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# Risk of Stroke-Associated Pneumonia With Acid-Suppressive Drugs

## *A Population-Based Cohort Study*

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**Abstract:** Acid-suppressive drugs, including histamine-2 receptor antagonists (H2RAs) and proton pump inhibitors (PPIs), are common medications used for treating upper gastrointestinal tract disorders. However, acid-suppressive drugs have been reported to increase the risk of pneumonia in numerous disease populations. However, the relationship between acid-suppressive drugs and stroke-associated pneumonia (SAP) remains controversial.

The purpose of this study was to investigate the association between acid-suppressive drug usage and pneumonia among patients with stroke by using a nationwide data set.

A population-based cohort study was conducted using a data set from the Taiwanese National Health Insurance Research Database. Data on patients with new-onset stroke from 2010 to 2011 were collected. Patients with and without acid-suppressive drug usage were followed up to identify the occurrence of any type of pneumonia. We estimated the adjusted hazard ratios (HRs) by using the Cox proportional hazards model.

The study cohort comprised 7965 patients with new-onset stroke. The incidence of pneumonia was 6.9% (552/7965) and more than 40% (225/552) of patients developed pneumonia within 3 months after an acute stroke. Acid-suppressive drug usage was an independent risk factor of pneumonia. The adjusted HR for the risk of pneumonia in patients with new-onset stroke using acid-suppressive drugs was 1.44 (95% confidence interval [CI] = 1.18–1.75,  $P < 0.01$ ). Only PPI usage increased risk of chronic SAP (adjusted HR = 1.46, 95% CI = 1.04–2.05).

Acid-suppressive drug usage was associated with a slightly increased risk of SAP. Physicians should exercise caution when prescribing acid-suppressive drugs to patients with stroke, particularly at the chronic stage.

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**Abbreviations:** CI = confidence intervals, GI = gastrointestinal, H2RAs = histamine-2 receptor antagonists, HRs = hazard ratios, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, LHID2010 = Longitudinal Health Insurance Database 2010, NHI = National Health Insurance, PPIs = proton pump inhibitors, SAP = stroke-associated pneumonia.

## INTRODUCTION

Stroke-associated pneumonia (SAP) is a common medical complication and is also a critical risk factor for mortality and morbidity after stroke.<sup>1,2</sup> The annual cost of pneumonia treatment after an acute stroke is approximately USD 459 million in the United States.<sup>3</sup> Therefore, identifying the risk factors of SAP is essential for clinical practice. Several recent studies have focused on the development of a risk score to predict SAP, but none have accounted for a patient's medication.<sup>4–6</sup> After a stroke, gastrointestinal (GI) disorders are common, and acid-suppressive drugs are frequently prescribed to treat diseases involving excessive acid production. However, a reduction in gastric acid secretion may allow pathogen colonization in the upper gastrointestinal tract.<sup>7,8</sup> Patients with stroke are likely to be more vulnerable to these pathogens because dysphagia can promote aspiration, causing pneumonia.

Acid-suppressive drugs including histamine-2 receptor antagonists (H2RAs) and proton pump inhibitors (PPIs) have been reported to be positively associated with the risk of pneumonia in various disease populations.<sup>9–11</sup> However, this association requires clarification regarding patients with stroke; therefore, we investigated the association between acid-suppressive drug usage and the risk of SAP in a large, population-based cohort.

## METHODS

### Data Source

The study protocol was approved by the Institutional Review Board of Chung Shan Medical University Hospital and exempt from full review because the insurance reimbursement claims data used in this study were available for public access. This dataset was obtained from the Longitudinal Health Insurance Database 2010 (LHID2010), which is a subset of the National Health Insurance Research Database that is managed by the Taiwanese National Health Research Institutes. This dataset contains benefit claims and details of patient care order for all health care services including the emergency department, inpatient, and outpatient care

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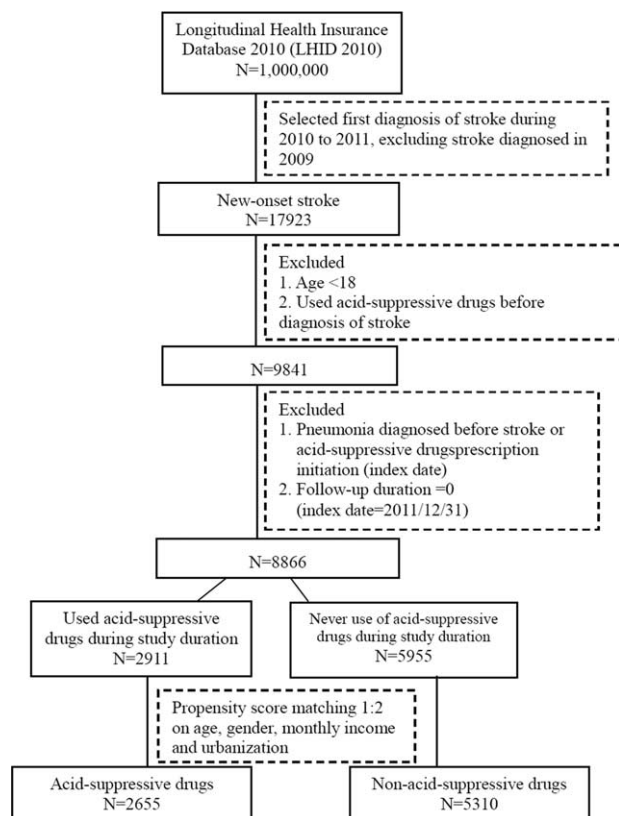


FIGURE 1. Flow chart for patient selection.

for one million beneficiaries randomly sampled between 2008 and 2012. The disease diagnosis codes in this study were derived from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Because all of the insurance claims were examined by medical reimbursement specialists and peer review, the diagnosis coding in this study was highly reliable. Taiwan National Health Insurance Administration issues certificates to patients who have major illness including hemorrhagic and ischemic stroke.<sup>12</sup>

## Study Population

A retrospective cohort study was designed in our study. All adult patients  $\geq 18$  years with new-onset ischemic and hemorrhagic stroke between January 1, 2010 and December 31, 2011 were identified. The diagnosis of stroke was defined according to (ICD-9-CM) Codes 430 (subarachnoid hemorrhage), 431–432 (intracerebral hemorrhage), 433–438 (ischemic cerebrovascular disease). The index date was defined as the date of new-onset stroke diagnosis. Subjects were excluded if they had a previous history of stroke before the index date, they were exposed to acid-suppressive drugs before the index date, and they had a history of pneumonia within 1 year before the index date. We additionally excluded patients presenting with pneumonia on the admission index date for new-onset stroke and index date on December 31, 2011. Figure 1 illustrates our study framework.

## Exposure to Acid-Suppressive Drugs

Patients with the diagnosis of stroke who had used acid-suppressive drugs after the index date were included in case group. In Taiwan, 5 H2RAs (cimetidine, famotidine, nizatidine, ranitidine, and roxatidine) and 5 PPIs (omeprazole, pantoprazole, lansoprazole, esomeprazole, and rabeprazole) are available. We used a 1:2 propensity score to match for age, sex, monthly income, and urbanization in the comparison cohort analysis. Our study endpoint was the diagnosis of pneumonia (ICD-9-CM codes 481, 482.xx, 483.xx, 485, and 486), withdrawal from the National Health Insurance (NHI) program, or December 31, 2011, whichever occurred first. So, each patient, regardless of acid-suppressive drug use, was followed up to identify the occurrence of pneumonia. The average follow-up duration was 0.9 years.

## Sociodemographic Characteristics and Comorbidities

Baseline sociodemographic characteristics, such as age, sex, level of urbanization, and income (less than NT\$ 19200 and more than NT\$ 19200), were recorded. Level of urbanization was classified as urban, suburban, and rural. All of the comorbidities included in the Charlson comorbidity index were recorded,<sup>13</sup> with the exception of human immunodeficiency virus/acquired immunodeficiency syndrome owing to insufficient numbers of patients with this disease. Additionally, patient conditions, such as artificial ventilation (tracheostomy or mechanical ventilation) usage, nasogastric tube feeding, angiotensin converting enzyme inhibitor usage, gastrostomy, consciousness status, and stroke-related disability, were also taken into consideration.

## Statistical Analysis

The differences in demographic variables between acid-suppressive drug usage and the nonacid-suppressive drug usage group were analyzed using a  $\chi^2$  test for categorical variable and an independent *t* test for continuous variables. The cumulative incidence of pneumonia was assessed using the Kaplan–Meier method between acid-suppressive drug cohort and the nonacid-suppressive drug cohort, and the significance was determined using a log-rank test. Cox proportional hazards model analysis was performed to estimate the hazard ratios (HRs) of pneumonia in the acid-suppressive drug usage and the nonacid-suppressive drug usage group. A multivariate Cox proportional hazard regression model analysis was performed to estimate the adjusted HRs and 95% CIs for SAP development in the acid-suppressive drug usage cohort compared with the control cohort, adjusting for sex, age, monthly income, urbanization, angiotensin converting enzyme inhibitor usage, artificial ventilation, nasogastric tube feeding, gastrostomy, and comorbidities. All statistical analyses were performed using SPSS Version 18.0 (SPSS Inc, Chicago, IL). A 2-sided *P* value  $< 0.05$  was considered statistically significant.

## RESULTS

In total, 17,923 patients with new-onset stroke were identified over a 2-year study period. After exclusions, the study cohort comprised 2911 and 5955 participants in the acid-suppressive drug usage and nonacid-suppressive drug usage groups, respectively. Overall, 7965 participants (2655 acid-suppressive drug usage and 5310 nonacid-suppressive drug usage) were eligible for final analysis after propensity-score

**TABLE 1.** Baseline Demographic and Clinical Data of Patients with Stroke Who Did and Did Not Use Acid-Suppressive Drugs (n = 2655 and 5310, Respectively)

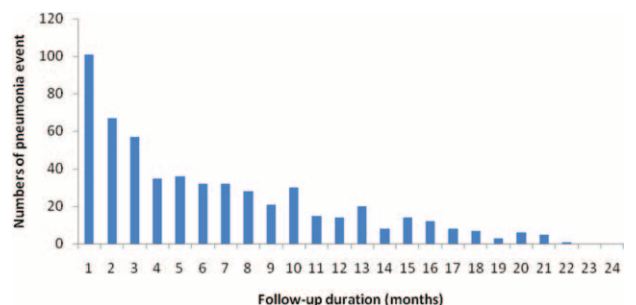
	Acid-Suppressive Drugs (N = 2655)		Non-Acid-Suppressive Drugs (N = 5310)		P-value
	n	%	n	%	
Sex					0.679
Female	1230	46.33	2434	45.84	
Male	1425	53.67	2876	54.16	
Age in index date, yr					0.453
18–39	170	6.40	372	7.01	
40–64	1144	43.09	2319	43.67	
≥ 65	1341	50.51	2619	49.32	
Mean ± SD	64.32 ± 15.05		64.02 ± 15.02	0.400	
Monthly income					0.835
≤ NT\$19200	1521	57.29	3055	57.53	
> NT\$19200	1134	42.71	2255	42.47	
Urbanization					0.873
Urban	1570	59.13	3172	59.74	
Suburban	857	32.28	1691	31.85	
Rural	228	8.59	447	8.42	
Angiotensin converting enzyme inhibitor	674	25.39	993	18.70	<0.001**
Artificial ventilation	530	19.96	149	2.81	<0.001**
Nasogastric tube feeding	739	27.83	302	5.69	<0.001**
Gastrostomy	7	0.26	1	0.02	0.003**
Myocardial infarction	54	2.03	74	1.39	0.032**
Congestive heart failure	194	7.31	288	5.42	0.001**
Peripheral vascular	89	3.35	133	2.50	0.030*
Dementia	245	9.23	474	8.93	0.658
Chronic pulmonary disease	551	20.75	894	16.84	<0.001**
Peptic ulcer disease	697	26.25	471	8.87	<0.001**
Mild liver disease	302	11.37	428	8.06	<0.001**
Moderate or severe liver disease	12	0.45	7	0.13	0.006**
Diabetes, uncomplicated	771	29.04	1490	28.06	0.361
Diabetes, complicated	247	9.30	430	8.10	0.069
Hemiplegia or paraplegia	122	4.60	127	2.39	<0.001**
Renal disease	248	9.34	344	6.48	<0.001**
Malignancy, including leukemia and lymphoma	247	9.30	272	5.12	<0.001**
Metastatic solid tumor	28	1.05	10	0.19	<0.001**
Gastrointestinal hemorrhage	175	6.59	85	1.60	<0.001**
Alcohol /drug abuse	55	2.07	72	1.36	0.016*
Consciousness disturbance	122	4.60	108	2.03	<0.001**
Aphasia	35	1.32	21	0.40	<0.001**

SD = standard deviation.  
\*P < 0.05, \*\*P < 0.01.

matching for age, sex, monthly income, and urbanization at a ratio of 1:2 (Figure 1).

Table 1 lists the demographic characteristics, comorbidities, and clinical condition of the patients with stroke who did and did not use acid-suppressive drugs. The mean ages of these 2 groups were 64.32 ± 15.05 and 64.02 ± 15.02 years, respectively. The patients diagnosed with stroke were predominantly men. Patients who received acid-suppressive drug therapy were more likely to have several preexisting illnesses, such as myocardial infarction, congestive heart failure, peripheral vascular disease, chronic pulmonary disease, peptic ulcer disease, liver disease, renal disease, malignancy, gastrointestinal hemorrhage, and alcohol or drug abuse.

Figure 2 illustrates the time elapsed from new-onset stroke to developing pneumonia. Over 40% (225/552) of patients



**FIGURE 2.** Time elapsed between new-onset stroke and development of pneumonia.

**TABLE 2.** Cox Proportional Hazards Model Analysis for the Risk of Developing Stroke-Associated Pneumonia

	Observed Person-Years	No. of Pneumonia Event	Incidence Density (Per 100 Person-Years)	Crude HR	95% CI		Adjusted HR <sup>†</sup>	95% CI	
					Lower	Upper		Lower	Upper
Acid-suppressive drugs									
No	5141	251	4.9	1			1		
Yes	1983	301	15.2	2.96**	2.50	3.50	1.44**	1.18	1.75
Acid-suppressive drugs									
None	5141	251	4.9	1			1		
H2RA alone	1159	123	10.6	2.07**	1.66	2.56	1.40**	1.11	1.76
PPI alone	355	65	18.3	3.53**	2.69	4.64	1.37*	1.01	1.86
Both	469	113	24.1	4.76**	3.81	5.94	1.57**	1.19	2.06

CI = confidence interval, H2RA = histamine-2 receptor antagonist, PPI = proton pump inhibitor.

<sup>†</sup> Adjusted for sex, age, monthly income, urbanization, angiotensin converting enzyme inhibitor, artificial ventilation, nasogastric tube feeding, gastrostomy, and comorbidities.

\**P* < 0.05, \*\**P* < 0.01.

developed pneumonia within 3 months after acute stroke. The incidence of acute (pneumonia developing within a month after stroke) and chronic (when it occurs later than a month) SAP was 1.27% (101/7965) and 6.15% (451/7330), respectively.

Table 2 shows the crude and adjusted HRs for developing pneumonia after stroke. The risk of pneumonia increased in patients with stroke receiving acid-suppressive drugs (crude HR = 2.96, 95% CI = 2.5–3.5). Acid-suppressive drug usage was an independent risk factor of pneumonia. The adjusted HR

for the risk of pneumonia was 1.44 (95% confidence interval [CI] = 1.18–1.75, *P* < 0.01). After adjustment for all potential confounders, risk of pneumonia increased in patients with stroke exposed to H2RAs, PPIs, or both (adjusted HR = 1.40, 1.38, and 1.57, respectively).

Table 3 shows the impact of acid-suppressive drugs on acute and chronic SAP. In acute SAP, the crude HR of acid-suppressive drugs was 2.91 (95% CI = 1.96–4.33). However, exposure to acid-suppressive drugs was not a risk factor of acute

**TABLE 3.** Cox Proportional Hazards Model Analysis for the Risk of Developing Acute and Chronic Stroke-Associated Pneumonia in Patients Who Did and Did Not Use Acid-Suppressive Drugs

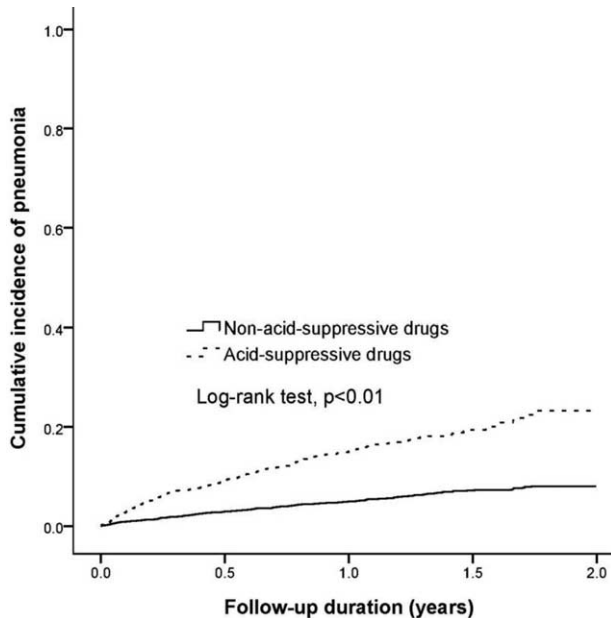
	No. of Patients	No. of Pneumonia Event	Crude HR	95% CI		Adjusted HR <sup>†,‡</sup>	95% CI	
				Lower	Upper		Lower	Upper
Follow-up duration (≤1 month)								
Acid-suppressive drugs								
No	5310	42	1			1		
Yes	2655	59	2.91**	1.96	4.33	1.01	0.63	1.62
Acid-suppressive drugs								
None	5310	42	1			1		
H2RA alone	1550	33	2.78**	1.76	4.39	1.39	0.85	2.29
PPI alone	536	13	3.30**	1.77	6.14	0.67	0.33	1.37
Both	569	13	2.93**	1.57	5.45	0.58	0.28	1.17
Follow-up duration (>1 month)								
Acid-suppressive drugs								
No	4987	209	1			1		
Yes	2343	242	2.97**	2.47	3.58	1.41**	1.13	1.76
Acid-suppressive drugs								
None	4987	209	1			1		
H2RA alone	1374	90	1.89**	1.47	2.42	1.26	0.97	1.64
PPI alone	445	52	3.59**	2.65	4.87	1.46*	1.04	2.05
Both	524	100	5.18**	4.08	6.57	1.72**	1.28	2.32

CI = confidence interval, H2RA = histamine-2 receptor antagonist, PPI = proton pump inhibitor.

<sup>†</sup> Follow-up duration (≤1 month): adjusted for sex, age, monthly income, urbanization, angiotensin converting enzyme inhibitor, artificial ventilation, nasogastric tube feeding, and comorbidities, excluding myocardial infarction, moderate or severe liver disease, and metastatic solid tumor.

<sup>‡</sup> Follow-up duration (>1 month): adjusted for sex, age, monthly income, urbanization, angiotensin converting enzyme inhibitor, artificial ventilation, nasogastric tube feeding, gastrostomy, and comorbidities.

\**P* < 0.05, \*\**P* < 0.01.



**FIGURE 3.** Kaplan–Meier curves of the cumulative incidence of stroke-associated pneumonia in patients who did and did not use acid-suppressive drugs.

SAP after adjustment for comorbidities and stroke severity. PPI usage was associated with an increased risk of pneumonia after similar adjustments for chronic SAP (adjusted HR = 1.46; 95% CI = 1.04–2.05).

Figure 3 depicts the Kaplan–Meier curves of the occurrence of pneumonia in patients with stroke exposed to acid-suppressive drugs. The cumulative incidence of pneumonia was higher in the acid-suppressive drug exposure group than in the nonacid-suppressive drugs exposure group throughout the 2-year follow-up period. The difference was significant, based on the log-rank test ( $P < 0.01$ ).

## DISCUSSION

SAP is a potentially preventable stroke complication, which can be classified as acute (when pneumonia develops within a month after stroke) and chronic (when it occurs later than a month) according to the Teramoto et al classification.<sup>14</sup> Previous studies have identified several risk factors associated with SAP, such as older age, male sex, higher stroke severity, lower level of consciousness, diabetes mellitus, dysphagia, middle cerebral artery infarction, and use of mechanical ventilation.<sup>15–18</sup> In this large population-based study, acid-suppressive drug usage was an independent risk factor of SAP. The incidence of pneumonia was 15.2 (301/1983) per 100 person-years. After adjustment for comorbidities and stroke severity, stroke patients exposed to acid-suppressive drugs were associated with an HR of 1.44 for the subsequent development of pneumonia, which is lower than that of a study conducted by Herzig et al, which reported an HR value of 2.3 (95% CI = 1.2–4.6) in a single hospital-based study.<sup>19</sup> Moreover, a Chinese single-hospital-based study also revealed a 2.8-fold increase in the development of SAP with H2RAs exposure.<sup>20</sup> Our study is the first to investigate the relationship between acid-suppressive drugs and patients with new-onset stroke by using a population-based data set. The strength of this cohort study was the use of the LHID2010, which is a nationwide database including

1 million insurants randomly selected from the 2010 Registry for Beneficiaries. The Taiwanese NHI system was established in 1995 and covers the medical expenses of approximately 98% of the Taiwanese population; thus, the data accurately represent medical conditions in Taiwan.

The incidence of SAP has been reported in the range of 2.7%–56.6%.<sup>20–22</sup> This wide range of SAP incidences can be explained by differing study settings. A high incidence rate of SAP is observed in intensive care units because it is associated with patients' stroke severity and use of mechanical ventilators. Our results revealed that the incidence rates of acute (<1 mo) and chronic (>1 mo) SAP were 1.27% (101/7965) and 6.15% (451/7330), respectively. Our results also demonstrated that acid-suppressive drug usage is a risk factor of chronic SAP (adjusted HR = 1.41, 95% CI = 1.13–1.76). Moreover, the risk of chronic SAP was significantly correlated with PPI exposure (Table 3). The results suggest that acid-suppressive drug usage is not a risk factor of acute SAP.

At the acute stroke stage, multiple risk factors are involved in the pathogenesis of pneumonia. SAP was mostly ascribed to aspiration of oropharyngeal or gastric content. Oral flora rapidly alters after stroke and is replaced by aerobic gram-negative bacilli colonization.<sup>23</sup> Impaired consciousness, dysphagia, absence of protective reflex, and use of mechanical ventilation play a crucial role in the development of pneumonia because they promote aspiration. Another new theory of SAP pathophysiology is stroke-induced immunodepression.<sup>18,24</sup> Systemic anti-inflammatory responses, such as lymphocyte apoptosis, suppression of peripheral cytokine release, inhibition of Th1, and alteration of Th1/Th2 ratio, have been observed in clinical studies of patients with acute stroke.<sup>25–27</sup> These immunological alterations possibly facilitate poststroke infections such as pneumonia and urinary tract infection.

During the chronic stroke stage, GI disorders such as gastroesophageal reflux, peptic ulcer disease, and GI bleeding are common. Infection, nasogastric tube placement, and chronic medications such as aspirin and clopidogrel are factors contributing to the aforementioned GI disorders. Acid-suppressive drugs are commonly prescribed to treat these GI disorders. The rate of exposure to acids-suppressive drugs in our study was 32.8% (2911/8866), which is lower than a general hospitalized patient population, for which an exposure rate of 40%–80% has been reported among new admissions.<sup>19,28,29</sup> A low exposure rate may be explained by the Taiwanese health policy; in Taiwan, PPIs are prescribed only to patients undergoing upper GI endoscopy and with a positive result of gastroesophageal reflux or peptic ulcer disease.

PPIs have been reported to increase the risk of pneumonia in various disease populations.<sup>9–12</sup> Several mechanisms have been proposed to explain how PPIs contribute to pneumonia. A high gastric pH value reduces the elimination of ingested pathogens because gastric acid is a critical barrier against pathogen invasion, thereby predisposing patients with stroke to pneumonia after aspiration.<sup>7,8</sup> Additionally, PPIs have been demonstrated to impair leukocyte function.<sup>30</sup> The impact of the aforementioned adverse effects is likely to be significant in patients with stroke because of easy aspiration and immunodepression. However, data on the association between PPIs and SAP is limited. Ran et al observed that PPI usage as a prophylactic treatment of stress-related mucosal damage was associated with a higher incidence of nosocomial pneumonia in patients with intracerebral hemorrhagic stroke.<sup>31</sup> Several recent studies have reported that the association between PPI usage and pneumonia may be confounded.<sup>32</sup> Sarkar et al observed that

PPI therapy initiated within 30 days after hemorrhagic stroke diagnosis was associated with an increased risk of community-acquired pneumonia but not with long-term usage.<sup>33</sup>

In our study, we observed a small increase in the risk of chronic SAP on PPI usage. However, the effect was stronger for combined PPI and H2RA usage. Therefore, physicians should exercise caution when prescribing acid-suppressive drugs to stroke patients. Limitations of our study should be considered. First, clinical parameters, such as scores of the Glasgow Coma Scale, National Institutes of Health Stroke Scale, and Modified Rankin Scale, of the patients with stroke were unavailable. Patients with a higher stroke severity and lower level of consciousness may have higher infection rates. To overcome this bias, we adjusted the potential stroke severity confounders by using ICD-9-CM codes for hemiplegia or paraplegia, aphasia, and unconsciousness for analysis. Second, the database does not include information on patient compliance with over-the-counter PPIs. Thus, the effects of PPIs usage may have been underestimated. Third, there were significant differences in baseline characteristics between those exposed and those unexposed to acid-suppressive drugs. Compared with those never exposed to acid-suppressive drugs, users of acid-suppressive drugs were generally less healthy. To overcome this potential bias, all factors that were different in the control group were adjusted for the subsequent analysis. Fourth, several potential lifestyle confounders associated with pneumonia, such as smoking, body weight, and poor dental hygiene, are not included in this database.

## CONCLUSIONS

In this large population-based study, acid-suppressive drug usage was associated with a slight increase in the risk of SAP. Moreover, a positive relationship was observed between PPIs and the risk of chronic SAP but not between PPIs and the risk of acute SAP. Therefore, physicians should exercise caution when prescribing acid-suppressive drugs to patients with stroke, particularly PPIs for patients with chronic stroke.

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## REFERENCES

- Ji R, Wang D, Shen H, et al., China National Stroke Registry (CNSR) Investigators. Interrelationship among common medical complications after acute stroke: pneumonia plays an important role. *Stroke*. 2013;44:3436–3444.
- Vermeij FH, Scholte op Reimer WJ, de Man P, et al., Netherlands Stroke Survey Investigators. Stroke-associated infection is an independent risk factor for poor outcome after acute ischemic stroke: data from the Netherlands Stroke Survey. *Cerebrovasc Dis*. 2009;27:465–471.
- Katzan IL, Dawson NV, Thomas CL, et al. The cost of pneumonia after acute stroke. *Neurology*. 2007;68:1938–1943.
- Ji R, Shen H, Pan Y, et al., China National Stroke Registry Investigators. Novel risk score to predict pneumonia after acute ischemic stroke. *Stroke*. 2013;44:1303–1309.
- Li L, Zhang LH, Xu WP, et al. Risk assessment of ischemic stroke associated pneumonia. *World J Emerg Med*. 2014;5:209–213.
- Harms H, Grittner U, Dröge H, et al. Predicting post-stroke pneumonia: the PANTHERIS score. *Acta Neurol Scand*. 2013;128:178–184.
- Thorens J, Froehlich F, Schwizer W, et al. Bacterial overgrowth during treatment with omeprazole compared with cimetidine: a prospective randomised double blind study. *Gut*. 1996;39:54–59.
- Giannella RA, Broitman SA, Zamcheck N. Influence of gastric acidity on bacterial and parasitic enteric infections. A perspective. *Ann Intern Med*. 1973;78:271–276.
- Laheij RJ, Sturkenboom MC, Hassing RJ, et al. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. *JAMA*. 2004;292:1955–1960.
- Chen CH, Lin HC, Lin HL, et al. Proton pump inhibitor usage and the associated risk of pneumonia in patients with chronic kidney disease. *J Microbiol Immunol Infect*. 2013pii: S1684-1182(13)00198-9. doi: 10.1016/j.jmii.2013.10.004.
- Dublin S, Walker RL, Jackson ML, et al. Use of proton pump inhibitors and H2 blockers and risk of pneumonia in older adults: a population-based case-control study. *Pharmacoepidemiol Drug Saf*. 2010;19:792–802.
- Ho SW, Tsai MC, Teng YH, et al. Population-based cohort study on the risk of pneumonia in patients with non-traumatic intracranial haemorrhage who use proton pump inhibitors. *BMJ Open*. 2014;4:e006710.
- Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373–383.
- Teramoto S. Novel preventive and therapeutic strategy for post-stroke pneumonia. *Expert Rev Neurother*. 2009;9:1187–1200.
- Walter U, Knoblich R, Steinhagen V, et al. Predictors of pneumonia in acute stroke patients admitted to a neurological intensive care unit. *J Neurol*. 2007;254:1323–1329.
- Alsumrain M, Melillo N, Debari VA, et al. Predictors and outcomes of pneumonia in patients with spontaneous intracerebral hemorrhage. *J Intensive Care Med*. 2013;28:118–123.
- Hilker R, Poetter C, Findeisen N, et al. Nosocomial pneumonia after acute stroke: implications for neurological intensive care medicine. *Stroke*. 2003;34:975–981.
- Emsley HC, Hopkins SJ. Acute ischaemic stroke and infection: recent and emerging concepts. *Lancet Neurol*. 2008;7:341–353.
- Herzig SJ, Doughty C, Lahoti S, et al. Acid-suppressive medication use in acute stroke and hospital-acquired pneumonia. *Ann Neurol*. 2014;76:712–718.
- Sui R, Zhang L. Risk factors of stroke-associated pneumonia in Chinese patients. *Neurol Res*. 2011;33:508–513.
- Lipson DM, Sangha H, Foley NC, et al. Recovery from stroke: differences between subtypes. *Int J Rehabil Res*. 2005;28:303–308.
- Yeh SJ, Huang KY, Wang TG, et al. Dysphagia screening decreases pneumonia in acute stroke patients admitted to the stroke intensive care unit. *J Neurol Sci*. 2011;306:38–41.
- Millns B, Gosney M, Jack CI, et al. Acute stroke predisposes to oral gram-negative bacilli: a cause of aspiration pneumonia? *Gerontology*. 2003;49:173–176.
- Haeusler KG, Schmidt WU, Föhring F, et al. Cellular immunodepression preceding infectious complications after acute ischemic stroke in humans. *Cerebrovasc Dis*. 2008;25:50–58.
- Vogelgesang A, Grunwald U, Langner S, et al. Analysis of lymphocyte subsets in patients with stroke and their influence on infection after stroke. *Stroke*. 2008;39:237–241.
- Prass K, Meisel C, Höflich C, et al. Stroke-induced immunodeficiency promotes spontaneous bacterial infections and is mediated by sympathetic activation reversal by poststroke T helper cell type 1-like immunostimulation. *J Exp Med*. 2003;198:725–736.

27. Chamorro Á, Meisel A, Planas AM, et al. The immunology of acute stroke. *Nat Rev Neurol*. 2012;8:401–410.
28. Nardino RJ, Vender RJ, Herbert PN. Overuse of acid-suppressive therapy in hospitalized patients. *Am J Gastroenterol*. 2000;95:3118–3122.
29. Pham CQ, Regal RE, Bostwick TR, et al. Acid suppressive therapy use on an inpatient internal medicine service. *Ann Pharmacother*. 2006;40:1261–1266.
30. Scaringi L, Cornacchione P, Fettucciari K, et al. Activity inhibition of cytolytic lymphocytes by omeprazole. *Scand J Immunol*. 1996;44:204–214.
31. Ran L, Khatibi NH, Qin X, et al. Proton pump inhibitor prophylaxis increases the risk of nosocomial pneumonia in patients with an intracerebral hemorrhagic stroke. *Acta Neurochir Suppl*. 2011;111:435–439.
32. Jena AB, Sun E, Goldman DP. Confounding in the association of proton pump inhibitor use with risk of community-acquired pneumonia. *J Gen Intern Med*. 2013;28:223–230.
33. Sarkar M, Hennessy S, Yang YX. Proton-pump inhibitor use and the risk for community-acquired pneumonia. *Ann Intern Med*. 2008;149:391–398.