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Subtotal Gastrectomy With Billroth II Anastomosis Is Associated With a Low Risk of Ischemic Stroke in Peptic Ulcer Disease Patients

A Nationwide Population-Based Study

Chien-Hua Chen, MD, MPH, Cheng-Li Lin, MSc, and Chia-Hung Kao, MD

Abstract: Duodenal diversion can ameliorate lipid and glucose metabolism. We assessed the risk of stroke after subtotal gastrectomy with Billroth II anastomosis (SGBIIA) in peptic ulcer disease (PUD).

We identified 6425 patients who received SGBIIA for PUD between 1998 and 2010 from the Taiwan National Health Insurance Research Database as the study cohort; we frequency-matched them with 25,602 randomly selected controls from the PUD population who did not receive SGBIIA according to age, sex, index year, and comorbidities including hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease (COPD), and obesity. All patients were followed until the end of 2011 to determine the incidence of stroke.

The incidence of stroke was lower in patients in the SGBIIA cohort than in those in the non-SGBIIA cohort (18.9 vs 22.9 per 1000 person-years, adjusted hazard ratio [aHR] 0.80, 95% confidence interval [CI] 0.72–0.89, $P < 0.001$). The risk of ischemic stroke (aHR 0.77, 95% CI 0.69–0.86, $P < 0.001$), rather than hemorrhagic stroke (aHR 1.00, 95% CI 0.78–1.28), was lower for the SGBIIA cohort than for the non-SGBIIA cohort according to the multivariable Cox proportional hazard regression analysis. The relative risk of ischemic stroke after SGBIIA was lower in men (aHR 0.77, 95% CI 0.69–0.86) than in women (aHR 0.80, 95% CI 0.65–0.99) and in patients aged ≥65 years (aHR 0.72, 95% CI 0.63–0.81) than in those of other age groups (≤49 years, aHR 0.82, 95% CI 0.48–1.39; 50–64 years, aHR 1.01, 95% CI 0.79–1.28). The relative risk of ischemic stroke after SGBIIA was also reduced in patients with comorbidities (aHR 0.84, 5% CI 0.75–0.95) rather than in those without comorbidities (aHR 0.81, 95% CI 0.59–1.12).

SGBIIA is associated with a low risk of ischemic stroke for PUD patients, and its protective effect is prominent in men, patients aged ≥65 years, and those with comorbidities.

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Abbreviations: aHR = adjusted hazard ratio, CI = confidence interval, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, PUD = peptic ulcer disease, SGBIIA = subtotal gastrectomy with Billroth II anastomosis.

INTRODUCTION

The discovery of proton pump inhibitors and *Helicobacter pylori* has contributed to the reduction in the incidence of peptic ulcer disease (PUD) during the last decades of the 20th century.[1] However, PUD currently remains a common ailment because of the extensive use of nonsteroidal anti-inflammatory drugs (NSAIDs) and low-dose aspirin.[1] Despite the decline in the rate of elective surgery over the last 30 years, the rate of emergent surgery may have increased because of complicated PUD.[2–4] Subtotal gastrectomy with Billroth II anastomosis (SGBIIA), sometimes indicated for complicated PUD, is a type of partial duodenal bypass operation because the patients usually undergo gastrojejunostomy after gastrectomy.[5,6] On the contrary, duodenal diversion induced by contact with ingested nutrients, in addition to elevated serum bile acid levels after altered enterohepatic circulation, may improve glucose and lipid metabolism.[7,8]

Stroke, such as ischemic and hemorrhagic strokes, is the second leading cause of preventable mortality and the fourth leading cause of productivity loss worldwide.[9] A previous study reported that 20% of stroke survivors required institutional care after 3 months of stroke onset and that 15% to 30% of the institutionalized patients were permanently disabled.[10] Therefore, stroke imposes a heavy socioeconomic burden on patients, family members, and health-providing systems. Furthermore, the incidence of stroke remains high, particularly in low-to-middle income countries, despite the decline in stroke-related

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From the Digestive Disease Center (C-HC), Show-Chwan Memorial Hospital (C-HC), Changhua; Department of Food Science and Technology (C-HC), Hungkuang University, Taichung; Meiho University of Technology, Pingtung; Management Office for Health Data (C-LL), China Medical University Hospital; Graduate Institute of Clinical Medical Science (C-HK, C-LL), School of Medicine, College of Medicine, China Medical University; and Department of Nuclear Medicine and Positron Emission Tomography Center (C-HK), China Medical University Hospital, Taichung, Taiwan.
Correspondence: Chia-Hung Kao, Graduate Institute of Clinical Medical Science, College of Medicine, China Medical University, No. 2, Yuh-Der Rd, Taichung 40447, Taiwan, Republic of China (e-mail: d10040@mail.cmuh.org.tw).
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deaths.[11] The reported stroke-related deaths and events were 5.7 and 16 million, respectively, in 2005. Moreover, stroke-related deaths and events are estimated to reach 7.8 and 23 million, respectively, by 2030.[9] Abnormality of glucose and lipid metabolism is considered a risk factor for stroke as the risk factors for stroke include several metabolic disorders such as hypertension, diabetes mellitus, hyperlipidemia, and obesity.[12]

Patients receiving SGBIIA might be unlikely to have a stroke due to the improvement of glucose and lipid metabolism. However, no study has explored the relationship between SGBIIA and stroke. In this study, we hypothesized that a history of SGBIIA for PUD might reduce the subsequent risk of stroke. We conducted a nationwide population-based cohort study by analyzing data from the National Health Insurance Research Database (NHIRD) of Taiwan to assess the association between SGBIIA and the subsequent risk of stroke in PUD patients.

METHODS

Data Source

We retrieved claims data from the data set of the NHIRD released by the Taiwan National Health Research Institutes. The NHIRD is an electronic claims database launched under the National Health Insurance (NHI) program, which covers >99% of Taiwan's population (23.74 million). Numerous studies that have applied data from the NHIRD data sets have been published (http://w3.nhri.org.tw/nhird/talk_07.htm). In the NHIRD, patient information is scrambled and encrypted to protect patient privacy, and each patient can be linked and followed continuously according to their claims data. We used the identification of residents to link 2 data files that included the inpatient claims and Registry of Beneficiaries. Diseases were identified according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic codes in the claims data. This study was approved by the ethics review board of China Medical University (CMUH104-REC2-115).

Sampled Participants

We recruited patients diagnosed with PUD (ICD-9-CM 531–533) between 1998 and 2010. Patients who received SGBIIA (ICD-9-CM 43.7) constituted the SGBIIA cohort. Patients with a history of stroke (ICD-9-CM 430–438) and those aged <20 years were excluded. The date of SGBIIA diagnosis was used as the index date. The comparison cohort comprised the remaining patients with PUD diagnosed by endoscopy, who received treatment with histamine-2 blockers or proton pump inhibitors but without surgery. For each patient in the SGBIIA cohort, 4 patients in the comparison cohort without a history of stroke were randomly identified and frequency-matched according to age (every 5 years), sex, the index year, and comorbidities including hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease (COPD), and obesity. Overall, 6425 SGBIIA patients and 25,602 non-SGBIIA patients were followed until an event of stroke, loss to follow-up, death, withdrawal from the NHI program, or the end of 2011.

COMORBIDITIES

A history of hypertension (ICD-9-CM 401–405), diabetes mellitus (ICD-9-CM 250), hyperlipidemia (ICD-9-CM 272), coronary artery disease (ICD-9-CM 410–414), congestive heart failure (ICD-9-CM 428), chronic kidney disease (ICD-9-CM 585), COPD (ICD-9-CM 490,491, 496), or obesity (ICD-9-CM 278.0) before the endpoint were considered as a comorbidity. In addition, the duration of comorbidities was also considered based on diagnoses in the claim records since the index date to the endpoint date.

Statistical Analysis

A χ^2 test was used for comparing the demographic characteristics, including age (20–49, 50–64, and ≥65 years), sex, and comorbidities, of patients in the SGBIIA and non-SGBIIA cohorts. The mean age and follow-up duration of both cohorts were measured and compared using the Student *t* test. The cumulative incidence curves of stroke for the 2 cohorts were compared using the Kaplan–Meier method and log-rank test. The incidences of stroke in the SGBIIA and non-SGBIIA cohorts were calculated by dividing the total number of stroke events by the total follow-up duration (per 1000 person-years). Univariable and multivariable Cox proportional hazard regression analyses were performed for estimating and comparing the hazard ratios (HRs) and 95% confidence intervals (CIs) of the risk of stroke in the 2 cohorts. Only significant values obtained in the univariable analysis were further examined in the multivariable analysis. Multivariable analysis was performed after adjustment for age, sex, and comorbidities of hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, congestive heart failure, chronic kidney disease, COPD, and obesity. Furthermore, the duration of hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, congestive heart failure, chronic kidney disease, COPD, and obesity has also been adjusted in multivariable analysis. All analyses were conducted using SAS (version 9.4 for Windows; Statistics Analysis System Institute, Inc, Cary, NC). A 2-tailed *P* value <0.05 was considered statistically significant.

RESULTS

Table 1 lists the demographic characteristics of and comorbidities in patients in both cohorts. In this study, 72.2% of the patients were men and 57.6% were aged >65 years. The mean patient ages for the SGBIIA and non-SGBIIA cohorts were 65.5 ± 14.4 and 65.4 ± 14.4 years, respectively. Both cohorts were similar to exhibit hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, congestive heart failure, chronic kidney disease, COPD, and obesity. The mean follow-up durations for the SGBIIA and non-SGBIIA cohorts were 3.64 ± 3.73 and 5.06 ± 3.83 years, respectively ($P < .001$, data not shown). The cumulative incidence of ischemic stroke was significantly lower for patients in the SGBIIA cohort than for those in the non-SGBIIA cohort (log-rank $P < 0.001$, Figure 1). Moreover, the incidence of ischemic stroke increased gradually with the follow-up duration in both cohorts.

Table 2 shows the incidence of stroke in patients in both the cohorts for PUD. The overall incidence density of stroke was significantly lower in the SGBIIA cohort than in the non-SGBIIA cohort (18.9 vs 22.9 per 1000 person-years, crude HR 0.82, 95% CI 0.74–0.90), with an adjusted hazard ratio (aHR) of 0.80 (95% CI 0.72–0.89, $P < 0.001$). Furthermore, patients in the SGBIIA cohort were 0.77-fold less likely to develop ischemic stroke (95% CI 0.69–0.86, $P < 0.001$) compared with those in the non-SGBIIA cohort after adjustment for age, sex, comorbidities, and duration of comorbidities. Consistently, SGBIIA was inversely related to the development of ischemic

TABLE 1. Comparisons in demographic characteristics and comorbidities in PUD patients with and without SGBIIA

	SGBIIA		
	No (N = 25602)	**Yes (N = 6425)**	***P***
Sex			0.99
Female	7107(27.8)	1786 (27.8)	
Male	18495 (72.2)	4639 (72.2)	
Age stratified, y			0.99
≤49	4207 (16.4)	1057 (16.5)	
50–64	6653 (26.0)	1670 (26.0)	
65+	14742 (57.6)	3698 (57.6)	
Age, mean ± SD*	65.4 (14.4)	65.5 (14.4)	0.42
Comorbidity			
Hypertension	10598 (41.4)	2660 (41.4)	0.99
Diabetes mellitus	6596 (25.8)	1664 (25.9)	0.82
Hyperlipidemia	2064 (8.06)	526 (8.19)	0.74
Coronary artery disease	5201 (20.3)	1310 (20.4)	0.89
Congestive heart failure	2690 (10.5)	686 (10.7)	0.69
Chronic kidney disease	1727 (6.75)	441 (6.86)	0.74
COPD	4139 (16.2)	1044 (16.3)	0.87
Obesity	53 (0.21)	21 (0.33)	0.07

COPD = chronic obstructive pulmonary disease, PUD = peptic ulcer disease, SGBIIA = subtotal gastrectomy with Billroth II anastomosis.
Chi-square test.
* *t*-test.

stroke; even the cumulating censoring rate (31.8%) of the SGBIA cohort was greater than that (14.4%) of the non-SGBIIA cohort between 1998 and 2011 (data not shown).

Table 3 lists the HRs of ischemic stroke in association with age, sex, and comorbidities according to the univariable and multivariable Cox regression models. Every 1-year increase in age was associated with a 1.05-fold increased risk of ischemic stroke (95% CI 1.05–1.06). In addition, men, hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, and COPD were associated with ischemic stroke. However, the risk of ischemic stroke was low in the SGBIIA cohort.

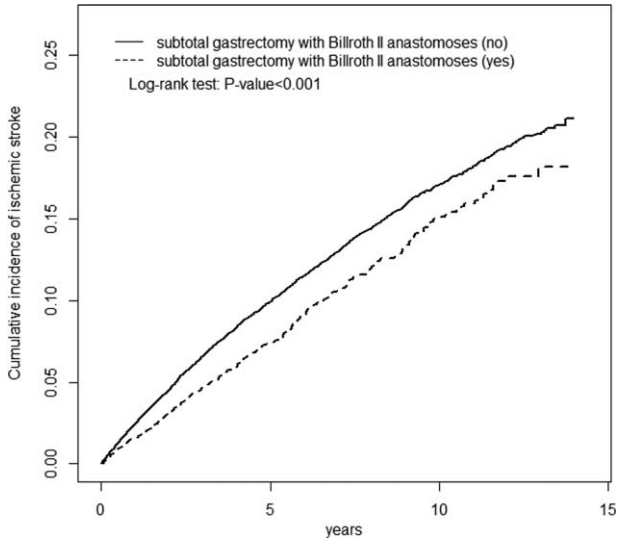

FIGURE 1. Cumulative incidence of ischemic stroke in PUD patients with and without SGBIIA. PUD = peptic ulcer disease, SGBIIA = subtotal gastrectomy with Billroth II anastomosis.

Table 4 shows a comparison of the ischemic stroke risks stratified according to sex, age, and comorbidities between both cohorts. In the SGBIIA cohort, the relative risk of ischemic stroke was lower in both men (aHR 0.77, 95% CI 0.68–0.87) and women (aHR 0.80, 95% CI 0.65–0.99), and in patients aged ≥65 years (aHR 0.72, 95% CI 0.63–0.81) than in those of other age groups (≤49 years, aHR 0.82, 95% CI 0.48–1.39; 50–64 years, aHR 1.01, 95% CI 0.79–1.28). The relative risk of ischemic stroke was reduced in SGBIIA patients with comorbidities than non-SGBIIA patients with comorbidities (aHR 0.84, 5% CI 0.75–0.95). Among the subjects with associated comorbidity, patients with SGBIIA had a lower risk of ischemic stroke compared with the non-SGBIIA cohort (aHR 0.81 for hypertension; aHR 0.77 for diabetes mellitus; aHR 0.71 for hyperlipidemia; aHR 0.80 for coronary artery disease; aHR 0.76 for COPD).

DISCUSSION

SGBIIA might be indicative of the presence of complicated PUD, and our results revealed that this procedure was performed mostly in men and in patients aged >65 years. The possible explanations for the predisposition of complicated PUD in elderly people might be that *H pylori* infections, poor mucosal resistance to acids, NSAID usage, and smoking are highly prevalent in elderly people.[13–15] Except for *H pylori* infection, which increases the risk of peptic ulcer bleeding rather than perforation, all the other aforementioned factors are associated with increased risks of peptic ulcer hemorrhage and perforation. The prevalence of *H pylori* infection, NSAID usage, and smoking was higher in men than in women.

According to the American Heart Association/American Stroke Association guidelines, hypertension, diabetes mellitus, hyperlipidemia, and smoking are associated with an increased risk of ischemic stroke.[10] Nevertheless, obesity is discussed separately because it may indirectly increase the risk of stroke by contributing to the development of metabolic syndrome, such as hypertension, diabetes mellitus, and hyperlipidemia. This suggestion is consistent with our findings, which indicated that hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, and COPD were associated with an increased risk of ischemic stroke. Hypertension is the leading cause of ischemic stroke. This condition reduces the vascular lumen size via hypertrophic remodeling of the smooth muscle in the vascular media or increases the vascular resistance via eutrophic remodeling accompanied by apoptosis of the outer vascular wall.[16] Furthermore, hypertension can lead to vessel inflammation and atherosclerosis by increasing the shear stress.[17] Diabetes mellitus can increase the intimal medial thickness and induce thin cap fibroatheroma; moreover, hypertension and diabetes mellitus contribute to the development of atherosclerosis.[18–20] Regarding hyperlipidemia, the cholesterol crystals in the intima can trigger the accumulation of macrophages to activate inflammatory cytokines and promote atherosclerosis.[21] On the contrary, smoking increases the risk of ischemic stroke by accelerating atherosclerosis and inducing thrombus formation in the atherosclerotic vessels.[22]

Our findings revealed that SGBIIA was associated with a low risk of ischemic stroke rather than hemorrhagic stroke. The possible explanation for the protective effects may be the potential contribution of SGBIIA to improved lipid and glucose

TABLE 2. Comparison of incidence densities of stroke between patients with and without SGBIIA for PUD

	SGBIIA							
	No			Yes				
Outcome	Event	PY	Rate[†]	Event	PY	Rate[†]	Crude HR[‡] (95% CI)	Adjusted HR[§] (95% CI)
All strokes	2965	129591	22.9	442	23386	18.9	0.82 (0.74, 0.90)[*]	0.80 (0.72, 0.89)[*]
Ischemic stroke	2568		19.8	369		15.8	0.79 (0.70, 0.88)[*]	0.77 (0.69, 0.86)[*]
Hemorrhagic stroke	397		3.06	73		3.12	1.01 (0.79, 1.30)	1.00 (0.78, 1.28)

CI = confidence interval, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, PUD = peptic ulcer disease, PY = person years, SGBIIA = subtotal gastrectomy with Billroth II anastomosis.

[*] $P < 0.001$.

[†] Rate, incidence rate, per 1000 person-years.

[‡] Crude HR, relative hazard ratio.

[§] Adjusted HR: mutually adjusted for age, sex, and comorbidities of hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, congestive heart failure, chronic kidney disease, COPD, and obesity in Cox proportional hazard regression. Furthermore, the duration of hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, congestive heart failure, chronic kidney disease, COPD, and obesity has also been adjusted in multivariable analysis.

metabolism, which has a predilection of diminishing the ischemic stroke risk.[8,23] Moreover, both hyperlipidemia and diabetes mellitus are mainly related to the development of ischemic stroke rather than hemorrhagic stroke. The total serum bile acid content will increase after gastric bypass surgery because of the increased synthesis of such acids in the liver. Bile acids can increase energy expenditure by promoting intracellular thyroid hormone activation, improve insulin resistance, and inhibit lipogenic activity through the nuclear farnesoid X-receptor.[24] Furthermore, low levels of taurine-conjugated bile acids after gastric bypass can increase lipid oxidation through the activation of the bile acid, G-protein–coupled bile acid receptor and type II iodothyronine deiodinase cascade in white adipose tissues.[23] Improved glucose metabolism after SGBIIA may be induced by the following mechanisms: improved lipid oxidation and insulin sensitivity engendered by reduced food intake postgastrectomy; reduced gastric ghrelin secretion, which results in easy satiety; increased insulin secretion and sensitivity after gastric bypass, which is induced by foregut theory by counter-regulating anti-secretin expression; activated insulin secretion and antagonized β-cell apoptosis after gastric bypass, which is caused by hindgut theory by upregulating the production of glucagon-like peptide 1 and reducing insulin resistance by upregulating peptide YY expression.[25–31] It is quite intriguing to note that SGBIIA reduces the risk of ischemic strokes but does not influence hemorrhagic

TABLE 3. Hazard ratios of ischemic stroke in association with age, sex, and comorbidities in univariable and multivariable Cox regression models

	Crude[†]		Adjusted[‡]	
Variable	HR	(95% CI)	HR	(95% CI)
SGBIIA	0.79	(0.70, 0.88)[***]	0.77	(0.69, 0.86)[***]
Age, y (every 1 y)	1.06	(1.06, 1.07)[***]	1.05	(1.05, 1.06)[***]
Sex (male vs female)	1.06	(0.98, 1.15)	1.10	(1.01, 1.20)[*]
Baseline comorbidities (no vs yes)				
Hypertension	3.33	(3.09, 3.60)[***]	3.83	(3.46, 4.23)[***]
Diabetes mellitus	2.02	(1.87, 2.18)[***]	2.26	(2.02, 2.52)[***]
Hyperlipidemia	1.93	(1.74, 2.14)[***]	3.92	(3.37, 4.56)[***]
Coronary artery disease	2.11	(1.95, 2.28)[***]	2.06	(1.83, 2.31)[***]
Congestive heart failure	1.98	(1.79, 2.18)[***]	1.07	(0.93, 1.22)
Chronic kidney disease	1.42	(1.24, 1.63)[***]	1.06	(0.87, 1.29)
COPD	1.96	(1.80, 2.13)[***]	1.70	(1.51, 1.92)[***]
Obesity	0.59	(0.22, 1.56)	0.75	(0.08, 7.10)

CI = confidence interval, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, SGBIIA = subtotal gastrectomy with Billroth II anastomosis.

[*] $P < 0.05$.

[***] $P < 0.001$.

[†] Crude HR represented relative HR.

[‡] Adjusted HR: mutually adjusted for age, sex, and comorbidities of hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, congestive heart failure, chronic kidney disease, COPD, and obesity in Cox proportional hazard regression. Furthermore, the duration of hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, congestive heart failure, chronic kidney disease, COPD, and obesity has also been adjusted in multivariable analysis.

TABLE 4. Comparison of ischemic stroke risks stratified by sex, age, and comorbidity between patients with and without SGBIIA for PUD

	SGBIIA							
	No			Yes				
	Event	PY	Rate[†]	Event	PY	Rate[†]	Crude HR[‡] (95% CI)	Adjusted HR[§] (95% CI)
Sex								
Female	694	36762	18.9	102	6488	15.7	0.83 (0.67, 1.02)	0.80 (0.65, 0.99)*
Male	1874	92829	20.2	267	16897	15.8	0.77 (0.68, 0.88)***	0.77 (0.68, 0.87)***
Stratify age, y								
≤49	87	28965	3.00	17	5861	2.90	0.96 (0.57, 1.61)	0.82 (0.48, 1.39)
50–64	413	37797	10.9	80	7082	11.3	1.03 (0.81, 1.31)	1.01 (0.79, 1.28)
65+	2068	62829	32.9	272	10442	26.1	0.79 (0.69, 0.89)***	0.72 (0.63, 0.81)***
Comorbidity[‖]								
No	307	54580	5.62	43	10073	4.27	0.73 (0.53, 1.01)	0.81 (0.59, 1.12)
Yes	2261	75011	30.1	326	13312	24.5	0.81 (0.72, 0.91)***	0.84 (0.75, 0.95)**
Hypertension								
No	884	82288	10.7	111	14767	7.52	0.68 (0.56, 0.83)***	0.73 (0.60, 0.90)**
Yes	1684	47302	35.6	258	8619	29.9	0.84 (0.74, 0.96)**	0.81 (0.71, 0.92)**
Diabetes mellitus								
No	1611	100330	16.1	228	18175	12.5	0.77 (0.67, 0.88)***	0.79 (0.69, 0.91)***
Yes	957	29261	32.7	141	5210	27.1	0.82 (0.69, 0.98)*	0.77 (0.65, 0.92)**
Hyperlipidemia								
No	2211	119797	18.5	321	21559	14.9	0.80 (0.71, 0.90)***	0.78 (0.69, 0.88)***
Yes	357	9794	36.5	48	1826	26.3	0.71 (0.53, 0.97)*	0.71 (0.52, 0.96)*
Coronary artery disease								
No	1732	105290	16.5	239	19091	12.5	0.75 (0.66, 0.86)***	0.76 (0.67, 0.88)***
Yes	836	24301	34.4	130	4295	30.3	0.87 (0.73, 1.05)	0.80 (0.67, 0.97)*
Congestive heart failure								
No	2157	118312	18.2	305	21351	14.3	0.77 (0.68, 0.87)***	0.77 (0.68, 0.87)***
Yes	411	11279	36.4	64	2035	31.5	0.86 (0.66, 1.12)	0.80 (0.61, 1.04)
Chronic kidney disease								
No	2377	122937	19.3	345	22229	15.5	0.79 (0.71, 0.89)***	0.78 (0.69, 0.87)***
Yes	191	6654	28.7	24	1157	20.8	0.71 (0.47, 1.09)	0.69 (0.45, 1.06)
COPD								
No	1937	111433	17.4	280	20179	13.9	0.79 (0.69, 0.89)***	0.79 (0.70, 0.90)***
Yes	631	18158	34.8	89	3207	27.8	0.80 (0.64, 1.00)*	0.76 (0.60, 0.95)*
Obesity								
No	2565	129326	19.8	368	23297	15.8	0.79 (0.70, 0.88)***	0.77 (0.69, 0.86)***
Yes	3	265	11.3	1	89	11.3	1.03 (0.11, 9.94)	—

CI = confidence interval, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, PUD = peptic ulcer disease, SGBIIA = subtotal gastrectomy with Billroth II anastomosis. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

[†]Rate, incidence rate, per 1000 person-years.

[‡]Crude HR, relative HR.

[§]Adjusted HR: mutually adjusted for age, sex, comorbidities of hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, congestive heart failure, chronic kidney disease, COPD, and obesity in Cox proportional hazard regression. Furthermore, the duration of hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, congestive heart failure, chronic kidney disease, COPD, and obesity has also been adjusted in multivariable analysis.

[‖]Comorbidity: patients with any 1 of the comorbidities hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, congestive heart failure, chronic kidney disease, COPD, and obesity were classified as the comorbidity group.

strokes in our study. Most epidemiological studies suggest hypercholesterolemia is mainly related to an increased risk of ischemic stroke and carotid artery atherosclerosis.[32,33] A 25% increase of ischemic stroke rate for every 1 mmol/L increment of total cholesterol level was found in a study conducted in the Asia Pacific area. Conversely, abnormally low cholesterol level is associated with an increased risk of hemorrhagic stroke.[32] The role of triglycerides in predicting the risk of ischemic stroke remain debated, but a study conducted in the Asia Pacific area found a 50% increased risk of ischemic stroke in subjects with the highest quintile of fasting triglycerides compared with those with the lowest quintile.[34] Diabetes mellitus leads to the susceptibility to atherosclerosis and frequently accompanies the proatherogenic risk factors, such as hypertension and hyperlipidemia.[35] Moreover, several epidemiological studies have reported that diabetes mellitus mainly increases the age-specific risk of ischemic stroke rather than hemorrhagic stroke.[36,37]

The low risk of ischemic stroke observed in the SGBIIA patients was perhaps a consequential effect of the SGBIIA status because the possible confounding effect of ischemic stroke risk factors was minimized profoundly in our study (Table 3). Moreover, we observed the that the protective effect of SGBIIA against the development of ischemic stroke was high in men, patients aged ≥65 years, and those with comorbidities because the aHR of ischemic stroke was significantly low for the SGBIIA patients in these aforementioned groups associated with a relatively high risk of ischemic stroke (Table 4). Our findings revealed that the protective effect against ischemic stroke risk in patients who received SGBIIA increased gradually over the follow-up duration (Figure 1). These findings, combined with the results of the subgroup analyses, confirm the possible inverse association between SGBIIA and ischemic stroke, and suggest that SGBIIA may be a protective factor against ischemic stroke.

To our knowledge, this is the first population-based study to investigate the association between SGBIIA for PUD and the risk of ischemic stroke. We adopted a longitudinal design, rather than a cross-sectional approach, to evaluate the temporal and casual associations between SGBIIA and ischemic stroke. The statistical analysis results were benefited from our use of data of the national database over a 14-year observation period. Furthermore, the patients were sampled from a stable population of Taiwan enrolled in the NHI program, which covers ~99% of the population.

These are the possible study limitations: the NHIRD lacks the data about the important risk factors such as the patient's family history, stroke-related lifestyle, and socioeconomic situation; there are lower evidence and quality from the retrospective study to compare with prospective randomized clinical trials because the retrospective study usually missed possibly unmeasured and unknown risk factors. However, the risk of ischemic stroke in each stratified comorbidity of patients with SGBIIA was consistently lower than that of the non-SGBIIA cohort. Therefore, the random chance for the association between SGBIIA and the low risk of ischemic stroke was low in our study. Moreover, we aimed to specifically examine the effect of SGBIIA on the risk of ischemic stroke for the patients with PUD by creating the control cohort with PUD alone to avoid the confounding effect of PUD in our study. In addition, we found the trend is similar after using the Longitudinal Health Insurance Database 2000, a database containing the claims data from 1996 to 2011 for 1 million people randomly sampled from 2000 NHIRD enrollment records, to do the same analysis (Appendix Table 1, http://links.lww.com/MD/A915). Second, our study had the inherent limitation to well recognize the severity of comorbidities, which might affect the end points and bias the results. However, SGBIIA was consistent to be inversely related to the development of ischemic stroke after we have adjusted the duration of comorbidities in multivariable Cox regression model. It is unclear whether the comorbidities were adequately controlled with medicine or whether they were observed without medication. However, the patients were sampled from a stable population of Taiwan with >99% population covered in the good accessibility of NHI program. In addition, the case number of patients with loss of contact would lead to underestimation of the risk of end points. The fact that the number of censored cases in the SGBIIA group is twice as large as the number of the control group might bias the result as more high-risk patients might drop out of the SGBIIA group, and more patients in the SGBIIA group might have had a stroke after loss of contact. Third, ascertaining the precise mechanism for the protective effect of SGBIIA against ischemic stroke is difficult. The aforementioned possible mechanisms always interact with one another and cannot function independently. Moreover, additional studies are required to ascertain the potential mechanisms of SGBIIA that protect against the development of ischemic stroke. The actual factor for diminishing the risk of ischemic stroke after SGBIIA might be improved metabolism of glucose and lipid, and SGBIIA might be a confounding factor. No data was available about how the risk factors in our cohort longitudinally changed over time in NHRID, such as obesity at the time of surgery but lost weight during follow-up. Although there are significant results, the clinical relevance between SGBIIA and the risk of ischemic stroke would be somewhat low as there was no consequence. Moreover, it might lead to the relevance of reducing the risk factor of metabolic syndrome. However, our results still support the inverse association, rather than the casual relationship, between SGBIIA and ischemic stroke even if this association was because of improved glucose and lipid metabolism after SGBIIA.

In conclusion, this population-based cohort study reveals that SGBIIA is associated with a low risk of ischemic stroke for PUD patients, and the protective effect is prominent in men, patients aged ≥65 years, and those with comorbidities.

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