JoS JOURNAL OF STROKE

Journal of Stroke 2024;26(2):342-346
https://doi.org/10.5853/jos.2023.04056

Letter to the Editor

Sodium-Glucose Cotransporter 2 Inhibitor Improves Neurological Outcomes in Diabetic Patients With Acute Ischemic Stroke

Wookjin Yang,[1] Jeong-Min Kim,[1] Matthew Chung,[1] Jiyeon Ha,[1] Dong-Wan Kang,[1*] Eung-Joon Lee,[1] Han-Yeong Jeong,[1] Keun-Hwa Jung,[1] Hyunpil Sung,[2] Jin Chul Paeng,[2] Seung-Hoon Lee[1]

[1]Department of Neurology, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea
[2]Department of Nuclear Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea

Dear Sir:

The benefits of sodium-glucose cotransporter 2 inhibitors (SGLT2i) in acute ischemic stroke (AIS) have been demonstrated preclinically.[1,2] However, clinical studies on the association between SGLT2i and stroke have been mainly focused on determining whether SGLT2i increase the risk of incident ischemic stroke in the stroke-naïve population.[3] Moreover, given the results of clinical trials suggested that SGLT2i use may be less beneficial with respect to stroke compared to other cardiovascular outcomes,[4,5] physicians may raise concerns that SGLT2i could elevate the vulnerability to ischemic stroke. From this perspective, SGLT2i might potentially lead to early neurological deterioration (END) in patients with AIS, resulting in poor neurological outcome. Due to the controversial nature of this issue, the role of SGLT2i in cerebral ischemia remains unclear in patients with ischemic stroke. We aimed to explore the association between SGLT2i treatment and stroke outcomes, including neurological deterioration and recovery up to 3 months after stroke.

This retrospective observational study reviewed consecutive diabetic patients with AIS enrolled in Seoul National University Hospital (SNUH) stroke registry from January 2018 to June 2022. Patients were grouped into SGLT2i and control groups according to their prescription of SGLT2i at admission. To investigate the mechanistic implications, we used data from another cohort where neurologically stabilized participants with AIS were prospectively enrolled and underwent ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET), to predict stroke recurrence. The Institutional Review Board of SNUH approved this study (No. 1009-062-332). The need for informed consent was waived for the SNUH stroke registry, owing to the retrospective nature of the study. For those included in the FDG-PET cohort, informed consent was obtained (No. 2105-013-1217).

Clinical data were collected upon admission from all patients. The decision to prescribe SGLT2i to diabetic patients with stroke was at the physician's discretion. Following 1:4 propensity score matching, binary and ordinal logistic regression analyses were performed to evaluate the association between SGLT2i use and clinical outcomes including END during admission, National Institutes of Health Stroke Scale (NIHSS) score at discharge, and modified Rankin Scale (mRS) scores at discharge and at 3 months. Using the FDG-PET cohort, we compared metabolic activity of various organs based on SGLT2i use, represented as the target-to-background ratio (Supplementary Methods).

Among the 806 eligible patients, 88 (10.9%) were prescribed SGLT2i on admission, and 74 continued the prescription at discharge. Two hundred fifty-nine controls were propensity score-matched to the 71 patients in the SGLT2i group (32 with dapagliflozin and with 39 empagliflozin) and were well-balanced (Supplementary Figure 1, Supplementary Table 1, and Table 1). During the total admission period of 7 [5–11] days, SGLT2i were prescribed for a median duration of 6 [4.5–10] days. Information regarding antidiabetic medications other than SGLT2i was summarized in Supplementary Table 2.

The SGLT2i group demonstrated a generally favorable functional outcome compared to the control group, both before and after propensity score matching, particularly at 3 months (Supplementary Figure 2). Binary logistic regression analyses of the matched

pISSN: 2287-6391 • eISSN: 2287-6405

Table 1. Baseline characteristics before and after propensity score matching

	Original dataset			Matched dataset		
	No SGLT2i (n=718)	SGLT2i (n=88)	*P*	No SGLT2i (n=259)	SGLT2i (n=71)	*P*
Age (yr)	72 [63; 79]	67 [58.5; 74.5]	0.001	68 [59.5; 76]	68 [61; 74.5]	0.910
Male sex	446 (62.1)	57 (64.8)	0.712	171 (66.0)	46 (64.8)	0.958
Hypertension	585 (81.5)	76 (86.4)	0.327	221 (85.3)	60 (84.5)	>0.999
Hyperlipidemia	501 (69.8)	72 (81.8)	0.026	197 (76.1)	56 (78.9)	0.735
Ever smoking	233 (32.5)	36 (40.9)	0.142	104 (40.2)	30 (42.3)	0.855
Stroke history	200 (27.9)	25 (28.4)	>0.999	80 (30.9)	24 (33.8)	0.746
Atrial fibrillation	145 (20.2)	17 (19.3)	0.958	44 (17.0)	14 (19.7)	0.719
Coronary heart disease	132 (18.4)	23 (26.1)	0.110	64 (24.7)	19 (26.8)	0.843
Heart failure	63 (8.8)	13 (14.8)	0.104	27 (10.4)	9 (12.7)	0.746
Active cancer	95 (13.2)	0 (0.0)	0.001	0 (0.0)	0 (0.0)	
HbA1c (%)	6.9 [6.5; 7.8]	7.8 [7.0; 9.1]	<0.001	7.4 [6.9; 8.3]	7.7 [7.0; 8.8]	0.072
Glucose control (%)			<0.001			0.860
<7.0	361 (50.3)	20 (22.7)		67 (25.9)	17 (23.9)	
≥7.0	357 (49.7)	68 (77.3)		192 (74.1)	54 (76.1)	
eGFR (mL/min/1.73 m^2)	75.3 [56.9; 88.1]	75.3 [61.9; 90.6]	0.308	77.3 [59.1; 90.5]	74.5 [58.1; 90.2]	0.808
eGFR category (mL/min/1.73 m^2)			0.080			>0.999
≥60	514 (71.6)	67 (76.1)		191 (73.7)	52 (73.2)	
30–59	155 (21.6)	16 (18.2)		58 (22.4)	16 (22.5)	
15–29	19 (2.6)	5 (5.7)		10 (3.9)	3 (4.2)	
<15	30 (4.2)	0 (0.0)		0 (0.0)	0 (0.0)	
Intracranial atherosclerosis	356 (49.6)	46 (52.3)	0.716	130 (50.2)	38 (53.5)	0.717
Total SVD score	2 [1; 3]	2 [1; 3]	0.033	2 [1; 3]	2 [1; 3]	0.747
Prestroke statin use	355 (49.4)	58 (65.9)	0.005	158 (61.0)	47 (66.2)	0.509
Prestroke mRS	0 [0; 1]	0 [0; 0.5]	0.544	0 [0; 0]	0 [0; 1]	0.619
Initial NIHSS	3 [1; 6]	3 [1.5; 6]	0.883	3 [2; 5]	3 [1.5; 5.5]	0.695
Intravenous thrombolysis	50 (7.0)	5 (5.7)	0.821	10 (3.9)	3 (4.2)	>0.999
Endovascular thrombectomy	54 (7.5)	8 (9.1)	0.757	10 (3.9)	3 (4.2)	>0.999
Stroke etiology			0.144			0.980
LAA	265 (36.9)	41 (46.6)		120 (46.3)	34 (47.9)	
SVO	150 (20.9)	18 (20.5)		61 (23.6)	15 (21.1)	
CE	144 (20.1)	18 (20.5)		50 (19.3)	14 (19.7)	
Others	159 (22.1)	11 (12.5)		28 (10.8)	8 (11.3)	

The data are presented as n (%) or median [interquartile range].
SGLT2i, sodium-glucose cotransporter 2 inhibitor; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; SVD, small vessel disease; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; LAA, large artery atherosclerosis; SVO, small vessel occlusion; CE, cardioembolism.

Table 2. Clinical outcomes according to the use of SGLT2i during the acute phase in patients with ischemic stroke

	No SGLT2i (n=259)	SGLT2i (n=71)	OR (95% CI) or β (SE)	*P*
END	30 (11.6)	6 (8.5)	0.70 (0.28–1.77)	0.455
NIHSS at discharge	2 [1; 4]	2 [1; 3]	-1.131 (0.923)*	0.221
mRS at discharge	2 [1; 3]	1 [1; 3]	1.43 (0.90–2.29)†	0.132
Favorable outcome at discharge	169 (65.3)	50 (70.4)	1.27 (0.72–2.24)	0.414
Excellent outcome at discharge	106 (40.9)	36 (50.7)	1.48 (0.88–2.51)	0.142
mRS at 3 months	2 [0; 3]	1 [0; 2]	1.71 (1.07–2.74)†	0.026
Favorable outcome at 3 months	169 (65.3)	54 (76.1)	1.69 (0.93–3.09)	0.087
Excellent outcome at 3 months	126 (48.6)	46 (64.8)	1.94 (1.13–3.35)	0.017

The data are presented as n (%) or median [interquartile range].
SGLT2i, sodium-glucose cotransporter 2 inhibitor; OR, odds ratio; CI, confidence interval; β, unstandardized coefficient; SE, standard error; END, early neurological deterioration; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale.
*Unstandardized coefficient and standard error by linear regression; †Proportional odds ratios for favorable mRS scores using ordinal logistic regression.

population showed significantly higher odds of achieving excellent 3-month functional outcomes and a trend toward favorable outcomes in the SGLT2i group. Ordinal logistic regression analysis indicated significantly higher odds of a better 3-month mRS score with SGLT2i use during admission. No significant differences in END occurrence, discharge NIHSS score, or discharge mRS score were found between the two groups (Table 2). There were no significant interactions between SGLT2i use and various clinical factors for excellent outcomes (Supplementary Figure 3).

In the SGLT2i group, 32 were pre-stroke SGLT2i users, while the remaining 39 were first prescribed SGLT2i during their admission. Clinical outcomes were comparable regardless of pre-stroke SGLT2i use (Supplementary Table 3). The patients discharged with SGLT2i had more favorable outcomes at discharge and at 3 months compared to those without SGLT2i prescription at discharge (Supplementary Table 4). In the sensitivity analysis encompassing all patients prescribed SGLT2i at admission as the SGLT2i group, consistent with the main analyses, the SGLT2i group

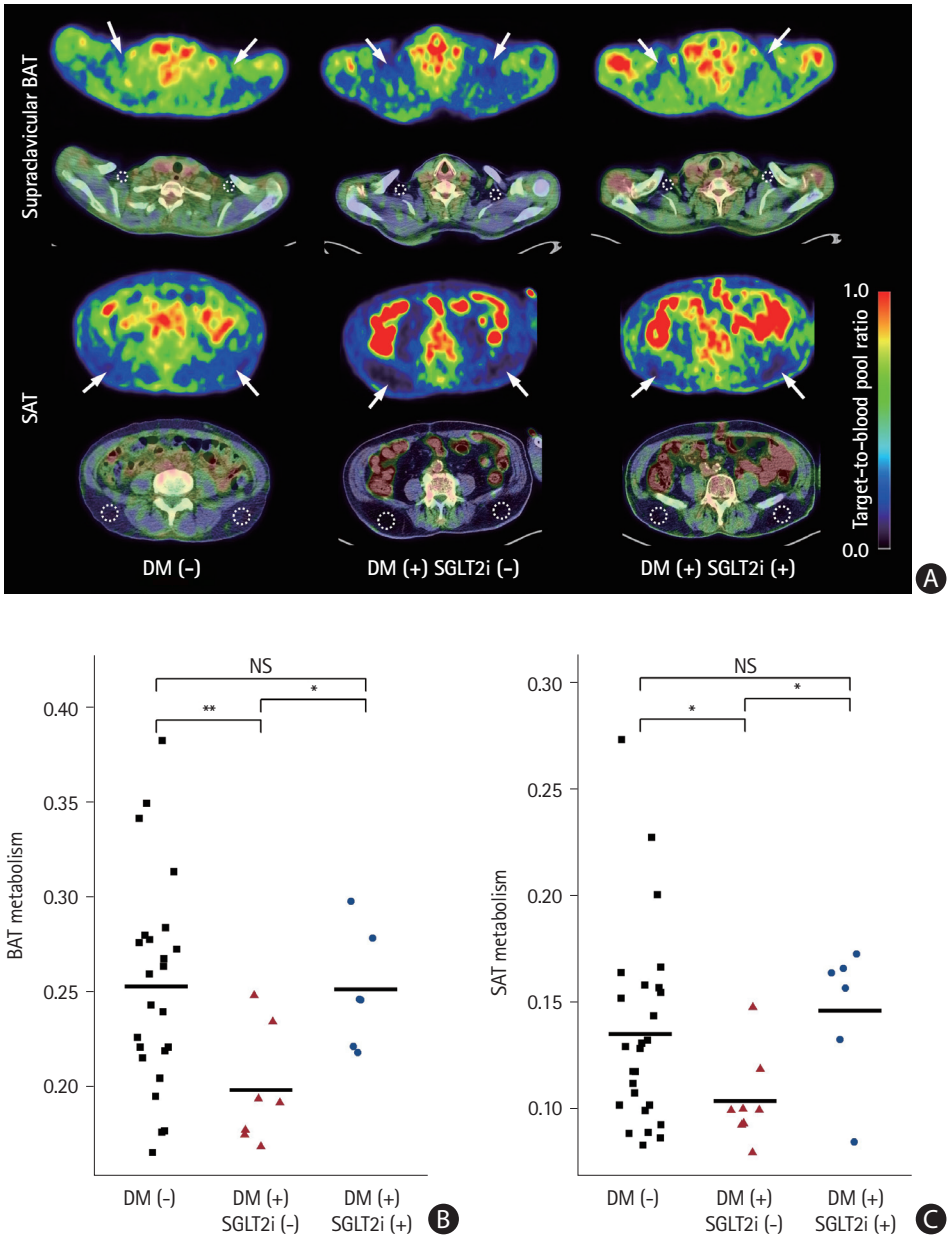

Figure 1. Impact of SGLT2i on the metabolism of various organs. (A) Representative ^{18}F-fluorodeoxyglucose positron emission tomography images of nondiabetic controls, diabetic patients without SGLT2i use, and diabetic patients with SGLT2i use, measured in supraclavicular brown and SAT. The measurement sites are indicated by arrows and dotted circles. Comparison of (B) brown and (C) SAT ^{18}F-fluorodeoxyglucose uptake among nondiabetic controls, diabetic patients without SGLT2i use, and diabetic patients with SGLT2i use. *P<0.05; **P<0.01. BAT, brown adipose tissue; DM, diabetes mellitus; SAT, subcutaneous adipose tissue; SGLT2i, sodium-glucose cotransporter 2 inhibitor; NS, no significant difference.

https://doi.org/10.5853/jos.2023.04056

had significantly higher odds of excellent outcomes at 3 months (Supplementary Tables 5 and 6).

Fourteen diabetic and 26 nondiabetic stroke survivors participated in the FDG-PET cohort, and six of diabetic patients were prescribed SGLT2i at admission. Diabetic patients using SGLT2i exhibited elevated metabolism in supraclavicular brown and subcutaneous adipose tissues compared to diabetic patients not using SGLT2i (Figure 1 and Supplementary Table 7).

Our study showed that SGLT2i may be safely used without increasing END after AIS. Remarkably, acute phase SGLT2i use was significantly associated with better neurological outcomes at 3 months, while acute outcomes at discharge were not affected. Continuing SGLT2i use beyond discharge, rather than transient use during admission, was associated with a more favorable 3-month functional outcome. Given that SGLT2i enhanced synaptic function in diabetic animal models and ameliorated neuronal loss in neurodegenerative animal models in previous studies,[6,7] our findings may imply a potential role of SGLT2i in post-stroke functional recovery as well as in neuroprotection against acute ischemia. The FDG-PET cohort findings indicate that brown adipose tissue and beige adipocytes, which reportedly benefit metabolic health and reduce arterial inflammation,[8,9] might have some role in the association between SGLT2i and favorable outcomes. However, the conclusions are tentative due to the small sample size, necessitating further research for validation.

This study had several limitations. Firstly, its retrospective design introduces the possibility of unmeasured confounders affecting the outcomes, such as the unavailability of post-discharge drug compliance data. Secondly, the limited generalizability due to the predominantly minor neurological deficits among study subjects and the small sample size, particularly in the SGLT2i group, calls for further validation in larger, more diverse cohorts. Finally, this study only included ischemic stroke patients with diabetes, and the neuroprotective effect of SGLT2i in non-diabetic stroke patients remains uncertain.

In conclusion, our findings suggest that SGLT2i may be a priority for diabetic patients with AIS because of its potential benefits on neurological outcomes. Dedicated studies are needed to validate whether SGLT2i have neuroprotective effects in ischemic stroke and explore its potential mechanism.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2023.04056.

Funding statement

This research was supported by a grant of Patient-Centered Clinical Research Coordinating Center (PACEN) funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HC23C0063). Funding source has no role in the conceptualization, design, data collection, analysis, decision to publish, or preparation of the manuscript.

Conflicts of interest

The authors have no financial conflicts of interest.

Author contribution

Conceptualization: WY, JMK, JCP. Study design: WY, JMK, MC, JH, DWK, EJL, HYJ, KHJ, JCP, SHL. Methodology: WY, JMK, JCP. Data collection: WY, JMK, HS, JCP. Investigation: WY, JMK, HS, JCP. Statistical analysis: WY, JMK. Writing—original draft: WY, JMK. Writing—review & editing: all authors. Funding acquisition: JMK. Approval of final manuscript: all authors.

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Correspondence: Jeong-Min Kim
Department of Neurology, Seoul National University Hospital, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea
Tel: +82-2-2072-4901
E-mail: bellokim1@gmail.com
https://orcid.org/0000-0001-7213-5527

Co-correspondence: Jin Chul Paeng
Department of Nuclear Medicine, Seoul National University Hospital, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea
Tel: +82-2-2072-3793
E-mail: paengjc@snu.ac.kr
https://orcid.org/0000-0002-7464-9342

*Current affiliation: Department of Neurosurgery, Seoul National University Bundang Hospital, Seongnam, Korea

Received: November 24, 2023
Revised: March 5, 2024
Accepted: March 19, 2024

https://doi.org/10.5853/jos.2023.04056

Supplementary Methods

Study population

The Seoul National University Hospital (SNUH) Stroke Registry is a prospective stroke registry that includes patients with acute stroke within 7 days who were admitted to SNUH, one of the largest tertiary care centers in Korea. From this registry, acute ischemic stroke (AIS) patients who arrived between January 2018 and June 2022 were reviewed, and those with a history of diabetes or those diagnosed with diabetes upon admission were included. Patients lost to follow-up at 3 months post-stroke or those with missing magnetic resonance imaging (MRI) scans were excluded. Patients who were prescribed sodium-glucose cotransporter 2 inhibitors (SGLT2i) at admission were classified into the SGLT2i group. Patients who were not prescribed SGLT2i during admission served as the control group. To investigate the mechanistic implications of SGLT2i use on clinical outcomes, we used data from another cohort study that employed ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) in stroke patients to predict stroke recurrence. In this cohort, neurologically stabilized participants with AIS were prospectively enrolled and underwent FDG-PET.

Data collection

Information on age, sex, hypertension, hyperlipidemia, smoking history, atrial fibrillation, coronary heart disease, heart failure, coexisting active cancer, hemoglobin A1c (HbA1c), estimated glomerular filtration rate (eGFR), presence of intracranial atherosclerosis, total small vessel disease (SVD) score, pre-stroke statin use, pre-stroke modified Rankin Scale (mRS), initial National Institutes of Health Stroke Scale (NIHSS) score, intravenous thrombolysis, endovascular thrombectomy, and stroke etiology was collected upon admission from all patients. Heart failure was defined as either a previous history of heart failure or a left ventricular ejection fraction of ≤40%. HbA1c was categorized into two categories as follows: <7.0% or ≥7.0%. The eGFR was categorized into four categories as follows: ≥60, 30–59, 15–29, or <15 mL/min/1.73 m^2. Intracranial atherosclerosis was defined as visible stenosis in the anterior, middle, or posterior cerebral arteries, basilar artery, intracranial vertebral artery, or intracranial internal carotid artery, as observed on initial magnetic resonance angiography, computer tomography angiography, or conventional angiography. The total SVD score was calculated on a 0–4-point scale by summing the points assigned to four MRI markers of SVD, i.e., lacunes, white matter hyperintensities, cerebral microbleeds, and visible perivascular spaces, following a previously described methodology.[1] The Trial of ORG 10172 in Acute Stroke Treatment classification with modification was utilized to assess stroke etiology,[2] and the categories included large artery atherosclerosis (LAA), small vessel occlusion (SVO), cardioembolism (CE), and others in the present study. The decision to prescribe SGLT2i to diabetic patients with stroke was at the physician's discretion. Data on the type, prescription duration during admission, pre-stroke prescription, and prescription of SGLT2i at discharge were obtained for the SGLT2i group. Pre-stroke and discharge prescription data for antidiabetic medications other than SGLT2i were also collected. Data on early neurological deterioration (END) during admission, NIHSS score at discharge, and mRS scores at discharge and at 3 months were collected as clinical outcomes. END was defined as either a ≥2-point increase in the total NIHSS score or a ≥1-point increase in the motor item scores during admission. Favorable and excellent outcomes were defined as mRS scores of 0–2 and 0–1, respectively.

For the FDG-PET cohort, we collected data on age, sex, HbA1c levels, eGFR, and fluorodeoxyglucose (FDG) uptake values represented as the target-to-background ratio (TBR) from various regions, including the brain amygdala, internal carotid arteries, bone marrow, psoas muscles, spleen, liver, visceral adipose tissue, brown adipose tissue, and subcutaneous adipose tissue. The peak standardized uptake value (SUV) was measured for distal and proximal internal carotid arteries, whereas the mean SUV was calculated for the remaining regions of interest as described previously.[3,4] The TBR was calculated by dividing the SUV for each area by the blood-pool SUV at the superior vena cava and right atrium.

Statistical analysis

Continuous variables were compared using Student's t-test or the Mann–Whitney U test, as appropriate. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Propensity score matching was performed to mitigate the effects of potential confounding factors. Eligible patients with and without SGLT2i use at admission were subjected to 1:4 propensity score matching using the nearest neighborhood method. Age, sex, hypertension, hyperlipidemia, atrial fibrillation, coronary heart disease, heart failure, active cancer, HbA1c (<7.0% or ≥7.0%), eGFR (≥60, 30–59, 15–29, or <15 mL/min/1.73 m^2), intracranial atherosclerosis, total SVD score, pre-stroke statin use, pre-stroke mRS, initial NIHSS score, intravenous thrombolysis, endovascular thrombectomy, and stroke etiology were used in a logistic regression model for calculating propensity scores. Following propensity score matching, the balance between the two groups was assessed with the standardized mean difference and ratio of variance, using cutoff values of <0.1 and 0.5–2.0, respectively. The main analysis excluded patients prescribed SGLT2i at admission, but not at discharge,

from propensity score matching to account for the potentially diminished impact of transient SGLT2i use on functional outcomes assessed at 3 months. A subsequent sensitivity analysis included all patients prescribed SGLT2i at admission, regardless of their discharge prescription. Binary logistic regression analyses were conducted to examine the relationship between SGLT2i use and clinical outcomes, including the occurrence of END, favorable and excellent outcomes at discharge, and at 3 months. The correlations between SGLT2i use and discharge NIHSS and discharge/3-month mRS scores were assessed using linear and ordinal logistic regression analyses, respectively. Subgroup analysis was performed using a multiplicative interaction term to investigate whether the effect of SGLT2i on outcomes varied according to clinical factors including age, sex, premorbid glycemic control (HbA1c), kidney function (eGFR), intracranial atherosclerosis, total SVD score, neurological severity (initial NIHSS score), stroke etiology, and END occurrence. FDG metabolism was exploratorily compared in various regions in a small number of patients who participated in the FDG-PET study using Student's t-test or one-way analysis of variance, as appropriate. Two-sided probability values <0.05 were considered statistically significant. Statistical analyses were performed using R (v4.1.3, R Foundation, Vienna, Austria).

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https://doi.org/10.5853/jos.2023.04056

Supplementary Table 1. Balance before and after propensity score matching for the main analysis

	Original dataset				Matched dataset			
	Mean control	Mean SGLT2i use	SMD	RV	Mean control	Mean SGLT2i use	SMD	RV
Propensity score	0.0838	0.1870	0.8134	2.1359	0.1708	0.1721	0.0104	1.0286
Age (yr)	70.6978	66.5676	-0.3565	1.1724	66.7488	67.4507	0.0606	0.9414
Male sex	0.6212	0.6622	0.0867	-	0.6667	0.6479	-0.0397	-
Hypertension	0.8148	0.8514	0.1029	-	0.8592	0.8451	-0.0396	-
Hyperlipidemia	0.6978	0.7973	0.2476	-	0.7676	0.7887	0.0526	-
Ever smoking	0.3245	0.4459	0.2443	-	0.4237	0.4225	-0.0024	-
Stroke history	0.2786	0.3378	0.1253	-	0.3134	0.3380	0.0521	-
Atrial fibrillation	0.2019	0.1892	-0.0326	-	0.1702	0.1972	0.0689	-
Coronary heart disease	0.1838	0.2838	0.2217	-	0.2711	0.2676	-0.0078	-
Heart failure	0.0877	0.1486	0.1712	-	0.1150	0.1268	0.0330	-
Active cancer	0.1323	0.0000	-0.4072	-	0.0000	0.0000	0.0000	-
HbA1c category (%)								
<7.0	0.5028	0.2297	-0.6491	-	0.2359	0.2394	0.0084	-
≥7.0	0.4972	0.7703	0.6491	-	0.7641	0.7606	-0.0084	-
eGFR category (mL/min/1.73 m^2)								
≥60	0.7159	0.7432	0.0626	-	0.7383	0.7324	-0.0134	-
30–59	0.2159	0.2162	0.0008	-	0.2230	0.2254	0.0057	-
15–29	0.0265	0.0405	0.0714	-	0.0387	0.0423	0.0179	-
<15	0.0418	0.0000	-0.2189	-	0.0000	0.0000	0.0000	-
Intracranial atherosclerosis	0.4958	0.5135	0.0354	-	0.5117	0.5352	0.0470	-
Total SVD score	2.3036	2.0676	-0.1792	1.0283	2.1491	2.0986	-0.0383	1.0491
Prestroke statin use	0.4944	0.6757	0.3872	-	0.6326	0.6620	0.0627	-
Prestroke mRS	0.5111	0.4054	-0.1306	0.6253	0.3779	0.4085	0.0377	1.0463
Initial NIHSS	5.1058	4.3378	-0.1511	0.7361	4.5540	4.4366	-0.0231	1.0692
Intravenous thrombolysis	0.0696	0.0405	-0.1475	-	0.0387	0.0423	0.0179	-
Endovascular thrombectomy	0.0752	0.0405	-0.1758	-	0.0364	0.0423	0.0298	-
Stroke etiology								
LAA	0.3691	0.4595	0.1814	-	0.4765	0.4789	0.0047	-
SVO	0.2089	0.2162	0.0177	-	0.2277	0.2113	-0.0399	-
CE	0.2006	0.2027	0.0053	-	0.1937	0.1972	0.0088	-
Others	0.2214	0.1216	-0.3054	-	0.1021	0.1127	0.0323	-

SGLT2i, sodium-glucose cotransporter 2 inhibitor; SMD, standardized mean difference; RV, ratio of variance; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; SVD, small vessel disease; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; LAA, large artery atherosclerosis; SVO, small vessel occlusion; CE, cardioembolism.

Supplementary Table 2. Summary of antidiabetic medication prescription other than SGLT2i

	No SGLT2i (n=259)	SGLT2i (n=71)	*P*
Prestroke antidiabetic medication			
Metformin	139 (53.7)	50 (70.4)	0.017
Sulfonylurea	65 (25.1)	32 (45.1)	0.002
DPP4 inhibitor	108 (41.7)	23 (32.4)	0.200
Thiazolidinedione	9 (3.5)	3 (4.2)	0.726
Insulin	39 (15.1)	6 (8.5)	0.214
Others	4 (1.5)	1 (1.4)	>0.999
Discharge antidiabetic medication			
Metformin	194 (74.9)	61 (85.9)	0.072
Sulfonylurea	73 (28.2)	25 (35.2)	0.317
DPP4 inhibitor	143 (55.2)	2 (2.8)	<0.001
Thiazolidinedione	12 (4.6)	2 (2.8)	0.742
Insulin	53 (20.5)	9 (12.7)	0.188
Others	1 (0.4)	1 (1.4)	0.385

The data are presented as n (%).
SGLT2i, sodium-glucose cotransporter 2 inhibitor; DPP4, dipeptidyl-peptidase 4.

Supplementary Table 3. Clinical characteristics and outcomes according to the prescription timing of SGLT2i

	SGLT2i use after stroke (n=39)	SGLT2i use before stroke (n=32)	*P*
Age (yr)	66.1±12.2	69.1±8.8	0.248
Male sex	29 (74.4)	17 (53.1)	0.106
Hypertension	33 (84.6)	27 (84.4)	>0.999
Hyperlipidemia	29 (74.4)	27 (84.4)	0.461
Ever smoking	21 (53.8)	9 (28.1)	0.052
Stroke history	12 (30.8)	12 (37.5)	0.731
Atrial fibrillation	6 (15.4)	8 (25.0)	0.476
Coronary heart disease	5 (12.8)	14 (43.8)	0.008
Heart failure	2 (5.1)	7 (21.9)	0.080
HbA1c (%)	7.8 [7.3; 9.7]	7.6 [6.9; 8.1]	0.147
eGFR (mL/min/1.73 m^2)	80.4 [62.8; 91.1]	71.2 [56.8; 84.3]	0.165
Intracranial atherosclerosis	20 (51.3)	18 (56.3)	0.858
Total SVD score	2 [1; 3]	2 [1.5; 3]	0.114
Prestroke statin use	20 (51.3)	27 (84.4)	0.007
Prestroke mRS	0 [0; 0.5]	0 [0; 1]	>0.999
Initial NIHSS	3 [2; 6]	3 [1; 4]	0.616
Intravenous thrombolysis	3 (7.7)	0 (0.0)	0.312
Endovascular thrombectomy	2 (5.1)	1 (3.1)	>0.999
Stroke etiology			0.390
LAA	18 (46.2)	16 (50.0)	
SVO	11 (28.2)	4 (12.5)	
CE	6 (15.4)	8 (25.0)	
Others	4 (10.3)	4 (12.5)	
END	5 (12.8)	1 (3.1)	0.302
NIHSS at discharge	2 [1; 3.5]	2 [0.5; 3]	0.660
mRS at discharge	2 [1; 3]	1 [1; 2.5]	0.355
Favorable outcome at discharge	26 (66.7)	24 (75.0)	0.614
Excellent outcome at discharge	18 (46.2)	18 (56.3)	0.543
mRS at 3 months	1 [0; 2.5]	1 [0; 2]	0.823
Favorable outcome at 3 months	29 (74.4)	25 (78.1)	0.928
Excellent outcome at 3 months	26 (66.7)	20 (62.5)	0.908

The data are presented as n (%), mean±standard deviation, or median [interquartile range].
SGLT2i, sodium-glucose cotransporter 2 inhibitor; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; SVD, small vessel disease; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; LAA, large artery atherosclerosis; SVO, small vessel occlusion; CE, cardioembolism; END, early neurological deterioration.

https://doi.org/10.5853/jos.2023.04056

Supplementary Table 4. Clinical characteristics and outcomes according to the SGLT2i prescription continuation at discharge

	SGLT2i withdrawal at discharge (n=14)	SGLT2i maintained at discharge (n=74)	*P*
Age (yr)	66.2±12.8	66.6±11.6	0.918
Male sex	8 (57.1)	49 (66.2)	0.729
Hypertension	13 (92.9)	63 (85.1)	0.728
Hyperlipidemia	13 (92.9)	59 (79.7)	0.430
Ever smoking	3 (21.4)	33 (44.6)	0.187
Stroke history	0 (0.0)	25 (33.8)	0.025
Atrial fibrillation	3 (21.4)	14 (18.9)	>0.999
Coronary heart disease	2 (14.3)	21 (28.4)	0.442
Heart failure	2 (14.3)	11 (14.9)	>0.999
HbA1c (%)	8.0 [7.0; 8.8]	7.8 [7.1; 9.1]	0.995
eGFR (mL/min/1.73 m^2)	75.1±25.9	74.6±19.1	0.936
Intracranial atherosclerosis	8 (57.1)	38 (51.4)	0.916
Total SVD score	1 [1; 3]	2 [1; 3]	0.197
Prestroke statin use	8 (57.1)	50 (67.6)	0.655
Prestroke mRS	0 [0; 0]	0 [0; 1]	0.281
Initial NIHSS	5.5 [2; 14]	3 [1; 5]	0.182
Intravenous thrombolysis	2 (14.3)	3 (4.1)	0.375
Endovascular thrombectomy	5 (35.7)	3 (4.1)	0.001
Stroke etiology			0.940
LAA	7 (50.0)	34 (45.9)	
SVO	2 (14.3)	16 (21.6)	
CE	3 (21.4)	15 (20.3)	
Others	2 (14.3)	9 (12.2)	
END	3 (21.4)	6 (8.1)	0.304
NIHSS at discharge	5 [2; 11]	2 [0; 3]	0.014
mRS at discharge	3.5 [1; 5]	1 [1; 3]	0.042
Favorable outcome at discharge	6 (42.9)	53 (71.6)	0.074
Excellent outcome at discharge	5 (35.7)	39 (52.7)	0.382
mRS at 3 months	4 [0; 5]	1 [0; 2]	0.006
Favorable outcome at 3 months	5 (35.7)	57 (77.0)	0.005
Excellent outcome at 3 months	4 (28.6)	49 (66.2)	0.019

The data are presented as n (%), mean±standard deviation, or median [interquartile range].
SGLT2i, sodium-glucose cotransporter 2 inhibitor; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; SVD, small vessel disease; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; LAA, large artery atherosclerosis; SVO, small vessel occlusion; CE, cardioembolism; END, early neurological deterioration.

Supplementary Table 5. Balance after propensity score matching for the sensitivity analysis

	Mean control (n=288)	Mean SGLT2i (n=83)	SMD	RV
Propensity score	0.1907	0.1916	0.0070	1.0197
Age (yr)	67.3916	67.1928	-0.0170	1.0714
Male sex	0.6667	0.6506	-0.0336	-
Hypertension	0.8705	0.8554	-0.0439	-
Hyperlipidemia	0.7871	0.8072	0.0521	-
Ever smoking	0.3976	0.4096	0.0245	-
Stroke history	0.2821	0.3012	0.0423	-
Atrial fibrillation	0.1928	0.1807	-0.0305	-
Coronary heart disease	0.2610	0.2530	-0.0183	-
Heart failure	0.1265	0.1205	-0.0170	-
Active cancer	0.0000	0.0000	0.0000	-
HbA1c category (%)				
<7.0	0.2440	0.2410	-0.0072	-
≥7.0	0.7560	0.7590	0.0072	-
eGFR category (mL/min/1.73 m^2)				
≥60	0.7420	0.7590	0.0400	-
30–59	0.1888	0.1928	0.0104	-
15–29	0.0693	0.0482	-0.0911	-
<15	0.0000	0.0000	0.0000	-
Intracranial atherosclerosis	0.4940	0.5181	0.0482	-
Total SVD score	2.1084	2.0723	-0.0274	1.0818
Prestroke statin use	0.6466	0.6506	0.0085	-
Prestroke mRS	0.3745	0.3614	-0.0172	0.8701
Initial NIHSS	5.0070	4.6265	-0.0703	0.9462
Intravenous thrombolysis	0.0763	0.0602	-0.0694	-
Endovascular thrombectomy	0.0924	0.0964	0.0140	-
Stroke etiology				
LAA	0.4428	0.4819	0.0785	-
SVO	0.2239	0.2048	-0.0473	-
CE	0.1918	0.1807	-0.0274	-
Others	0.1416	0.1325	-0.0273	-

SGLT2i, sodium-glucose cotransporter 2 inhibitor; SMD, standardized mean difference; RV, ratio of variance; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; SVD, small vessel disease; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; LAA, large artery atherosclerosis; SVO, small vessel occlusion; CE, cardioembolism.

Supplementary Table 6. Clinical outcomes according to the SGLT2i use during admission in patients with ischemic stroke

	No SGLT2i (n=288)	SGLT2i (n=83)	OR (95% CI) or β (SE)	*P*
END	28 (9.7)	8 (9.6)	0.99 (0.43–2.26)	0.982
NIHSS at discharge	2 [1; 5]	2 [1; 3.5]	-0.565 (0.946)*	0.551
mRS at discharge	2 [1; 3]	1 [1; 3]	1.30 (0.84–2.03)†	0.237
Favorable outcome at discharge	187 (64.9)	57 (68.7)	1.18 (0.70–2.00)	0.527
Excellent outcome at discharge	128 (44.4)	42 (50.6)	1.28 (0.79–2.09)	0.322
mRS at 3 months	2 [0; 3]	1 [0; 3]	1.54 (0.99–2.40)†	0.055
Favorable outcome at 3 months	188 (65.3)	60 (72.3)	1.39 (0.81–2.38)	0.233
Excellent outcome at 3 months	141 (49.0)	51 (61.4)	1.66 (1.01–2.74)	0.046

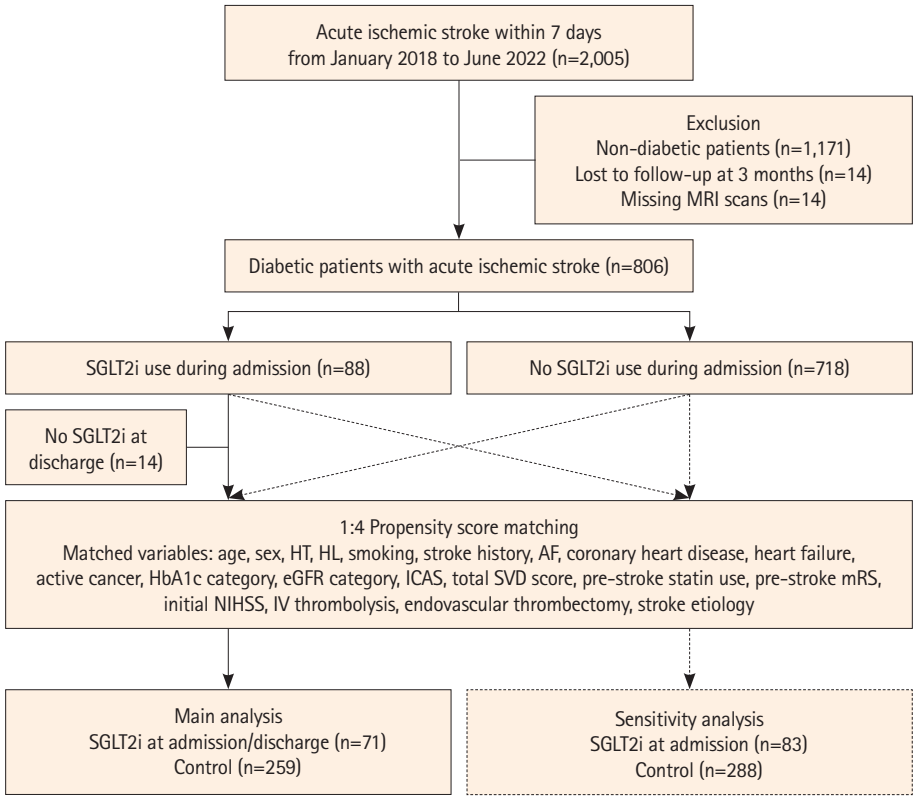
The data are presented as n (%) or median [interquartile range].
SGLT2i, sodium-glucose cotransporter 2 inhibitor; OR, odds ratio; CI, confidence interval; β, unstandardized coefficient; SE, standard error; END, early neurological deterioration; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale.
*Unstandardized coefficient and standard error by linear regression; †Proportional odds ratios for favorable mRS scores by ordinal logistic regression.

Supplementary Table 7. Comparison of FDG uptake in various regions according to SGLT2i use during the acute phase in patients with ischemic stroke

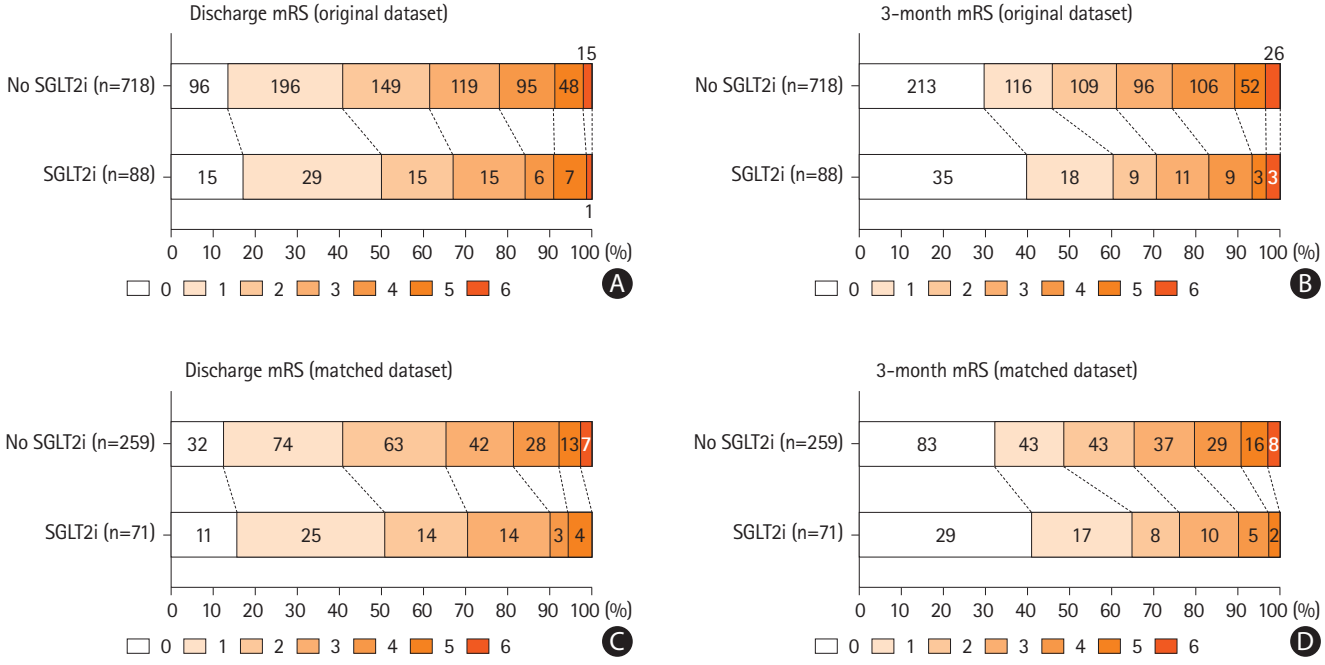
	Nondiabetic control (n=26)	Diabetic patients without SGLT2i (n=8)	Diabetic patients with SGLT2i (n=6)	*P*
Age (yr)	61.2±15.2	70.1±11.1	67.5±10.0	0.239
Male sex	13 (50.0)	7 (87.5)	4 (66.7)	0.153
HbA1c (%)	5.75±0.39	7.11±0.62	7.43±0.71	<0.001
eGFR (mL/min/1.73 m^2)	86.7±17.8	76.6±21.5	83.4±20.4	0.423
FDG uptake (TBR)				
Amygdala	3.55±0.84	2.95±0.58	2.96±0.72	0.089
Distal ICA	1.02±0.13	0.95±0.15	1.01±0.10	0.437
Proximal ICA	1.12±0.12	1.08±0.09	1.13±0.09	0.604
Spleen	1.18±0.23	1.06±0.11	1.12±0.07	0.307
Liver	1.00±0.10	0.94±0.15	0.99±0.07	0.300
Bone marrow	1.20±0.89	0.86±0.17	0.92±0.08	0.434
Psoas muscle	0.37±0.06	0.33±0.13	0.43±0.11	0.110
Visceral adipose tissue	0.22±0.07	0.18±0.06	0.17±0.04	0.110
Brown adipose tissue	0.25±0.06	0.20±0.03	0.25±0.03	0.044
Subcutaneous adipose tissue	0.13±0.05	0.10±0.02	0.15±0.03	0.109

The data are presented as n (%) or mean±standard deviation.
FDG, fluorodeoxyglucose; SGLT2i, sodium-glucose cotransporter 2 inhibitor; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; TBR, target-to-background ratio; ICA, internal carotid artery.

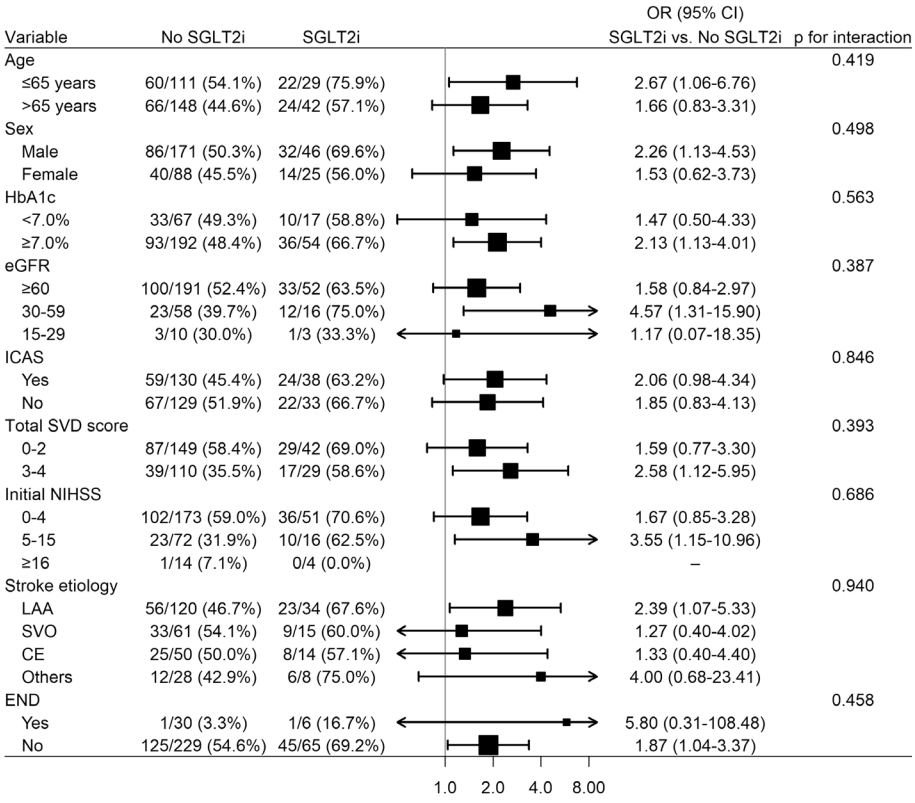
https://doi.org/10.5853/jos.2023.04056



Supplementary Figure 1. Flowchart of patient inclusion and exclusion. MRI, magnetic resonance imaging; SGLT2i, sodium-glucose cotransporter 2 inhibitor; HT, hypertension; HL, hyperlipidemia; AF, atrial fibrillation; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; ICAS, intracranial atherosclerosis; SVD, small vessel disease; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; IV, intravenous.



Supplementary Figure 2. Functional outcome at discharge and at 3 months based on the use of SGLT2i during admission before and after propensity score matching. Distribution of mRS scores at discharge and at 3 months based on SGLT2i use for (A and B) the original dataset and (C and D) the propensity score-matched dataset. mRS, modified Rankin Scale; SGLT2i, sodium-glucose cotransporter 2 inhibitor.



Supplementary Figure 3. Odds of excellent outcome at 3 months stratified by clinical factors. Forest plot illustrating the ORs and 95% CIs for the association between SGLT2i use and 3-month excellent outcome. The strata included age, sex, glycemic control, renal function, intracranial atherosclerosis, total SVD score, neurological severity, stroke etiology, and END. ORs were calculated from binary logistic regression analysis with multiplicative interaction terms on propensity score-matched data and plotted on the x-axis on a log scale. SGLT2i, sodium-glucose cotransporter 2 inhibitor; OR, odds ratio; CI, confidence interval; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; ICAS, intracranial atherosclerosis; SVD, small vessel disease; NIHSS, National Institutes of Health Stroke Scale; LAA, large artery atherosclerosis; SVO, small vessel occlusion; CE, cardioembolism; END, early neurological deterioration.

https://doi.org/10.5853/jos.2023.04056