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Injectable Non-Insulin Antidiabetic Therapy and Aspiration Pneumonia in Adults With Type 2 Diabetes Hospitalized for Acute Ischemic Stroke: A Nationwide Inpatient Sample Analysis, 2022–2023

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Abstract

Purpose: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) delay gastric emptying, raising concern that they may compound post-stroke dysphagia and increase aspiration risk. We examined whether coded long-term use of injectable non-insulin antidiabetic drugs was associated with aspiration pneumonia among adults with type 2 diabetes hospitalized for acute ischemic stroke.

Methods: We analyzed the 2022–2023 National Inpatient Sample. Adults with a principal diagnosis of ischemic stroke and type 2 diabetes were grouped hierarchically by medication-use codes. The primary comparison was injectable non-insulin therapy (Z79.85) versus oral antidiabetic therapy (Z79.84); the primary outcome was aspiration pneumonia (J69.0). Survey-weighted multivariable regression, propensity-score matching, inverse probability weighting, alternative comparators, a negative-control outcome and sensitivity analyses were performed.

Results: Among 84,860 diabetic stroke hospitalizations (weighted 424,300), 1,295 were Z79.85-coded and 27,776 Z79.84-coded. Aspiration pneumonia occurred in 1.0% versus 2.1% (unadjusted odds ratio [OR] 0.48, 95% confidence interval [CI] 0.28–0.82). The association attenuated after full adjustment (adjusted OR [aOR] 0.59, 95% CI 0.33–1.03; p = 0.064), matching (conditional OR 0.62, 95% CI 0.31–1.24) and weighting (OR 0.76, 95% CI 0.26–2.18). Upper confidence limits across active-comparator analyses ranged from 1.00 to 1.13. Adjusted odds of dysphagia (aOR 0.81, 95% CI 0.67–0.98) and in-hospital death (aOR 0.44, 95% CI 0.20–0.94) were lower, but estimates strengthened against non-active comparators, consistent with residual confounding.

Conclusion: Coded use of injectable non-insulin antidiabetic drugs, predominantly GLP-1 RAs, was not associated with increased aspiration pneumonia after acute ischemic stroke. Apparently favorable associations likely reflect healthy-user bias rather than protection.

Keywords: Acute ischemic stroke; Aspiration pneumonia; Glucagon-like peptide-1 receptor agonists; Type 2 diabetes mellitus; Dysphagia; National Inpatient Sample

1 Introduction

Acute ischemic stroke (AIS) remains a major cause of mortality and morbidity worldwide, often leaving patients with substantial neurological impairments and major complications [1]. Although a stroke is multifactorial in origin, diabetes mellitus remains a significant modifiable risk factor associated with its development [2]. Diabetes does not only predispose individuals to stroke but also influence the stroke severity, trajectory of recovery and development of serious complications, including aspiration. Therefore, prioritizing the management of stroke among individuals with diabetes is crucial for enhancing patient outcome and reducing complications, particularly to mitigate the broader public health burden associated with diabetes.

Among available diabetes pharmacological therapies, injectable non-insulin anti-diabetic drugs, particularly, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have demonstrated benefits beyond glycemic control. Studies have consistently demonstrated the beneficial cardiovascular effects of GLP-1 RAs, as well as their neuroprotective effects in neurodegenerative diseases and cerebrovascular diseases, specifically stroke [3, 4].

The major mechanism of action of GLP-1 RAs includes improved post-prandial glucose control [5], achieved partly through delayed gastric emptying [6]. As extensive data have shown that stroke patients are already at risk of developing aspiration, this delayed gastric emptying theoretically increases the risk of aspiration pneumonia, which is a serious, potentially life-threatening complication [6]. Aspiration pneumonia complicates the recovery and prolongs the hospitalization in stroke patients, becoming one of the major causes of morbidity and mortality in these patients [7]. Despite the plausible biological link, the association between prolonged

exposure of GLP-1 RAs and other injectable non insulin antidiabetics agents with comparable mode of action and the risk of aspiration pneumonia remains inadequately explored.

In addition to the risk of aspiration pneumonia, several other clinically relevant outcomes should be evaluated. The National Institutes of Health Stroke Scale (NIHSS) is widely used to assess stroke severity [8], which influences the need for therapeutic interventions, advanced supportive care, as well as overall patient prognosis. Evaluating the relationship between the prior use of these drugs and stroke severity may provide insight into their potential neuroprotective or detrimental effects. In-hospital mortality and the need for percutaneous endoscopic gastrostomy (PEG) placement serve as important indicators of stroke prognosis and feeding-related complications, respectively [9]. Furthermore, reperfusion therapies carry a risk of hemorrhagic complications, including intracerebral hemorrhage (ICH), making the association between antidiabetic therapies and bleeding risk clinically relevant [10]. The patient's clinical status at discharge also provides an insight into functional recovery and post stroke care needs.

This study aims to address the knowledge gap using a nationally representative patient database spanning from 2022 to 2023, to investigate the association between long-term use of injectable non-insulin anti-diabetic drugs, primarily GLP-1 RAs and the key clinical outcomes among diabetic adults hospitalized due to acute ischemic stroke. Our primary focus is on aspiration pneumonia, a potentially life-threatening complication related to drug induced gastric motility changes combined with a stroke-induced dysphagia. Secondary endpoints include dysphagia, stroke severity (NIHSS), in-hospital mortality, PEG placement, mechanical ventilation, reperfusion-related ICH, discharge disposition, length of stay and hospital charges.

By exploring these associations this study seeks to provide further insight into the potential risk and safety profile of these antidiabetic therapies among patients with acute

ischemic stroke. Identifying drug specific associations with clinical outcomes may help to facilitate individualized risk stratification and improve patient outcomes.

2 Methods

2.1 Study design and data source

We conducted a retrospective cross-sectional study comparing in-hospital aspiration pneumonia between hospitalizations with coded injectable non-insulin antidiabetic therapy and those with coded oral antidiabetic therapy among adults with type 2 diabetes mellitus (type 2 DM) hospitalized with acute ischemic stroke in the United States in 2022–2023. Data were obtained from the National Inpatient Sample (NIS), part of the Healthcare Cost and Utilization Project (HCUP) family of databases [11]. The NIS is an approximately 20% stratified sample of all discharges from US community hospitals, excluding rehabilitation and long-term acute care hospitals, and contains approximately 7 million unweighted (35 million weighted) hospital stays each year. Since October 2015, diagnoses and procedures in the NIS have been coded with the International Classification of Diseases, Tenth Revision, Clinical Modification and Procedure Coding System (ICD-10-CM/PCS).

2.2 Ethics statement

The NIS contains de-identified data and protects the privacy of patients, physicians and hospitals. Because the data are de-identified and publicly available, institutional review board approval and informed consent were not required. The data were obtained under license from HCUP, and the study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline [12]. In accordance with the HCUP Data Use Agreement, no cell based on 10 or fewer unweighted discharges is reported.

2.3 Study population

We identified hospitalizations of adults aged 18 years or older with a principal diagnosis of acute ischemic stroke (ICD-10-CM I63.x) and coexisting type 2 DM (E11.x in any diagnosis field). Hospitalizations were divided into mutually exclusive groups according to antidiabetic medication-use codes: Z79.85 (long-term use of injectable non-insulin antidiabetic drugs), regardless of concurrent insulin or oral antidiabetic codes; Z79.84 (long-term use of oral antidiabetic drugs) without Z79.85; Z79.4 (long-term use of insulin) without Z79.85 or Z79.84; and no antidiabetic medication-use code.

The primary analysis compared Z79.85-coded hospitalizations with Z79.84-coded hospitalizations without Z79.85. The Z79.85 group was also compared with the insulin-only group, the group without antidiabetic medication-use codes and all other eligible diabetic stroke hospitalizations. Because the NIS is a discharge-level database, the hospitalization rather than the individual was the unit of analysis.

Elective admissions, hospitalizations with missing data on age, sex, in-hospital mortality, length of stay or survey weight, and hospitalizations with type 1 diabetes mellitus (E10.x) were excluded. Hospitalizations with type 1 diabetes were added back in a sensitivity analysis. All diagnosis and procedure codes are listed in Online Resource 1, Table S1.

2.4 Outcomes

The primary outcome was aspiration pneumonia (ICD-10-CM J69.0).

Secondary outcomes were dysphagia (R13.1x), gastrostomy (PEG), in-hospital mortality, invasive mechanical ventilation, intracranial hemorrhage (I61.x or I62.x) among patients who received intravenous thrombolysis or endovascular thrombectomy, other pneumonia (J12–

J18), stroke severity (NIHSS ≥16, derived from ICD-10-CM codes R29.700–R29.742), length of stay, discharge disposition and total hospital charges. Hip fracture (S72.0–S72.2) was evaluated as a negative-control outcome that should be unrelated to the exposure.

2.5 Statistical analysis

All analyses were performed in Stata version 17 (StataCorp LLC, College Station, TX, USA) with survey procedures that account for the NIS sampling weights, clustering by hospital and stratification. Because hospital and stratum identifiers are defined within each data year, year-specific clusters and strata were used for the pooled data, and all estimates were obtained by subpopulation analysis, in accordance with established methodological standards [11–13]. Categorical variables are reported as weighted counts and percentages and were compared with the Rao-Scott design-adjusted chi-square test; continuous variables are reported as weighted means with standard deviations (and medians with interquartile ranges for skewed variables) and were compared with survey-weighted linear regression. Standardized mean differences (SMDs) were used to assess balance, with an absolute SMD below 0.1 indicating adequate balance. Comorbidity was captured with the 31 Elixhauser comorbidities (Quan ICD-10 algorithm) and summarized with the van Walraven composite score.

The association between Z79.85 and each outcome, relative to Z79.84, was estimated with survey-weighted logistic regression in three sequential models: M1, unadjusted; M2, adjusted for age, sex, primary payer, median household income quartile, weekend admission, hospital bed size, hospital location and teaching status, and calendar

year; and M3 (primary model), which additionally included NIHSS band (with uncoded NIHSS as a separate category), body mass index category, van Walraven score and complicated diabetes. Race and hospital region were not included because they are not available in the 2023 NIS. Length of stay was modeled with negative binomial regression, total charges with a gamma generalized linear model with a log link, admission NIHSS score with linear regression (without NIHSS band as a covariate) and discharge disposition among survivors with multinomial logistic regression, using routine home discharge as the reference. Effect modification was examined with exposure-by-subgroup interaction terms for NIHSS band, age (≥65 vs <65 years), sex, obesity coding and reperfusion therapy.

Robustness was assessed in several ways. First, 1:1 nearest-neighbor propensity-score matching without replacement was performed with a caliper of 0.2 standard deviations of the logit of the propensity score, which was estimated from demographic, socioeconomic, hospital and calendar-year variables, NIHSS band, body mass index category and the 31 Elixhauser comorbidities; matched outcomes were compared with conditional logistic regression and McNemar tests (binary outcomes) or paired t and Wilcoxon signed-rank tests (continuous outcomes). Second, inverse probability of treatment weighting with stabilized weights was combined with the survey weights. Third, the Z79.85 group was compared with three alternative, non-active comparator groups. Fourth, sensitivity analyses excluded hospitalizations with concurrent insulin coding, added hospitalizations with type 1 diabetes, excluded transfers, were

restricted to 2023 and to NIHSS-coded records, added reperfusion therapy as covariates, replaced the composite score with individual Elixhauser comorbidities, broadened the outcome to any pneumonia and trimmed the propensity score to 0.05–0.95 before re-matching. Finally, an E-value was calculated to quantify the strength of unmeasured confounding needed to explain the primary estimate.

Results are reported as odds ratios (ORs) with 95% confidence intervals (CIs). Two-sided p values below 0.05 were considered statistically significant. Secondary outcomes were not adjusted for multiple comparisons.

3 Results

3.1 Study Population, Cohort Selection, and Baseline Characteristics

A total of 13,322,088 unweighted hospital discharges (weighted national estimate, 66,610,434) were identified in the National Inpatient Sample (NIS) from 2022–2023. After restricting the cohort to adults aged 18 years or older, 11,331,434 discharges remained. Among these, 219,825 hospitalizations had a principal diagnosis of ischemic stroke (ICD-10-CM I63.x), and 86,823 also had type 2 diabetes (E11.x in any diagnosis field). After excluding elective admissions, 84,926 hospitalizations remained; after excluding records with missing age, sex, mortality, length of stay, or survey weight, 84,877 remained; and after excluding type 1 diabetes (E10.x), the final cohort comprised 84,860 diabetic stroke hospitalizations, representing an estimated 424,300 hospitalizations nationally (Fig. 1). The ICD-10 codes used are listed in Online Resource 1, Table S1.

Hospitalizations were assigned to mutually exclusive groups using the hierarchy Z79.85 > Z79.84 > Z79.4. The cohort comprised 1,295 hospitalizations with a code for long-term use of

injectable non-insulin antidiabetic drugs (Z79.85; weighted estimate, 6,475), 27,776 with an oral hypoglycemic code (Z79.84) without Z79.85 (138,880), 16,364 with an insulin-only code (Z79.4; 81,820), and 39,425 with no antidiabetic drug code (197,125). The primary comparison included the 1,295 Z79.85 hospitalizations and the 27,776 Z79.84 hospitalizations without Z79.85 (29,071 in total). Z79.85 was coded in 106 hospitalizations in 2022 and 1,189 in 2023 (unweighted counts), corresponding to 0.25% and 2.76% of diabetic stroke hospitalizations, respectively (survey-weighted percentages) (Online Resource 1, Table S2).

Z79.85-coded hospitalizations involved younger patients than Z79.84-coded hospitalizations (mean age, 65.9 ± 11.7 vs 69.3 ± 11.8 years; $p < 0.001$), and 12.0% versus 21.3% were aged 80 years or older. Women accounted for 50.3% and 43.9% of the respective groups ($p < 0.001$). Medicare was the primary payer for 54.4% versus 62.2%, and private insurance for 28.6% versus 19.8% (overall $p < 0.001$). Most Z79.85 hospitalizations occurred in 2023 (91.8%, compared with 51.9% of Z79.84 hospitalizations; $p < 0.001$). Concurrent insulin coding (Z79.4) was more frequent in the Z79.85 group (46.3% vs 24.2%; $p < 0.001$), as were obesity (E66 or Z68.3x–Z68.4x; 35.4% vs 25.2%; $p < 0.001$) and complicated diabetes (67.6% vs 59.4%; $p < 0.001$). Stroke severity coded by the National Institutes of Health Stroke Scale (NIHSS) was lower in the Z79.85 group: 54.1% versus 45.7% had an NIHSS of 0–4, NIHSS was not coded in 22.2% versus 27.2% (overall $p < 0.001$), and the mean NIHSS among coded records was 4.4 ± 5.6 versus 5.1 ± 6.0 ($p < 0.001$). The proportions receiving intravenous thrombolysis (9.7% vs 8.3%; $p = 0.074$) and endovascular thrombectomy (1.9% vs 2.2%; $p = 0.509$) were similar. The mean Elixhauser comorbidity score was 9.0 ± 8.1 versus 9.8 ± 8.3 ($p < 0.001$).

Online Resource 1, Table S3 summarizes the baseline characteristics of the primary comparison groups.

3.2 Primary Outcome: Aspiration Pneumonia

Aspiration pneumonia (ICD-10-CM J69.0) was the primary outcome. In the unadjusted analysis, aspiration pneumonia was recorded in 1.0% of hospitalizations in the Z79.85 group compared with 2.1% in the Z79.84 group (p = 0.006; standardized mean difference [SMD] = −0.088) (Online Resource 1, Table S4).

In survey-weighted multivariable logistic regression, the association weakened progressively with additional adjustment (Table 1). The unadjusted model (M1) yielded an odds ratio (OR) of 0.48 (95% CI: 0.28–0.82; p = 0.007), and the model adjusted for demographic, socioeconomic, hospital-level, and calendar-year covariates (M2) yielded an adjusted OR (aOR) of 0.54 (95% CI: 0.31–0.94; p = 0.029). In the primary adjusted model (M3), which additionally included NIHSS band, body mass index category, the van Walraven Elixhauser score, and complicated diabetes, Z79.85 was associated with lower odds of aspiration pneumonia than Z79.84, but the estimate did not reach statistical significance (aOR = 0.59, 95% CI: 0.33–1.03; p = 0.064). When the outcome was broadened to aspiration or other pneumonia, the M3 estimate was likewise nonsignificant (aOR = 0.73, 95% CI: 0.50–1.06; p = 0.101).

In subgroup analyses, no subgroup showed a statistically significant association, and there was no evidence of effect modification by NIHSS band (p for interaction = 0.720), age (p = 0.952), sex (p = 0.761), obesity coding (p = 0.295), or receipt of reperfusion therapy (p = 0.494). The aORs were 0.59 (95% CI: 0.30–1.17) for age ≥65 years and 0.60 (95% CI: 0.22–1.69) for age <65 years; 0.53 (95% CI: 0.22–

1.29) for women and 0.64 (95% CI: 0.31–1.31) for men; 0.31 (95% CI: 0.08–1.26) with an obesity code and 0.72 (95% CI: 0.39–1.33) without; and 0.28 (95% CI: 0.03–2.33) with reperfusion therapy and 0.63 (95% CI: 0.36–1.13) without. By NIHSS band, the aORs were 0.36 (95% CI: 0.09–1.45) for NIHSS 0–4, 0.99 (95% CI: 0.39–2.52) for NIHSS 5–15, 0.65 (95% CI: 0.14–2.95) for NIHSS 21–42, and 0.62 (95% CI: 0.22–1.71) for NIHSS not coded; the NIHSS 16–20 stratum was not estimable. Several subgroup estimates had wide confidence intervals (Fig. 2; Online Resource 1, Table S5).

In exploratory analyses stratified by dysphagia coding and mechanical ventilation, the aORs were 0.54 (95% CI: 0.22–1.37; p = 0.195) with and 0.69 (95% CI: 0.34–1.39; p = 0.300) without a dysphagia code (p for interaction = 0.672), and 0.75 (95% CI: 0.26–2.13; p = 0.583) among ventilated and 0.59 (95% CI: 0.30–1.16; p = 0.128) among non-ventilated hospitalizations (p for interaction = 0.744) (Online Resource 1, Table S6). Dysphagia and ventilation are recorded after admission and may lie on the causal pathway, so these strata are descriptive.

3.3 Secondary Clinical Outcomes

3.3.1 Dysphagia

Dysphagia (R13.1x) was recorded less often in the Z79.85 group than in the Z79.84 group in the unadjusted analysis (8.4% vs 11.1%; p = 0.001). This association remained statistically significant after multivariable adjustment (aOR = 0.81, 95% CI: 0.67–0.98; p = 0.031) (Online Resource 1, Table S4; Table 1).

3.3.2 In-Hospital Mortality

Unadjusted in-hospital mortality was 1.8% in the Z79.84 group (Online Resource 1, Table S4); the corresponding Z79.85 estimate is not reported because it is based on 10 or fewer unweighted events, in accordance with the Healthcare Cost and Utilization Project (HCUP) data use agreement. After multivariable adjustment, Z79.85 was associated with lower odds of in-hospital death (aOR = 0.44, 95% CI: 0.20–0.94; p = 0.033) (Table 1).

3.3.3 Gastrostomy, Mechanical Ventilation, Other Pneumonia, and Intracranial Hemorrhage

Gastrostomy (PEG) was performed in 1.5% of the Z79.85 group and 1.9% of the Z79.84 group (p = 0.376); the adjusted association was not statistically significant (aOR = 0.93, 95% CI: 0.58–1.48; p = 0.764). Invasive mechanical ventilation was recorded in 1.9% versus 2.6% (p = 0.092), with an aOR of 0.80 (95% CI: 0.52–1.23; p = 0.300). Other pneumonia (J12–J18) occurred in 1.6% versus 2.1% (p = 0.238) in the unadjusted analysis. Among hospitalizations that received intravenous thrombolysis or thrombectomy, the adjusted odds of intracranial hemorrhage (I61.x or I62.x in any diagnosis field) did not differ significantly (aOR = 0.76, 95% CI: 0.35–1.64; p = 0.488); the timing of hemorrhage relative to reperfusion could not be determined (Online Resource 1, Table S4; Table 1).

3.3.4 Stroke Severity

Among NIHSS-coded records, severe stroke (NIHSS ≥16) was present in 6.2% of the Z79.85 group and 7.4% of the Z79.84 group (p = 0.186). In models that excluded the NIHSS band, the adjusted odds of severe stroke did not differ significantly (aOR = 0.95, 95% CI: 0.72–1.26; p = 0.745), whereas the adjusted mean NIHSS was 0.50 points lower in

the Z79.85 group (95% CI: −0.85 to −0.16; p = 0.004) (Online Resource 1, Table S4; Table 1).

3.3.5 Discharge Disposition

Among survivors, the distribution of discharge disposition differed between groups in the unadjusted analysis (overall $p < 0.001$). Routine home discharge occurred in 47.8% of the Z79.85 group versus 41.1% of the Z79.84 group, home health care in 15.0% versus 18.2%, discharge to a skilled nursing, intermediate care, or other facility in 34.5% versus 37.4%, transfer to a short-term hospital in 1.1% versus 2.1%, and discharge against medical advice in 1.6% versus 1.2%. Facility or hospital discharge was less frequent in the Z79.85 group (35.6% vs 39.5%; p = 0.006), but this difference was not significant after adjustment (aOR = 0.94, 95% CI: 0.82–1.06; p = 0.313). In the multinomial model with routine home discharge as the reference, the relative risk ratios (RRR) were 0.86 (95% CI: 0.72–1.02; p = 0.080) for home health care, 0.93 (95% CI: 0.81–1.07; p = 0.288) for skilled nursing, intermediate care, or other facility, 0.45 (95% CI: 0.26–0.78; p = 0.004) for transfer to a short-term hospital, and 1.22 (95% CI: 0.77–1.96; p = 0.399) for discharge against medical advice (Online Resource 1, Table S4; Table 1).

3.3.6 Length of Stay and Hospital Charges

The mean length of stay was 4.5 ± 4.5 days in the Z79.85 group and 4.8 ± 5.6 days in the Z79.84 group (p = 0.011); the median was 3 days (interquartile range [IQR], 2–6) in both groups. The adjusted negative binomial model showed a borderline difference that did not reach statistical significance (adjusted incidence rate ratio [aIRR] = 0.95, 95% CI: 0.91–1.00; p = 0.052) (Online Resource 1, Table S4; Table 1).

Total hospital charges were available only for 2022 discharges because total charges were not available in the 2023 NIS file; all charge analyses therefore include 2022 hospitalizations

only (n = 13,330 in the adjusted model). Mean total charges, in US dollars, were $59,145.20 ± $46,390.70 in the Z79.85 group and $76,298.90 ± $83,349.90 in the Z79.84 group ($p < 0.001$); the corresponding medians were $46,886 (IQR, 67,611) and $51,388 (IQR, 90,526). The adjusted charge ratio was 0.80 (95% CI: 0.70–0.91; $p < 0.001$), indicating lower total charges in the Z79.85 group after adjustment (Online Resource 1, Table S4; Table 1).

3.3.7 Negative-Control Outcome

Hip fracture (S72.0–S72.2) was examined as a negative-control outcome that should not be related to the exposure. The adjusted odds were nonsignificant, with a point estimate above 1 and a wide confidence interval (aOR = 3.88, 95% CI: 0.84–17.86; $p = 0.081$) (Table 1). Unadjusted counts are not reported because the Z79.85 cell contains 10 or fewer unweighted events (Online Resource 1, Tables S4 and S7).

The complete adjusted outcome estimates are presented in Table 1. Detailed unadjusted results are provided in Online Resource 1, Table S4, crude outcomes by coded antidiabetic therapy group in Online Resource 1, Table S7, and the full coefficient tables for the primary models in Online Resource 1, Table S8.

3.4 Alternative Comparator Groups

The association between Z79.85 and each outcome was re-estimated using the M3 model against three other comparator groups: insulin only (Z79.4), no antidiabetic drug code, and all other diabetic stroke hospitalizations (Table 2). These groups are not active comparators.

In crude analyses, the weighted percentage with aspiration pneumonia was 1.00% (95% CI: 0.47–1.54) in the Z79.85 group, 2.09% (95% CI: 1.91–2.27) in the Z79.84 group, 3.44% (95% CI: 3.15–3.73) in the insulin-only group, and 5.33% (95% CI: 5.08–5.57) in the group with no antidiabetic drug code (Online Resource 1, Table S7).

Aspiration pneumonia was significantly less likely in the Z79.85 group than in each alternative comparator after adjustment: aOR = 0.43 (95% CI: 0.25–0.76; p = 0.004) versus insulin only, aOR = 0.32 (95% CI: 0.19–0.56; p < 0.001) versus no antidiabetic drug code, and aOR = 0.40 (95% CI: 0.23–0.70; p = 0.001) versus all other diabetic stroke. Dysphagia was likewise less likely (aOR = 0.79, 95% CI: 0.65–0.97; p = 0.027; aOR = 0.71, 95% CI: 0.59–0.86; p < 0.001; and aOR = 0.76, 95% CI: 0.63–0.92; p = 0.005, respectively), as was in-hospital death (aOR = 0.28, 95% CI: 0.13–0.62; p = 0.001; aOR = 0.20, 95% CI: 0.09–0.42; p < 0.001; and aOR = 0.25, 95% CI: 0.12–0.54; p < 0.001, respectively). Gastrostomy did not differ significantly against any comparator (aOR = 0.86, 95% CI: 0.53–1.37; p = 0.518; aOR = 0.66, 95% CI: 0.42–1.04; p = 0.070; and aOR = 0.76, 95% CI: 0.49–1.20; p = 0.245, respectively).

For the hip fracture negative control, the estimates were nonsignificant but above 1 in each comparison (aOR = 1.42, 95% CI: 0.33–6.15; p = 0.636; aOR = 1.70, 95% CI: 0.41–7.14; p = 0.467; and aOR = 2.03, 95% CI: 0.49–8.35; p = 0.326, respectively) (Table 2).

3.5 Propensity-Score Matching and Weighted Analyses

3.5.1 Propensity-Score Matching

One-to-one nearest-neighbor propensity-score matching without replacement produced 1,295 matched pairs. Matching reduced the maximum absolute SMD from 0.990 before matching, which reflected the imbalance in discharge year, to 0.081 after matching, and all covariates had an absolute SMD below 0.1 after matching (Online Resource 1, Table S9 and Fig. S1).

In the matched cohort, aspiration pneumonia occurred in 13 (1.0%) Z79.85 and 21 (1.6%) Z79.84 hospitalizations (conditional OR = 0.62, 95% CI: 0.31–1.24; McNemar p = 0.170), consistent with the

nonsignificant primary adjusted estimate. Aspiration or other pneumonia occurred in 32 (2.5%) versus 48 (3.7%) (conditional OR = 0.66, 95% CI: 0.42–1.04; McNemar p = 0.070). Dysphagia remained less frequent in the Z79.85 group (109 [8.4%] vs 146 [11.3%]; conditional OR = 0.72, 95% CI: 0.56–0.94; McNemar p = 0.015). Gastrostomy (20 [1.5%] vs 31 [2.4%]; conditional OR = 0.65, 95% CI: 0.37–1.13; McNemar p = 0.123) and invasive mechanical ventilation (24 [1.9%] vs 33 [2.5%]; conditional OR = 0.72, 95% CI: 0.42–1.23; McNemar p = 0.225) did not differ significantly. Among pairs with NIHSS coded for both members, severe stroke (NIHSS ≥16) occurred in 63 (6.3%) versus 53 (5.2%) (conditional OR = 1.53, 95% CI: 0.98–2.39; McNemar p = 0.059). The difference in in-hospital death was not statistically significant (McNemar p = 0.127); the event counts are not shown because the Z79.85 cell contains 10 or fewer events. Length of stay (4.5 ± 4.5 vs 4.8 ± 5.3 days; paired t test p = 0.135; Wilcoxon signed-rank p = 0.127) and total hospital charges, available for 2022 only ($59,145.20 ± $46,390.70 vs $65,420.00 ± $48,660.80; paired t test p = 0.279; Wilcoxon signed-rank p = 0.274), did not differ significantly between matched groups (Online Resource 1, Table S10).

3.5.2 Inverse Probability of Treatment Weighting

In the stabilized inverse probability of treatment weighted survey regression, the association between Z79.85 and aspiration pneumonia was nonsignificant (OR = 0.76, 95% CI: 0.26–2.18; p = 0.610), with a wide confidence interval. The maximum absolute SMD after weighting was 0.107, slightly above the conventional 0.10 threshold (Online Resource 1, Table S11).

3.6 Sensitivity Analyses

Sensitivity analyses examined exclusion of hospitalizations with concurrent insulin coding, inclusion of type 1 diabetes, exclusion of transfers, restriction to 2023, restriction to NIHSS-coded records, additional adjustment for reperfusion therapy, individual Elixhauser comorbidities, a broader pneumonia outcome, and alternative propensity-score approaches (Online Resource 1, Table S11).

The estimates were below 1 in every analysis, and none had a p value below 0.05. The association was unchanged when type 1 diabetes was added (aOR = 0.59, 95% CI: 0.33–1.03; p = 0.064) or when intravenous thrombolysis and thrombectomy were added as covariates (aOR = 0.59, 95% CI: 0.34–1.03; p = 0.066). It remained nonsignificant when transfers were excluded (aOR = 0.61, 95% CI: 0.33–1.13; p = 0.116), when analyses were restricted to 2023 (aOR = 0.61, 95% CI: 0.34–1.11; p = 0.104), when restricted to NIHSS-coded records (aOR = 0.56, 95% CI: 0.28–1.12; p = 0.102), and when individual Elixhauser comorbidities replaced the composite score (aOR = 0.61, 95% CI: 0.35–1.08; p = 0.090). Excluding hospitalizations with concurrent insulin coding yielded a lower estimate with the upper confidence limit at the null (aOR = 0.41, 95% CI: 0.17–1.00; p = 0.050). In propensity-score analyses, the conditional logistic regression estimate in the matched cohort was 0.62 (95% CI: 0.31–1.24; p = 0.174), and the estimate after

trimming the propensity score to 0.05–0.95 and re-matching was 0.90 (95% CI: 0.37–2.21; p = 0.819).

The E-value for the primary estimate was 2.79, and the E-value for the confidence limit nearest the null was 1.00 because the 95% CI included the null.

3.7 Temporal Trends in Z79.85 Coding

The NIS 2022–2023 files contain two data years; trends are therefore described by year and by discharge quarter. Z79.85 coding increased from 0.25% of diabetic stroke hospitalizations in 2022 to 2.76% in 2023 (OR for 2023 vs 2022 = 11.20, 95% CI: 9.16–13.70; p < 0.001) (Fig. 3; Online Resource 1, Table S12). By quarter, Z79.85 was coded in 0.00% of diabetic stroke hospitalizations in each of the first three quarters of 2022 and in 1.01% in the fourth quarter of 2022, followed by 2.83%, 2.27%, 2.99%, and 2.96% in the four quarters of 2023 (Fig. 4; Online Resource 1, Table S13).

Over the same period, the proportion with Z79.84 coding increased from 32.03% to 35.37% (30.96% in the first quarter of 2022 to 36.56% in the fourth quarter of 2023), and the proportion with Z79.4 coding from 27.46% to 28.35%. Aspiration pneumonia was recorded in 3.91% of all diabetic stroke hospitalizations in 2022 and 3.77% in 2023. Within the primary comparison, aspiration pneumonia occurred in 2.06% of Z79.84 hospitalizations in 2022 and 2.11% in 2023; year-specific estimates for the Z79.85 group are not reported because the 2022 cell contains 10 or fewer events (Fig. 3; Online Resource 1, Table S12).

4 Discussion

4.1 Principal findings

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) slow gastric emptying, and acute ischemic stroke impairs swallowing. Together, these effects predict a higher risk of aspiration in

stroke patients who take these drugs. In this nationally representative analysis, we found no evidence that such a risk materializes. Among adults with type 2 diabetes hospitalized for ischemic stroke, the association remained consistent across all models, comparators, subgroups, and sensitivity analyses. Although the initial analysis suggested nearly half the odds compared with oral antidiabetic agent users, this association progressively attenuated after adjustment (OR 0.48, 0.54, and 0.59, respectively) and was not statistically significant in the primary model (95% CI 0.33-1.03). Overall, these findings suggest no clinically meaningful excess risk of aspiration pneumonia, rather than establishing a protective effect of injectable therapy.

4.2 Interpretation of the primary finding

The hypothesis rested on periprocedural evidence and in nearly one million endoscopies, GLP-1 RA use was associated with a higher hazard of aspiration pneumonia (0.83% vs 0.63%), particularly during upper endoscopy and procedures involving propofol sedation [14]. Similarly, semaglutide use has been associated with a greater prevalence of retained gastric contents at endoscopy [15]. These findings prompted anesthesia and multisociety guidance on periprocedural management of GLP-1 RAs [16, 17]. Stroke further increases this risk, as dysphagia is common in these patients and is a major contributor to post-stroke pneumonia [18, 19].

Several factors may explain the absence of the expected association. First, the effect of GLP-1 RAs on gastric emptying diminishes with prolonged use [20], with the greatest risk occurring during dose escalation rather than maintenance therapy [17]. Second, aspiration following stroke is driven primarily by oropharyngeal dysfunction and impaired consciousness rather than gastric regurgitation [18, 19]. Although delayed gastric emptying may be more relevant in patients who are vomiting, intubated, or receiving enteral feeding, our ventilated

subgroup was too small to support reliable conclusions (aOR 0.75, 95% CI 0.26-2.13). Finally, routine stroke care incorporates swallowing assessments before oral feeding, and patients who fail screening are kept nil by mouth [21]. These routine precautions may help explain why GLP-1 RA use was not associated with an increased risk of aspiration pneumonia in our cohort.

The consistently low estimates should not be interpreted as evidence of a protective effect. Coded users were younger, more privately insured, and had less severe strokes and fewer comorbidities. The gradient in aspiration pneumonia across treatment groups (1.0% with injectable non-insulin agents, 2.1% with oral agents, 3.4% with insulin only and 5.3% with no coded therapy) may therefore reflect differences in baseline health rather than treatment effects. Progressive attenuation with adjustment, and near-null estimates after inverse probability weighting (OR 0.76, 95% CI 0.26-2.18) and after propensity-score trimming (OR 0.90), are characteristic of healthy user and related biases [22]. The E-value of 2.79 also indicates that unmeasured factors, such as frailty and functional status, could plausibly account for the observed association [23]. Nevertheless, across the primary and sensitivity analyses using the active comparator, upper confidence limits ranged from 1.00 to 1.13, providing some reassurance against a substantial increase in risk.

4.3 Secondary outcomes and sources of bias

The secondary outcomes support this interpretation. Lower adjusted odds of coded dysphagia (aOR 0.81) persisted after matching. Dysphagia, however, closely correlates with stroke severity and its identification depends partly on the documentation of swallowing assessments. This finding therefore provides limited evidence against a higher baseline aspiration risk among medication users. The association with lower in-hospital mortality (aOR 0.44) rests on ten or fewer exposed deaths and was not significant after matching (McNemar P = 0.127).

The substantially lower estimates observed against non-active comparators (aOR 0.20-0.28) further suggest residual confounding rather than a true therapeutic effect [22].

Although cardiovascular outcome trials have established that GLP-1 RAs reduce stroke incidence [24–26], whether this benefit extends to stroke severity remains uncertain. The adjusted NIHSS difference (-0.50 points) is clinically negligible, severe stroke was not reduced (aOR 0.95), and the matched estimate pointed the other way (conditional OR 1.53, 95% CI 0.98-2.39). NIHSS capture in administrative data is also incomplete and non-random [27]. Other outcomes, including gastrostomy, mechanical ventilation, post-reperfusion intracranial hemorrhage and adjusted discharge disposition did not differ between groups. The reduction in hospital charges was limited to 106 exposed admissions in late 2022 and was not sustained after matching.

Comparator choice substantially influenced the results. Using an active comparator helps restrict the analysis to patients with similar treatment indications and reduces confounding related to baseline health and frailty [28]. The estimated association increased in magnitude when injectable therapy was compared with insulin-only users and those with no coded treatment, rather than oral-agent users (aOR 0.59, 0.43, and 0.32, respectively). A true drug effect should not depend on the comparator, so this gradient is better read as a measure of the confounding that the primary design removes. The hip-fracture negative control [29] was uninformative. Its estimates exceeded unity but were based on ten or fewer exposed events, with wide confidence intervals extending to 17.9, limiting their ability to confirm or exclude systematic bias.

The exposure itself warrants scrutiny. Z79.85 entered ICD-10-CM on 1 October 2022 [30], meaning injectable non-insulin therapy was previously captured under the nonspecific code

Z79.899. This explains the absence of Z79.85 in the first three quarters of 2022 and its plateau at 2.3-3.0% of diabetic stroke admissions through 2023, a small fraction of contemporary GLP-1 RA use among US adults with type 2 diabetes. This undercapture may have resulted in exposure misclassification, while early code adoption might have favored hospitals with more structured medication reconciliation and documentation practices. Comparator misclassification is also possible, as oral semaglutide is coded under Z79.84, and patients using both oral and injectable agents may have been classified as oral-agent users when injectable therapy was not separately recorded.

The code also includes tirzepatide, a dual GIP and GLP-1 receptor agonist that delays gastric emptying, as well as less commonly used agents such as pramlintide. Exposure was strongly associated with the calendar year (91.8% vs 51.9% of admissions in 2023), raising concern for temporal confounding. This was addressed by adjustment and a 2023 only analysis (aOR 0.61), and stable aspiration rates among comparator patients across years (2.06% and 2.11%) argue against substantial temporal changes in outcome coding.

4.4 Strengths and limitations

This study has several strengths. It uses a nationally representative, survey-weighted sample analyzed according to HCUP methodological standards [13]. It is an active comparator design with a hierarchical exposure definition and adjusts for coded stroke severity. The findings were also examined across multiple approaches, including propensity score matching, inverse probability weighting, alternative comparators, negative control analysis, and E-value assessment.

Several limitations should also be considered. The exposure lacked information on the specific agent, dose, duration, time since the last dose and inpatient continuation. Aspiration

pneumonia is a clinical diagnosis that is coded inconsistently, although it yielded a similar association (aOR 0.73). Present-on-admission status could not be reliably established, and post-discharge events were not noted. With roughly 13 exposed events, the study had limited power for moderate associations, and subgroup analyses were exploratory. Pre-stroke function, frailty, level of consciousness, swallowing assessment practices and goals-of-care decisions were unavailable, and NIHSS was missing in 22-27% of records. Additionally, the NIS captures hospital discharges rather than patients. Secondary outcomes were not corrected for multiplicity, and residual imbalance after weighting slightly exceeded the conventional threshold (maximum SMD 0.107).

4.5 Clinical implications

For clinicians, these findings do not support treating GLP-1 RA exposure as an independent indication for aspiration precautions beyond those required for all stroke patients. Routine dysphagia screening and early swallow assessment remain the cornerstone of aspiration prevention [21]. However, these findings do not address patients undergoing thrombectomy under sedation or general anesthesia (1.9% of exposed admissions), for whom periprocedural guidance [16, 17] may reasonably apply, nor patients with vomiting, gastroparesis or enteral feeding. Further research should focus on linking medication dispensing records with clinical data to establish the timing of the last dose relative to stroke onset, prospective studies assessing gastric emptying and swallowing function in stroke units, validation of Z79.85 against actual medication records, and more accurate evaluation of stroke severity accounting for pre-existing functional status.

4.6 Conclusion

In conclusion, among adults with type 2 diabetes hospitalized for acute ischemic stroke, coded use of injectable non-insulin antidiabetic drugs, predominantly GLP-1 RAs, was not associated with an increased risk of aspiration pneumonia. Despite the theoretical concern that delayed gastric emptying could compound post-stroke swallowing dysfunction, we found no evidence of a corresponding increase in aspiration pneumonia at the population level. The apparently favorable associations with dysphagia and survival most probably reflect who receives these drugs, and who is coded as receiving them.

Statements and Declarations

Funding: No funding was received for conducting this study.

Competing interests: The authors have no relevant financial or non-financial interests to disclose.

Ethics approval: This study used the National Inpatient Sample, a de-identified, publicly available database of the Healthcare Cost and Utilization Project (HCUP), Agency for Healthcare Research and Quality. Institutional review board approval was therefore not required. The data were used in accordance with the HCUP Data Use Agreement.

Consent to participate: Not applicable.

Consent for publication: Not applicable.

Data availability: The National Inpatient Sample is available for purchase from HCUP (https://www.hcup-us.ahrq.gov). The analytic code is available from the corresponding author on reasonable request.

Author contributions: Conceptualization: Sheraz Qasim, Ali Hassan; Data curation: Sheraz Qasim, Ali Hassan; Formal analysis: Sheraz Qasim; Methodology: Sheraz Qasim; Writing – original draft: all authors contributed to manuscript drafting; Writing – review and editing: Ali Hassan. All authors read and approved the final manuscript.

Clinical trial number: Not applicable.

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Figure captions

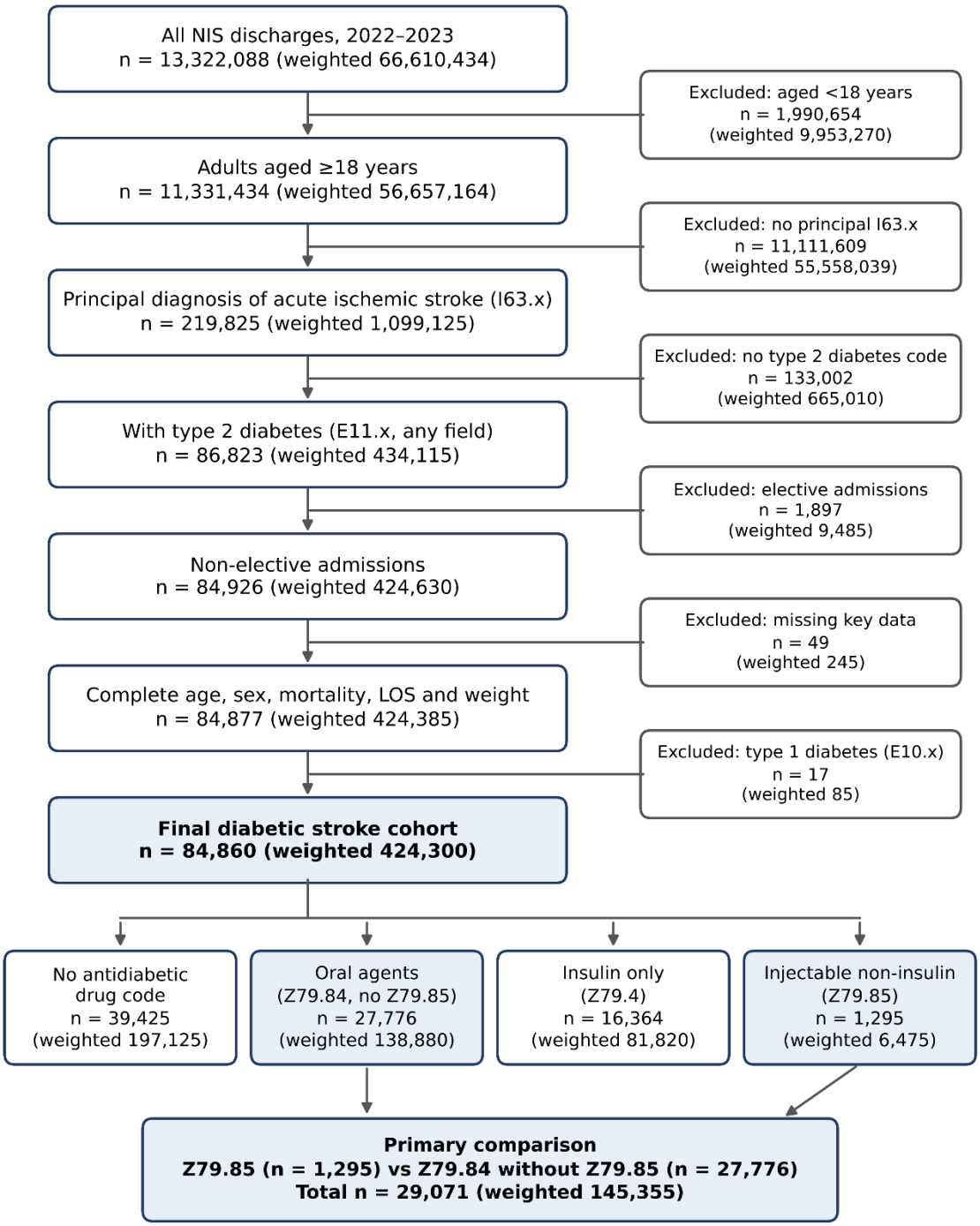
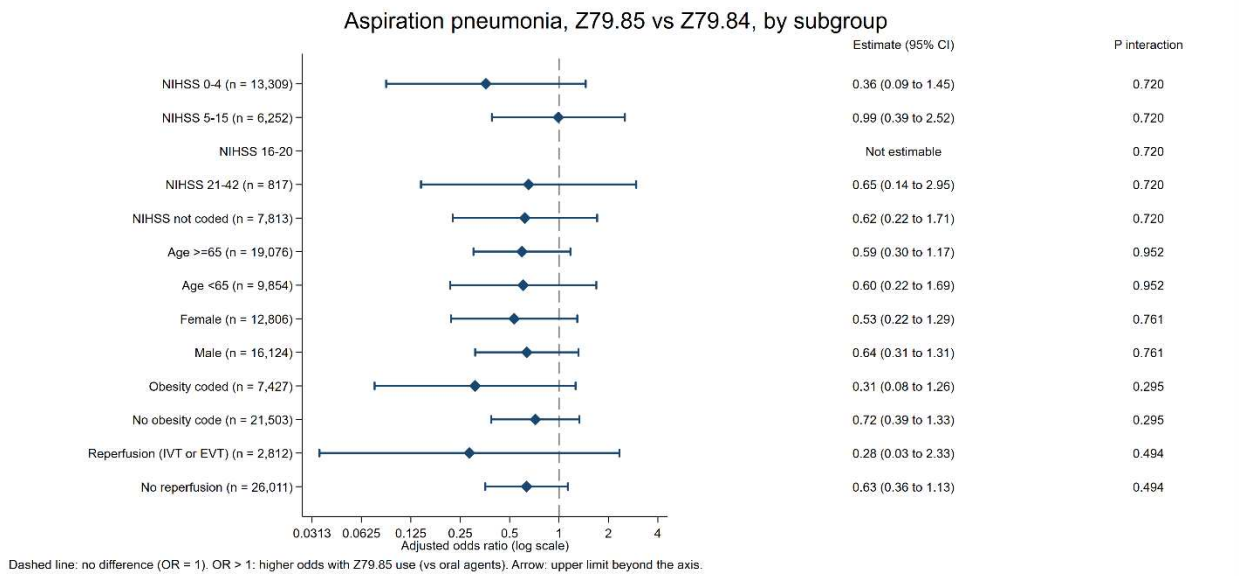
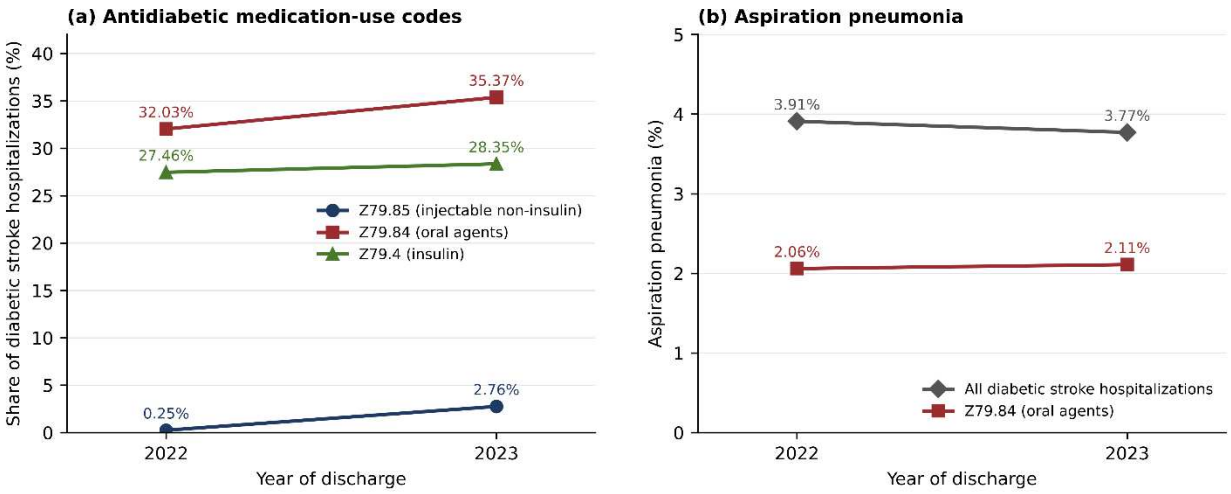


Fig. 1 Flow diagram of cohort selection from the 2022–2023 National Inpatient Sample. Counts are unweighted discharges with weighted national estimates. LOS, length of stay



673

674 **Fig. 2** Adjusted odds ratios (model M3) for aspiration pneumonia, injectable non-insulin
675 antidiabetic therapy (Z79.85) versus oral antidiabetic therapy (Z79.84), by subgroup, with p
676 values for interaction. The NIHSS 16–20 stratum was not estimable. EVT, endovascular
677 thrombectomy; IVT, intravenous thrombolysis; NIHSS, National Institutes of Health Stroke
678 Scale

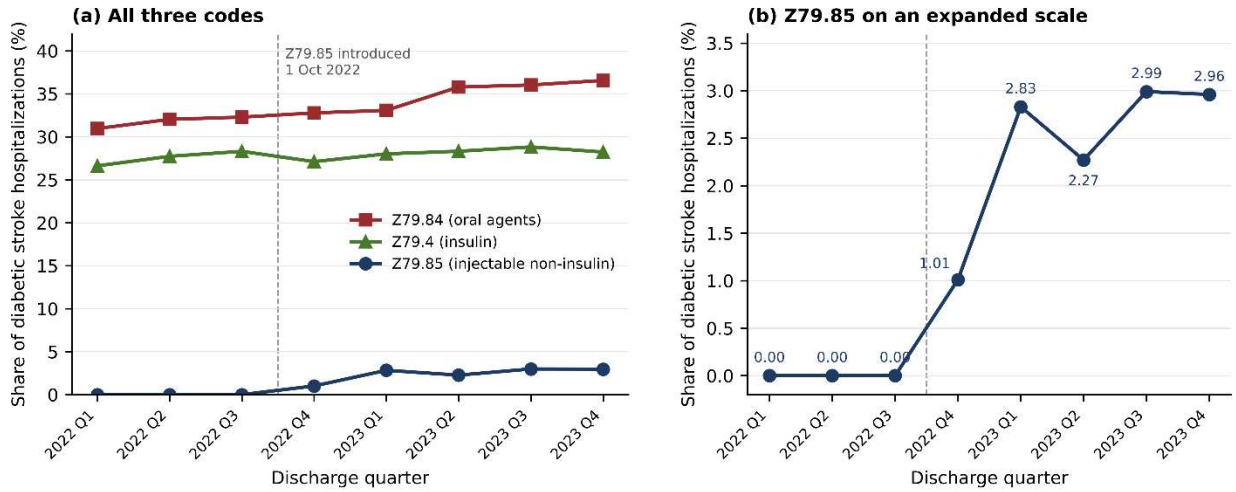


679

680 **Fig. 3** Annual trends among diabetic stroke hospitalizations, 2022–2023. (a) Share of
681 hospitalizations with Z79.85, Z79.84 and Z79.4 codes. (b) Aspiration pneumonia among all

682 diabetic stroke hospitalizations and among Z79.84-coded hospitalizations. Year-specific Z79.85

683 estimates are not shown because the 2022 cell contains 10 or fewer events



684

685 **Fig. 4** Quarterly share of diabetic stroke hospitalizations with Z79.85, Z79.84 and Z79.4 codes,

686 2022 Q1 to 2023 Q4. (a) All three codes. (b) Z79.85 on an expanded scale. The dashed line

687 marks the introduction of Z79.85 on 1 October 2022

688

Table 1 Survey-weighted associations between coded injectable non-insulin antidiabetic therapy (Z79.85) and in-hospital outcomes compared with coded oral antidiabetic therapy (Z79.84)

Model / outcome	Estimate	N	Z79.85 vs Z79.84 (95% CI)	P value
PRIMARY OUTCOME: ASPIRATION PNEUMONIA				
Aspiration pneumonia, M1 (unadjusted)	OR	29,071	0.48 (0.28-0.82)	0.007
Aspiration pneumonia, M2	aOR	28,930	0.54 (0.31-0.94)	0.029
Aspiration pneumonia, M3 (primary)	aOR	28,930	0.59 (0.33-1.03)	0.064
Aspiration or other pneumonia, M3	aOR	29,019	0.73 (0.50-1.06)	0.101
SECONDARY OUTCOMES (M3)				
Dysphagia	aOR	29,071	0.81 (0.67-0.98)	0.031
Gastrostomy (PEG)	aOR	29,019	0.93 (0.58-1.48)	0.764
In-hospital death	aOR	29,019	0.44 (0.20-0.94)	0.033
ICH after reperfusion (IVT or EVT patients only)	aOR	2,926	0.76 (0.35-1.64)	0.488
Mechanical ventilation	aOR	29,071	0.80 (0.52-1.23)	0.300
Facility/hospital discharge among survivors	aOR	28,557	0.94 (0.82-1.06)	0.313
Length of stay (negative binomial)	aIRR	29,071	0.95 (0.91-1.00)	0.052
Total charges (gamma GLM, log link)	Cost ratio	13,330	0.80 (0.70-0.91)	<0.001
STROKE SEVERITY AT ADMISSION (NIHSS-coded records; M3 without NIHSS band)				
Severe stroke (NIHSS ≥ 16)	aOR	21,227	0.95 (0.72-1.26)	0.745
NIHSS score, adjusted mean difference	Mean difference	21,227	-0.50 (-0.85 to -0.16)	0.004
Disposition: Home health care vs routine home	RRR	28,556	0.86 (0.72-1.02)	0.080
Disposition: SNF/ICF/other facility vs routine home	RRR	28,556	0.93 (0.81-1.07)	0.288
Disposition: Short-term hospital vs routine home	RRR	28,556	0.45 (0.26-0.78)	0.004
Disposition: Against medical advice vs routine home	RRR	28,556	1.22 (0.77-1.96)	0.399
NEGATIVE-CONTROL OUTCOME (M3)				
Hip fracture[a]	aOR	21,201	3.88 (0.84-17.86)	0.081

M1, unadjusted; M2, adjusted for age, sex, primary payer, income quartile, weekend admission, hospital bed size, hospital location/teaching status and year; M3 (primary), M2 plus NIHSS band (uncoded as a separate category), body mass index category, van Walraven Elixhauser score and complicated diabetes. Stroke-severity models exclude NIHSS band. [a] Covariate categories without events were dropped because they predicted the outcome perfectly, which reduced the analytic sample. aIRR, adjusted incidence rate ratio; aOR, adjusted odds ratio; CI, confidence interval; EVT, endovascular thrombectomy; GLM, generalized linear model; ICH, intracranial hemorrhage; IVT, intravenous thrombolysis; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; PEG, percutaneous endoscopic gastrostomy; RRR, relative risk ratio; SNF/ICF, skilled nursing/intermediate care facility

Table 2 Association of coded injectable non-insulin antidiabetic therapy (Z79.85) with selected outcomes against alternative comparator groups (model M3)

Comparator / outcome	Estimate	N	Z79.85 vs comparator (95% CI)	P value
Comparator: Oral agents (Z79.84) [primary]				
Aspiration pneumonia (J69.0)	aOR	28,930	0.59 (0.33-1.03)	0.064
Dysphagia (R13.1x)	aOR	29,071	0.81 (0.67-0.98)	0.031
Gastrostomy (PEG)	aOR	29,019	0.93 (0.58-1.48)	0.764
In-hospital death	aOR	29,019	0.44 (0.20-0.94)	0.033
Hip fracture (negative control)	aOR	21,201	3.88 (0.84-17.86)	0.081
Comparator: Insulin only (Z79.4)				
Aspiration pneumonia (J69.0)	aOR	17,631	0.43 (0.25-0.76)	0.004
Dysphagia (R13.1x)	aOR	17,659	0.79 (0.65-0.97)	0.027
Gastrostomy (PEG)	aOR	17,631	0.86 (0.53-1.37)	0.518
In-hospital death	aOR	17,563	0.28 (0.13-0.62)	0.001
Hip fracture (negative control)	aOR	14,925	1.42 (0.33-6.15)	0.636
Comparator: No antidiabetic drug code				
Aspiration pneumonia (J69.0)	aOR	40,720	0.32 (0.19-0.56)	<0.001
Dysphagia (R13.1x)	aOR	40,720	0.71 (0.59-0.86)	<0.001
Gastrostomy (PEG)	aOR	40,720	0.66 (0.42-1.04)	0.070
In-hospital death	aOR	40,720	0.20 (0.09-0.42)	<0.001
Hip fracture (negative control)	aOR	38,349	1.70 (0.41-7.14)	0.467
Comparator: All other diabetic stroke				
Aspiration pneumonia (J69.0)	aOR	84,860	0.40 (0.23-0.70)	0.001
Dysphagia (R13.1x)	aOR	84,860	0.76 (0.63-0.92)	0.005
Gastrostomy (PEG)	aOR	84,860	0.76 (0.49-1.20)	0.245
In-hospital death	aOR	84,860	0.25 (0.12-0.54)	<0.001
Hip fracture (negative control)	aOR	83,268	2.03 (0.49-8.35)	0.326

All estimates are from the primary adjusted model (M3). The insulin-only, no-antidiabetic-code and all-other-diabetic-stroke groups are not active comparators. aOR, adjusted odds ratio; CI, confidence interval; PEG, percutaneous endoscopic gastrostomy

Supplementary Files

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