Association between Angiotensin-Converting Enzyme Inhibitors and Post-Stroke Aspiration Pneumonia

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Background: Previous small studies conducted around 2000 suggested an association between the use of angiotensin-converting enzyme inhibitors (ACEIs) and a reduction in post-stroke aspiration pneumonia (AP) in Japan. However, it is unclear whether receiving ACEIs can reduce post-stroke AP in the current clinical environment, where stroke management has been improved. This study aimed to re-evaluate the preventive effect of ACEIs on post-stroke AP, compared with that of angiotensin II receptor blockers (ARBs). *Methods:* Using the Japanese Diagnosis Procedure Combination database, we identified patients who were hospitalized for stroke and developed AP during hospitalization from July 2010 to December 2016. After applying the exclusion criteria, we performed 1:1 propensity score matching between patients receiving ACEIs and those receiving ARBs after discharge. The outcomes were 14-day, 30-day, and 90-day readmission for post-stroke AP among patients with stroke who had AP during their initial hospitalization. Cox regression was performed to analyze these readmissions. *Results:* In total, 35,586 eligible patients were identified. Of these patients, 5846 (16%) received ACEIs. Propensity score matching created 5789 pairs. No significant difference was seen in 14-day readmission (0.7% versus 0.8%), 30-day readmission (1.3% versus 1.3%), or 90-day readmission (2.4% versus 2.6%) between the ARB and ACEI groups. The hazard ratio of the ACEI group compared with the ARB group was not significant (1.21; 95% confidence interval: 0.98-1.48). *Conclusions:* In this retrospective nationwide study, ACEIs could not be concluded to have a preventive effect on post-stroke AP in the current clinical environment.

Key Words: Stroke—aspiration pneumonia—angiotensin-converting enzyme inhibitors—angiotensin II receptor blockers—patient readmission

Introduction

Patients with stroke have a higher risk of aspiration pneumonia (AP), compared with those who have not had a stroke.[1] A previous study showed that the risk of dying after a stroke was 3 times higher for patients diagnosed with AP.[2] Moreover, AP has been associated with the highest attributable mortality of all medical complications following stroke.[3] Thus, preventing post-stroke AP is important for reducing the risk of death from stroke.

Several studies have suggested a preventive effect of angiotensin-converting enzyme inhibitors (ACEIs) on AP after a stroke.[4-6] The findings of a previous observational study (n = 468) indicated that patients receiving ACEIs had a lower risk of AP after a stroke than did those who were not receiving ACEIs.[4] Another study (n = 404) showed that the incidence of pneumonia was significantly

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lower in ACEI-treated post-stroke patients (4.4%) than in those treated with angiotensin II receptor blockers (ARBs; 11.2%).[5] Based on these studies, the 2015 guidelines of the Japan Stroke Society recommended ACEIs for the pharmacological prevention of AP. In contrast, the European and American guidelines did not even mention this issue. Thus, ACEIs have been routinely used to reduce AP in older patients with stroke mainly in Japan.

The previous observational studies cited above were published around 2000 and were mostly small studies. However, it is unclear whether receiving ACEIs reduces the incidence of AP after a stroke in the current improved clinical environment. We believe that a re-evaluation of the preventive effect of ACEIs on post-stroke AP is essential. In this study, we aimed to assess whether ACEIs had a larger preventive effect on post-stroke AP than did ARBs, using a nationwide database in Japan.

Methods

Data Source

This study used the Diagnosis Procedure Combination database, a nationwide inpatient database in Japan.[7] Briefly, about 1000 hospitals in Japan, including all 82 academic hospitals, participate in the database and provide data on approximately 8 million inpatient admissions annually, representing about 50% of all acute-care inpatients in Japan.[8] The database contains discharge abstracts and administrative reimbursement data for inpatient episodes supplied by the participating hospitals. The following data are included: dates of admission and discharge; patient age and sex; body weight and height; smoking index; level of consciousness at admission, based on the Japan Coma Scale[9]; activities of daily living at admission and discharge, based on the Barthel index[10]; degree of disability in patients who have suffered a stroke, based on the modified Rankin scale at preclinical stage and at discharge[11,12]; primary and secondary diagnoses; pre-existing comorbidities on admission and complications after admission; procedures performed; medications and devices used; and in-hospital mortality. Diagnoses, comorbidities, and complications are recorded using International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) codes and text data in Japanese. A previous validation study showed good sensitivity and excellent specificity of diagnoses in the database.[13]

Study Design and Patient Selection

This study was a retrospective cohort study. Data from 1 July 2010 to 31 March 2017 were used for the present study. We included patients who were hospitalized for stroke (ICD-10 codes: I60-I63) and developed AP (J13-J18 and J69) during hospitalization. We excluded patients who (i) died during hospitalization; (ii) were aged less than or equal to 49 years at admission; (iii) underwent laryngoplasty, surgeries for swallowing disorders, tracheoplasty, or tracheostomy before or during the hospitalization for stroke; (iv) had tumors of the oral cavity, nasopharynx, hypopharynx, or neck; (v) were discharged on 1 January 2017 or later; (vi) were admitted more than 8 days after the onset of stroke or had an unknown date of the onset of stroke; or (vii) received both ACEIs and ARBs or neither of these 2 medicines. We included both AP (J69) and bacterial pneumonia (J13-J18) because AP is clinically difficult to distinguish from other types of pneumonia.[14]

Outcome Measurements

The outcomes were 14-day, 30-day, and 90-day readmission for post-stroke AP after discharge from 1 July 2010 to 31 March 2017.

Statistical Analysis

We used *t*-tests to compare averages for continuous variables and χ^2 tests to compare proportions for categorical variables between the ACEI and ARB groups.

We performed 1:1 nearest-neighbor matching between the ACEI and ARB groups based on estimated propensity scores for each patient receiving ACEIs or ARBs at discharge.[15] Propensity scores were calculated using a logistic regression model with 56 covariates (12 covariates on patient information, 12 on diseases, 19 on drugs, 13 on interventions; Table S1). After propensity score matching with a calliper width set at 20% of the standard deviation, the balancing properties of the matching covariates were examined through standardized differences between the ACEI and ARB groups.[15] An absolute standardized difference greater than 10% was considered to indicate a meaningful imbalance.[15]

We performed a Cox proportional hazard regression analysis for days from discharge to readmission to assess the hazard ratio (95% confidence interval) of the ACEI group compared with the ARB group with adjustment for patient backgrounds, while also adjusting for within-hospital clustering.

We also conducted subgroup analyses for 30-day readmission. Subgroups were defined by age, sex, severity (modified Rankin Scale at preclinical stage, Activities of Daily Living at admission), and stroke subtypes (subarachnoid hemorrhage, intracerebral hemorrhage, and cerebral infarction). We used χ^2 tests and Wilcoxon rank-sum tests to compare proportions for the outcomes between the ACEI and ARB groups within each subgroup.

The threshold for significance was set at $P < .05$. All statistical analyses were conducted using IBM SPSS, Version 25.0 and Stata/MP, Version 16.

Ethical Approval

Written informed consent was not required because of the anonymous nature of the data. The Ethics Committee of The University of Tokyo formally waived the requirement for written consent. The University of Tokyo Institutional Review Board approved the study.

Results

Data were analyzed for 166,033 patients with stroke and AP from 1 July 2010 to 31 March 2017. After the exclusion criteria were applied, the study cohort comprised 35,586 eligible patients (Figure 1). These patients were categorized into the ACEI (n = 5,846) and ARB (n = 29,740) groups, and 5789 propensity score-matched pairs were generated. Before propensity score matching, the median age (interquartile range) of patients was 81 (74-87) years in the ACEI group and 78 (68-84) years in the ARB group; after matching, these numbers were 81 (73.5-87) years in the ACEI group and 81 (73-87) years in the ARB group.

Tables 1 and 2 show the baseline characteristics of the unmatched ACEI and ARB groups (n = 35,586) and of the propensity score-matched groups (n = 11,578). In the unmatched groups, the ACEI group had higher proportions of cerebral infarction, use of antithrombotic drugs, nasal feeding, and gastrostomy. Patient characteristics were well balanced between the groups after propensity score matching.

Table 3 shows the proportions of 14-day, 30-day, and 90-day readmission for post-stroke AP. No significant difference between the ACEI and ARB groups was seen in 14-day, 30-day, or 90-day readmission.

In the Cox regression analysis, the hazard ratio for readmission for post-stroke AP was 1.21 (95% confidence interval: 0.98-1.48; $P = .072$).

Table S2 shows the percentages for the outcomes in each subgroup for the ACEI and ARB groups. There were no significant differences between the ACEI group and the ARB group.

Discussion

Using a nationwide inpatient database, this study examined the proportions of readmission for post-stroke AP among patients with stroke who had AP during their

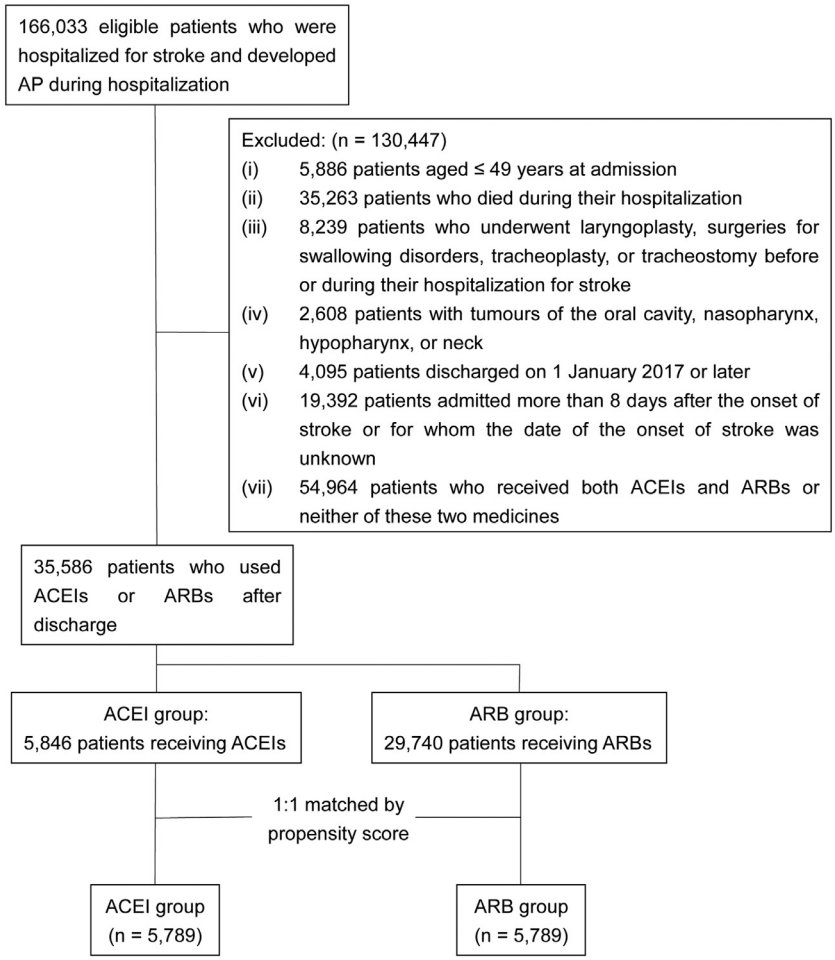

Figure 1. *Flowchart of selection of study subjects. Abbreviation: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; AP, aspiration pneumonia.*

Table 1. *Baseline characteristics before and after 1:1 propensity score matching*

	Unmatched groups			Propensity score- matched groups		
	ARB (n = 29,740) (%)	ACEI (n = 5846) (%)	ASD (%)	ARB (n = 5789) (%)	ACEI (n = 5789) (%)	ASD (%)
Sex						
Male	59.4	59.9	1.0	59.9	59.8	0.2
Age (years)						
50-60	9.9	4.7	20.1	5.1	4.8	1.4
61-70	20.2	13.2	18.9	13.6	13.3	0.9
71-80	30.8	29.3	3.3	28.8	29.4	1.3
81-90	32.5	41.2	18.1	40.9	41.1	0.4
≥91	6.7	11.5	16.7	11.6	11.4	0.6
Body mass index (kg/m^2)						
<18.5	13.9	18.3	12.0	17.8	18.1	0.8
18.5-20.9	20.0	21.7	4.2	21.3	21.7	1.0
21.0-22.9	18.8	18.2	1.5	18.0	18.3	0.8
23.0-24.9	15.5	13.8	4.8	13.6	13.9	0.9
25.0-29.9	16.0	11.5	13.1	11.8	11.5	0.9
≥30.0	3.2	1.9	8.3	2.0	1.9	0.7
Missing	12.6	14.7	6.1	15.5	14.6	2.5
Smoking						
Non-smoker	58.3	59.6	2.6	59.1	59.6	1.0
Ex- or current smoker	41.7	40.4	2.6	40.9	40.4	1.0
JCS at admission						
Alert	14.5	14.6	0.3	14.9	14.7	0.6
Dizziness	40.4	42.5	4.3	41.6	42.4	1.6
Somnolence	26.7	26.3	0.9	26.8	26.4	0.9
Coma	18.4	16.6	4.7	16.6	16.5	0.3
JCS at discharge						
Alert	39.9	38.2	3.5	38.3	38.3	0.0
Dizziness	48.3	47.6	1.4	47.5	47.6	0.2
Somnolence	9.2	10.9	5.7	10.9	10.9	0.0
coma	2.6	3.3	4.1	3.2	3.2	0.0
mRS at preclinical stage						
0	36.0	28.6	15.9	27.9	28.8	2.0
1	10.7	10.0	2.3	9.9	9.9	0.0
2	8.1	8.4	1.1	8.6	8.4	0.7
3	8.8	9.9	3.8	10.8	9.9	3.0
4	14.0	16.7	7.5	16.7	16.6	0.3
5	21.0	24.6	8.6	24.1	24.5	0.9
Missing	1.4	1.8	3.2	1.9	1.8	0.7
mRS at discharge						
0	3.1	2.1	6.3	2.0	2.1	0.7
1	5.6	4.2	6.5	3.7	4.2	2.6
2	8.4	6.6	6.8	7.3	6.6	2.8
3	11.6	10.5	3.5	11.1	10.5	1.9
4	31.8	29.9	4.1	30.1	30.0	0.2
5	38.3	45.5	14.6	44.7	45.3	1.2
Missing	1.0	1.3	2.8	1.3	1.3	0.0
ADL at admission						
0	60.4	60.1	0.6	60.0	60.1	0.2
5-50	13.7	14.5	2.3	14.7	14.6	0.3
55-95	3.2	3.1	0.6	3.2	3.1	0.6
100	4.5	3.6	4.6	3.7	3.7	0.0
Missing	18.1	18.6	1.3	18.4	18.5	0.3
ADL at discharge						
0	42.0	49.8	15.7	49.4	49.6	0.4
5-50	28.3	25.9	5.4	26.6	26.0	1.4

Table 1 (*Continued*)

	Unmatched groups			Propensity score- matched groups		
	ARB (n = 29,740) (%)	ACEI (n = 5846) (%)	ASD (%)	ARB (n = 5789) (%)	ACEI (n = 5789) (%)	ASD (%)
55-95	9.6	6.8	10.2	6.5	6.9	1.6
100	8.0	5.4	10.4	5.4	5.4	0.0
Missing	12.0	12.1	0.3	12.2	12.0	0.6
Destination after discharge						
Home	18.0	16.2	4.8	16.1	16.3	0.5
Other hospital	74.7	74.2	1.1	74.3	74.3	0.0
Others	7.3	9.6	8.3	9.6	9.4	0.7
Length of stay (days, mean [standard deviation])	56.1 (54.7)	58.0 (79.2)	2.8	57.6 (65.8)	58.0 (79.6)	0.5
Type of stroke						
Subarachnoid hemorrhage	8.0	4.1	16.4	4.1	4.1	0.0
Intracerebral hemorrhage	50.6	28.9	45.5	29.8	29.2	1.3
Other non-traumatic intracranial hemorrhage	1.5	1.6	0.8	1.5	1.7	1.6
Cerebral infarction	45.8	69.2	48.7	68.5	68.9	0.9
Diabetes	24.3	22.9	3.3	22.8	23.0	0.5
Hypertension	72.7	63.4	20.0	63.8	63.7	0.2
Dyslipidaemia	10.0	10.3	1.0	10.3	10.4	0.3
Dementia	6.5	9.0	9.4	9.5	8.9	2.1
Gastroesophageal reflux disease	14.2	14.3	0.3	14.2	14.3	0.3
Disorder after digestive system treatment	0.1	0.1	0.0	0.1	0.1	0.0
Parkinson's disease or Parkinsonian disorder	1.6	2.2	4.4	2.4	2.2	1.3
Epilepsy	13.4	9.4	12.6	9.7	9.4	1.0

Abbreviation: ACEI, angiotensin converting enzyme inhibitor; ADL, activities of daily living; ARB, angiotensin II receptor blocker; ASD, absolute standardized difference; JCS, Japan Coma Scale; mRS, modified Rankin Scale.

initial hospitalization, comparing those who received ACEIs with those who received ARBs. The proportions of readmission showed no significant difference between the 2 groups.

Previous studies indicated that ACEIs were associated with an increase in serum substance P levels in hypertensive patients with stroke.[5,16] Because substance P stimulates the swallowing reflex, ACEIs were found to have beneficial effects on the impaired swallowing reflex in patients with AP.[17] ACEIs inhibit not only the activation of angiotensin II, but also the degradation of substance P.[5] However, ARBs only have a mechanism to block angiotensin-II type I receptors. ACEIs may therefore be more beneficial than ARBs in preventing AP in older patients with hypertension and stroke.[5]

In the present study, we focused on patients with stroke. This is because post-stroke patients are generally susceptible to pneumonia because of the risk of aspiration associated with decreased protective reflexes of the respiratory system, mediated by substance P and post-stroke dysphagia.[18] Our study showed that the preventive effect of ACEIs on post-stroke AP was not significantly different from that of ARBs in patients who had a history of AP after stroke. Our results suggested that post-stroke patients receiving ACEIs and post-stroke patients receiving ARBs developed AP requiring hospital treatment at the same level of frequency. Our results also indicated that all differences between these treatment groups were insignificant when patients were divided into subgroups by age, sex, and severity of stroke. Thus, it could not be concluded that ACEIs prevent severe post-stroke AP.

Several limitations of this study should be acknowledged. First, we attempted to adjust for measured confounders by using propensity score matching, but we were not able to adjust for unmeasured confounders, such as severity of neurological dysfunction and pneumonia. Second, we used readmission rates as primary outcomes in this study, but not the recurrence of AP. This is because it was impossible to detect post-stroke AP treated in outpatient clinical settings using this dataset. Third, we could not include cases where patients were readmitted to another hospital because patient identifiers differ across hospitals. Additionally, we could not identify death events occurring outside the hospital.

In summary, although ACEIs have been routinely used to reduce AP in older patients with stroke, our findings suggest that ACEIs cannot be concluded to have a preventive effect on post-stroke AP. Our study presents clinicians with an opportunity to reconsider how they use ACEIs for preventing AP after stroke.

Table 2. *Baseline characteristics before and after 1:1 propensity score matching*

	Unmatched groups			Propensity score- matched groups		
	ARB (n = 29,740) (%)	ACEI (n = 5846) (%)	ASD (%)	ARB (n = 5789) (%)	ACEI (n = 5789) (%)	ASD (%)
Drug						
Antipsychotic drugs	57.4	54.6	5.6	54.7	54.6	0.2
Anti-dementia drugs	4.9	5.6	3.1	5.8	5.6	0.9
Antiemetic drugs	33.5	24.7	19.5	24.1	24.8	1.6
Antiepileptic drugs	21.1	16.5	11.8	17.2	16.5	1.9
Antitussive drugs	1.3	1.1	1.8	1.1	1.1	0.0
Muscle relaxants	19.1	9.3	28.4	9.5	9.4	0.3
Antidiabetic drugs	30.4	28.1	5.1	27.7	28.2	1.1
Steroids	14.5	11.0	10.5	11.4	11.0	1.3
Immunosuppressive drugs	0.3	0.3	0.0	0.4	0.3	1.7
Gastric secretion inhibitors	90.8	89.1	5.7	89.5	89.0	1.6
Antidyslipidemic drugs	22.1	24.2	5.0	24.5	24.3	0.5
Antithrombotic drugs	75.7	84.3	21.6	84.9	84.1	2.2
Antihypertensive drugs (CaB, αB, or βB)	90.1	76.5	37.1	77.0	77.0	0.0
Antihypertensive drugs (except ACEI, ARB, CaB, αB, and βB)	0.9	0.5	4.8	0.5	0.5	0.0
Diuretic drugs	36.1	42.6	13.3	42.9	42.5	0.8
Amantadine	5.2	10.5	19.8	9.6	10.1	1.7
Hange-koboku-to†	0.7	2.8	16.1	2.1	2.3	1.4
Nicergoline	1.6	2.0	3.0	2.2	2.0	1.4
Severe pneumonia antibiotics	74.0	77.0	7.0	76.0	76.9	2.1
Intervention						
Endoscopic swallowing function tests	4.1	5.4	6.1	5.5	5.4	0.4
Cerebrovascular rehabilitation fee	96.0	94.7	6.2	94.6	94.7	0.4
Feeding function therapy	27.2	26.5	1.6	26.0	26.6	1.4
Catheter exchange method for tube feeding or drug administration	1.0	0.9	1.0	0.8	0.9	1.1
Endotracheal intubation as a lifesaving measure	8.6	5.7	11.3	5.6	5.7	0.4
Ventilation	14.6	9.3	16.4	9.2	9.4	0.7
Liquid diet administered via gastrostomy	4.6	6.9	9.9	6.9	6.9	0.0
Nasal feeding	63.8	69.0	11.0	68.8	68.7	0.2
Craniotomy	4.7	2.3	13.1	2.4	2.4	0.0
Percutaneous surgery on the brain	4.1	3.8	1.5	3.8	3.9	0.5
Gastrostomy	8.2	11.1	9.8	11.4	11.0	1.3
Liberation from nasal feeding by discharge	63.5	56.1	15.1	56.6	56.5	0.2
Liberation from gastrostomy feeding by discharge	96.2	94.2	9.4	94.2	94.2	0.0

Abbreviation: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ASD, absolute standardized difference; CaB, calcium blocker; αB, alpha-blocker; βB, beta-blocker.

†Herbal medicine used for anxiety neurosis and swallowing disorder.

Table 3. *Outcomes after 1:1 propensity score matching*

	ARB		ACEI		*P* value
	n = 5789	(%)	n = 5789	(%)	
14-day readmission	38	0.7	44	0.8	.48
30-day readmission	75	1.3	76	1.3	.92
90-day readmission	141	2.4	149	2.6	.59

Abbreviation: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

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Conflicts of Interest

The authors declare that they have no competing interests.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2019.104444.

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