihood of bias.^{16,17,19} It was deemed appropriate for investigating the causality between SGLT2i exposure and severe hypovolemia events based on the following assumptions: (1) severe hypovolemia events were rare and occurred independently and consistently during the follow-up period; (2) severe hypovolemia events did not change the probability of subsequent outcomes and exposures; and (3) fetal events of severe hypovolemia were very limited. In our study, severe hypovolemia events were rare; 1234 patients (0.7%) experienced the events out of 186 324 patients with type 2 diabetes mellitus before applying the exclusion criteria (Figure 1). Severe hypovolemia was consistently observed during the unexposed period (Figure S2). Our study included patients with two or more severe hypovolemia events; however, the

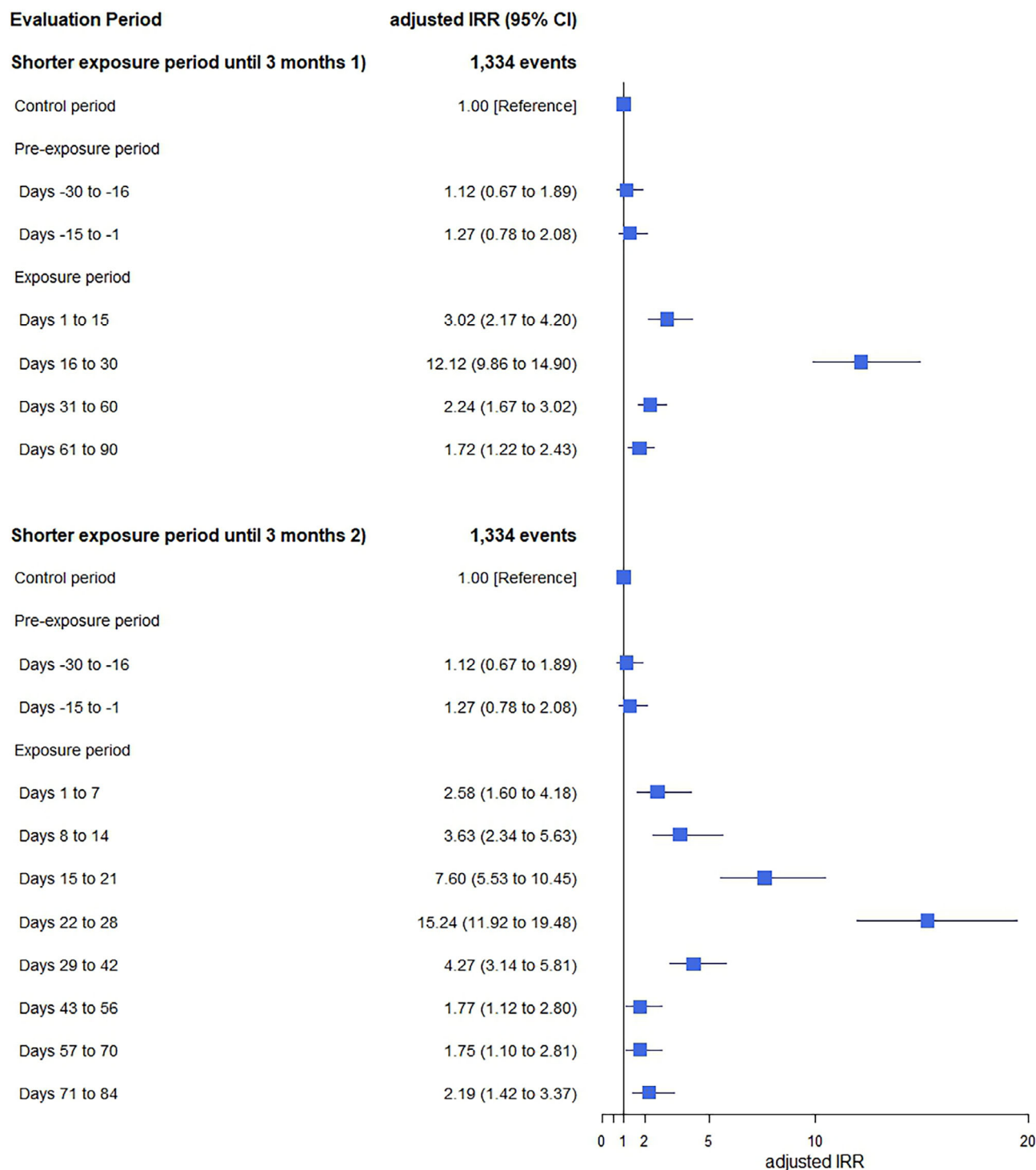


FIGURE 3 Secondary analysis by shorter exposure period during the first 3 months after the index date. IRR, incidence risk ratio.

results of the sensitivity analysis, excluding a second or subsequent event, were consistent with those of the primary analysis. Severe hypovolemia was neither fatal nor considered to affect subsequent exposure, because only 1.0% of the enrolled patients (12 cases) died within 90 days of experiencing it. Sensitivity analysis results, excluding patients who died within 90 days after severe hypovolemia events, were consistent with those of the primary analysis.

4.4 | Limitations

Our study had several limitations. First, it was a retrospective database study, and potential misclassification of diseases or medication codes should be considered. Second, no validation study was conducted to assess the incidence of hypovolemia using observational studies. Defining hypovolemia using ICD-10 codes may result in

misclassification; however, we defined a more restricted case of severe hypovolemia than previous observational studies.^{22,23} We also repeated the sensitivity analysis with a further restricted definition of severe hypovolemia, incorporating the volume of specific hypovolemia treatments. This sensitivity analysis result was consistent with that of the primary analysis. Third, the claims database cannot provide information on drug adherence,¹⁴ which might lead to misclassification of the exposure length and affect the results. Fourth, the JMDC Claims Database¹⁴ contains accumulated receipts and annual medical check-up data for insured individuals covered by health insurance societies, primarily employees of large companies or their family members. Hence, the data primarily reflected individuals aged <75 years, highlighting the need for caution regarding a potential selection bias. Fifth, although we adjusted for key time-varying covariates, including age, renal dysfunction defined by eGFR <60 mL/min/1.73 m² and prescription of diuretics, there may still be residual confounding factors despite the robustness of our findings in the sensitivity analyses. These confounders could include factors such as changes in economic status, job status and detailed lifestyle (e.g., exercise and dietary habits) during the follow-up period, which were not included in the database.

In conclusion, the use of SGLT2i in patients with type 2 diabetes mellitus was associated with a high risk of severe hypovolemia, particularly in the first 30 days after treatment initiation. Our study identified the period between the first 22 and 28 days after the initiation of SGLT2i treatment as having the highest risk of severe hypovolemia in patients with type 2 diabetes mellitus.

AUTHOR CONTRIBUTIONS

All authors contributed to the conception and design of this study. Material preparation, and data collection and analyses were performed by MS and AT. The first draft of the manuscript was written by MS and AT, and all authors commented on previous versions of the manuscript. All the authors have read and approved the final version of the manuscript. MS, AT and KK are the guarantor of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICT OF INTEREST STATEMENT

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PEER REVIEW

The peer review history for this article is available at <https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.16259>.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analysed during the current study are not publicly available. The JMDC makes its database widely available, on a fee-payment basis, for the use of surveys, research and commercial purposes. Inquiries about this database can be made via the JMDC's website (<https://www.jmdc.co.jp/en/bigdata>), and it may be accessed after completing the contract for the use of specific data.

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REFERENCES

- Ong KL, Stafford LK, McLaughlin SA, Boyko EJ, Vollset SE, Smith AE. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the global burden of disease study 2021. *Lancet*. 2023;402(10397):203-234.
- Padda I, Mahtani A, StatPearls PM. Sodium-Glucose Transport Protein 2 (SGLT2) Inhibitors-StatPearls-NCBI Bookshelf [Cited 2024 May 30]. 2023 Available from: <https://www.ncbi.nlm.nih.gov/books/NBK576405/?report=printable>.
- Bonora BM, Avogaro A, Fadini GP. Extraglycemic effects of SGLT2 inhibitors: a review of the evidence. *Diabetes Metab Syndr Obes*. 2020;13:161-174.
- Shikamura M, Takayama A, Takeuchi M, Kawakami K. Comparative effectiveness of sodium-glucose cotransporter-2 inhibitors and dipeptidyl peptidase-4 inhibitors in improvement of fatty liver index in patients with type 2 diabetes mellitus and metabolic dysfunction-associated steatotic liver disease: a retrospective nationwide claims database study in Japan. *Diabetes Obes Metab*. 2024;26(8):3099-3109.
- Vardeny O, Vaduganathan M. Practical guide to prescribing sodium-glucose cotransporter 2 inhibitors for cardiologists. *JACC Heart Fail*. 2019;7(2):169-172.
- McGill JB, Subramanian S. Safety of sodium-glucose co-transporter 2 inhibitors. *Am J Cardiol*. 2019;124(suppl 1):S45-S52.
- Takeuchi T, Dohi K, Omori T, et al. Diuretic effects of sodium-glucose cotransporter 2 inhibitor in patients with type 2 diabetes mellitus and heart failure. *Int J Cardiol*. 2015;201:1-3.
- Kawasoe S, Maruguchi Y, Kaiji S, et al. Mechanism of the blood pressure-lowering effect of sodium-glucose cotransporter 2 inhibitors in obese patients with type 2 diabetes. *BMC Pharmacol Toxicol*. 2017;18(1):23.

9. Delanaye P, Scheen AJ. The diuretic effects of SGLT2 inhibitors: a comprehensive review of their specificities and their role in renal protection. *Diabetes Metab.* 2021;47(6):101285.
10. Mukai J, Kanno S, Kubota R. A literature review and meta-analysis of safety profiles of SGLT2 inhibitors in Japanese patients with diabetes mellitus. *Sci Rep.* 2021;11(1):13472.
11. Rong X, Zhu Y, Wen B, et al. Risk of hypovolemia associated with sodium-glucose cotransporter-2 inhibitors treatment: a meta-analysis of randomized controlled trials. *Front Cardiovasc Med.* 2022;9:973129.
12. Jiang Y, Yang P, Fu L, Sun L, Shen W, Wu Q. Comparative cardiovascular outcomes of SGLT2 inhibitors in type 2 diabetes mellitus: a network meta-analysis of randomized controlled trials. *Front Endocrinol.* 2022;13:802992.
13. Lu H, Lu H, Kosinski C, et al. SGLT2 inhibitors, what the emergency physician needs to know: a narrative review. *J Clin Med.* 2021;10(9):2036.
14. Nagai K, Tanaka T, Kodaira N, Kimura S, Takahashi Y, Nakayama T. Data resource profile: JMDC claims database sourced from health insurance societies. *J Gen Fam Med.* 2021;22(3):118-127.
15. Zheng Y, Fukasawa T, Yamaguchi F, Takeuchi M, Kawakami K. Cardiovascular safety of atomoxetine and methylphenidate in patients with attention-deficit/hyperactivity disorder in Japan: a self-controlled case series study. *J Atten Disord.* 2024;28(4):10870547231214993.
16. Iwagami M, Takeuchi Y. Introduction to self-controlled study design. *Ann Clin Epidemiol.* 2021;3(3):67-73.
17. Petersen I, Douglas I, Whitaker H. Self controlled case series methods: an alternative to standard epidemiological study designs. *BMJ.* 2016;354:i4515.
18. Jackson JW. The cardiovascular safety of methylphenidate. *BMJ.* 2016;353:i2874.
19. Shin JY, Roughead EE, Park BJ, Pratt NL. Cardiovascular safety of methylphenidate among children and young people with attention-deficit/hyperactivity disorder (ADHD): Nationwide self controlled case series study. *BMJ.* 2016;353:i2550.
20. Fukasawa T, Takahashi H, Takahashi K, Tanemura N, Amagai M, Urushihara H. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis associated with anticonvulsants in a Japanese population: matched case-control and cohort studies. *Allergol Int.* 2021;70(3):335-342.
21. Yoshida K, Solomon DH, Kim SC. Active-comparator design and new-user design in observational studies. *Nat Rev Rheumatol.* 2015;11(7):437-441.
22. Fu EL, D'Andrea E, Wexler DJ, Paterno E, Paik JM. Safety of sodium-glucose Cotransporter-2 inhibitors in patients with CKD and type 2 diabetes: population-based US cohort study. *Clin J Am Soc Nephrol.* 2023;18(5):592-601.
23. D'Andrea E, Wexler DJ, Kim SC, Paik JM, Alt E, Paterno E. Comparing effectiveness and safety of SGLT2 inhibitors vs DPP-4 inhibitors in patients with type 2 diabetes and varying baseline HbA_{1c} levels. *JAMA Intern Med.* 2023;183(3):242-254.
24. Taylor K. *Adult dehydration - StatPearls - NCBI bookshelf.* StatPearls; 2022.
25. Ikuta K, Nakagawa S, Yamawaki C, et al. Use of proton pump inhibitors and macrolide antibiotics and risk of acute kidney injury: a self-controlled case series study. *BMC Nephrol.* 2022;23(1):383.
26. Bode B, Stenlöf K, Harris S, et al. Long-term efficacy and safety of canagliflozin over 104 weeks in patients aged 55–80 years with type 2 diabetes. *Diabetes Obes Metab.* 2015;17(3):294-303.
27. Kang M, Heo KN, Ah YM, Yang BR, Lee JY. Age- and sex-specific risk of urogenital infections in patients with type 2 diabetes treated with sodium-glucose co-transporter 2 inhibitors: a population-based self-controlled case-series study. *Maturitas.* 2021;150:30-36.
28. Scheen AJ, Bonnet F. Efficacy and safety profile of SGLT2 inhibitors in the elderly: how is the benefit/risk balance? *Diabetes Metab.* 2023;49(2):101419.
29. Kim JH, Yoon D, Ko HY, et al. Risk of encephalitis and meningitis after COVID-19 vaccination in South Korea: a self-controlled case series analysis. *BMC Med.* 2024;22(1):123.
30. Eickhoff MK, Dekkers CCJ, Kramers BJ, et al. Effects of dapagliflozin on volume status when added to renin-angiotensin system inhibitors. *J Clin Med.* 2019;8(6):779.
31. Masuda T, Ohara K, Murakami T, et al. Sodium-glucose cotransporter 2 inhibition with dapagliflozin ameliorates extracellular volume expansion in diabetic kidney disease patients. *POJ Diabetes Obes.* 2017;1(1):1-8.
32. Tanaka S, Fujishiro M, Watanabe K, et al. Seasonal variation in hydration status among community-dwelling elderly in Japan. *Geriatr Gerontol Int.* 2020;20(10):904-910.
33. World Health Organization. WHO newsroom. Heat and health [Cited 2024 Nov 18]. 2024 Available from: <https://www.who.int/news-room/fact-sheets/detail/climate-change-heat-and-health>.
34. American Red Cross. Extreme heat safety. Extreme Heat Safety | Heat Exhaustion Safety | Red Cross. [Cited 2024 Nov 18]. Available from: <https://www.redcross.org/get-help/how-to-prepare-for-emergencies/types-of-emergencies/extreme-heat-safety.html?srsltid=AfmBOookK5Y5b6BHpMnJxkEoPXBIn4GBtbc7NC4-2F09oBY5EbNleeBNe>.
35. Ramsay EN, Roughead EE, Ewald B, Pratt NL, Ryan P. A self-controlled case series to assess the effectiveness of beta blockers for heart failure in reducing hospitalisations in the elderly. *BMC Med Res Methodol.* 2011;11:106.
36. Lin J, Pearson SA, Greenfield JR, et al. Trends in use of sodium-glucose co-transporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA) in Australia in the era of increased evidence of their cardiovascular benefits (2014–2022). *Eur J Clin Pharmacol.* 2023;79(9):1239-1248.
37. Peach EJ, Pearce FA, Gibson J, Cooper AJ, Chen LC, Knaggs RD. Opioids and the risk of fracture: a self-controlled case series study in the clinical practice research datalink. *Am J Epidemiol.* 2021;190(7):1324-1331.
38. Takeuchi Y, Ando T, Ishiguro C, Uyama Y. Risk of acute asthma attacks associated with nonsteroidal anti-inflammatory drugs: a self-controlled case series. *Ther Innov Regul Sci.* 2017;51(3):332-341.
39. Hubbard R, Lewis S, West J, et al. Bupropion and the risk of sudden death: a self-controlled case-series analysis using the health improvement network. *Thorax.* 2005;60:848-850.
40. Requena G, Douglas IJ, Huerta C, De Abajo F. Impact of pre-exposure time bias in self-controlled case series when the event conditions the exposure: hip/femur fracture and use of benzodiazepines as a case study. *Pharmacoepidemiol Drug Saf.* 2020;29(4):388-395.

SUPPORTING INFORMATION

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

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