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).

Supplementary References

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