The Risk Of Intracranial Hemorrhage In Alzheimer's Disease Patients Treated With Antiplatelet Therapy

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Introduction

Antiplatelet therapy(APT), which comprises aspirin, clopidogrel, ticagrelor, etc, commonly used in primary prevention or secondary prevention for cardiovascular diseases or ischemic stroke. Patient on APT may at a higher risk of intracerebral hemorrhage (ICH). Cerebral amyloid angiopathy and cerebral microbleeds, which is commonly noted in Alzheimer's disease (AD), may precipitate a risk of antiplatelet-related cerebral hemorrhage. Two RCTs have observed a trend for increasing risk of ICH in AD patients who on aspirin treatment(1,2), but the sample size was small. This study aims to provide a large epidemiologic study that estimates the risk of ICH in patients with AD treated with APT.

Methods

We conducted a retrospective population-based cohort study, case-control-matched analysis. The AD cohort and non-AD cohort were selected from the National Health Insurance Research Database (NHIRD) from Taiwan. This study used NHIRD data from 2000-2013. The AD cohort was selected as patients diagnosed with AD or dementia (ICD-9 331.0, 290.0 to 290.3, 294.1, 331.2), who had received prescriptions of acetylcholinesterase inhibitors and memantine, between 2000 to 2012. AD patients with APT were then selected from AD cohort according to the use of APT. APT includes the use of aspirin at least 100mg, clopidogrel at least 75 mg, cilostazol at least 100 mg, ticlopidine at least 100 mg, aggrenox (aspirin 50 mg plus dipyridamole 400 mg), and ticagrelor 90 mg. The definition of APT was patients on continuous APT for at least 3 months. The cohort of AD without APT use were selected by 1:1 frequency match based on index year during 2000-2012. Non-AD groups were extracted from the remaining groups in NHIRD. The cohort of non-AD with APT use or without APT use were selected by 1:10 frequency match based on index year during 2000-2012 and the total non-AD group provided 16480 candidates.
To adjust for the potential baseline confounding factors due to imbalance in age, sex, or other covariates in four groups while preserving sample size, we used inverse probability of treatment weighting (IPTW) based on the propensity score. Primary outcome was the occurrence of ICH and subarachnoid hemorrhage (ICD-9-CM code 430-432). AD and non-AD groups with or without APT use were followed from index diagnosis of AD or index date of APT use until Dec. 31, 2013. Weighted Cox Proportional Hazards regression was used to estimate the risk of ICH in other 3 cohorts compared with non-AD without APT use (reference) group. Subgroup analyses were performed for the risk of ICH in categories defined by age and sex.

Result

The study results were presented in table 1-4.

Table 1: Demographic data (unweighted cohort)

	Unweighted cohort %				
	AD with APT (N=824)	AD without APT (N=824)	Non-AD with APT (N=8240)	Non-AD without APT (N=8240)	*p-value*[a]
Age					<0.01
40-64	6.92	14.93	55.87	85.01	
≥65	93.08	85.07	44.13	14.99	
Mean ± SD	76.79 ± 7.56	75.45 ± 9.71	63.16 ± 11.38	53.42 ± 10.63	<0.01
Gender					<0.01
Women	54.25	60.92	43.75	50.69	
Men	45.75	39.08	56.25	49.31	
Living area					<0.01
North	42.84	44.66	43.4	48.97	
Central	24.39	21.48	25.33	21.26	
South	29.73	30.22	27.43	27.05	
East and offshore	3.03	3.64	3.85	2.72	
Urbanization					<0.01
1 (most)	30.22	32.77	29.68	33.19	
2 (medium)	25.85	24.64	26.01	28.63	
3 (least)	43.93	42.6	44.31	38.18	
Enrollee category					<0.01
Comorbidity					
Ischemic Stroke	33.86	5.46	16.67	0.32	<0.01
Diabetes mellitus	40.29	21.36	36.29	7.74	<0.01
Hyperlipidemia	29.13	15.05	41.63	10.11	<0.01
Hypertension	79.37	45.51	78.87	17.71	<0.01
Coronary heart disease	41.75	8.74	49.09	3.16	<0.01
Heart failure	14.93	5.34	11	0.62	<0.01
CKD/ESRD	7.28	3.52	5.23	0.7	<0.01
Malignancy	8.74	10.32	6.12	3.51	<0.01
PAOD	4.61	1.7	5.39	0.51	<0.01
Alcohol use	0.24	0.24	0.25	0.12	0.15
Liver cirrhosis	9.59	7.77	11.84	6.06	<0.01

[a]Chi-square test or ANOVA.
[b]Fisher's exact test.

Table 2 Crude and adjusted hazard ratios for ICH among the four cohorts

Outcome	AD with APT	AD without APT	Non-AD with APT	Non-AD without APT
Person-year	3374.32	3393.03	50462.15	52130.32
No. of overall ICH	21	18	121	43
Incidence rate (10^{-3})	6.22	5.30	2.40	0.82
Person-year[a]	3476.09	4452.28	44638.32	70789.35
No. of overall ICH[a]	10	12	100	85
Incidence rate (10^{-3})[a]	2.88	2.70	2.24	1.20
Crude HR (95% CI)[a]	2.43 (1.28, 4.63)**	2.27 (1.25, 4.12)**	1.83 (1.37, 2.44)***	1.00
Adjusted HR (95% CI)[ab]	2.29 (1.19, 4.38)*	1.97 (1.08, 3.61)*	1.80 (1.34, 2.42)***	1.00
CRR (95% CI)[ac]	2.41 (1.23, 4.71)*	2.02 (1.10, 3.72)*	2.27 (1.67, 3.10)***	1.00

[a]Weighted by inverse probability of treatment weights method (IPTW).
[b]Adjustments for age, gender, living area, urbanization, enrollee category, monthly income and comorbidities.
[c]Fine and Gray competing risk regression model.
[d]Using a stratified Cox regression model.
*: p<0.05, **: p<0.01, ***: p<0.001.

Table 3. Crude and adjusted hazard ratios for ICH among the four cohorts (age stratification)

	40≤Age<65			
Outcome	AD with APT	AD without APT	Non-AD with APT	Non-AD without APT
Crude HR (95% CI)[a]	1.49 (0.47, 4.73)	2.65 (1.16, 6.01)*	1.48 (0.93, 2.34)	1.00
Adjusted HR (95% CI)[ab]	1.07 (0.32, 3.62)[d]	2.08 (0.87, 5.00)[d]	1.33 (0.82, 2.16)[d]	1.00
CRR (95% CI)[ac]	0.98 (0.27, 3.64)[d]	2.28 (0.94, 5.55)[d]	1.57 (0.98, 2.53)[d]	1.00
Outcome	Age ≥ 65			
Crude HR (95% CI)[a]	3.79 (1.74, 8.27)***	2.19 (0.91, 5.25)	2.30 (1.58, 3.35)***	1.00
Adjusted HR (95% CI)[ab]	2.57 (1.16, 5.72)*	1.37 (0.55, 3.44)	1.95 (1.32, 2.87)***	1.00
CRR (95% CI)[ac]	3.04 (1.28, 7.19)*	1.56 (0.58, 4.19)	2.53 (1.61, 3.98)***	1.00

[a]Weighted by inverse probability of treatment weights method (IPTW).
[b]Adjustments for age, gender, living area, urbanization, enrollee category, monthly income and comorbidities.
[c]Fine and Gray competing risk regression model.
[d]Using a stratified Cox regression model.
*: p<0.05, **: p<0.01, ***: p<0.001.

Table 4. Crude and adjusted hazard ratios for ICH among the four cohorts (sex stratification)

	Male			
Outcome	AD with APT	AD without APT	Non-AD with APT	Non-AD without APT
Crude HR (95% CI)[a]	3.20 (1.44, 7.10)**	0.81 (0.20, 3.37)	2.67 (1.81, 3.93)***	1.00
Adjusted HR (95% CI)[ab]	2.68 (1.19, 6.05)*[d]	0.61 (0.13, 2.76)[d]	2.32 (1.55, 3.47)***[d]	1.00
CRR (95% CI)[ac]	3.04 (1.28, 7.24)*[d]	0.72 (0.15, 3.50)[d]	3.17 (2.07, 4.84)***[d]	1.00
Outcome	Female			
Crude HR (95% CI)[a]	1.65 (0.54, 5.09)	3.42 (1.75, 6.72)***	1.07 (0.66, 1.71)	1.00
Adjusted HR (95% CI)[ab]	1.29 (0.41, 4.02)	1.59 (0.77, 3.28)	0.88 (0.54, 1.43)	1.00
CRR (95% CI)[ac]	1.36 (0.43, 4.27)	1.74 (0.80, 3.80)	1.00 (0.59, 1.68)	1.00

[a]Weighted by inverse probability of treatment weights method (IPTW).
[b]Adjustments for age, gender, living area, urbanization, enrollee category, monthly income and comorbidities.
[c]Fine and Gray competing risk regression model.
[d]Using a stratified Cox regression model.
*: p<0.05, **: p<0.01, ***: p<0.001.

Conclusion

Our retrospective, population-based cohort study suggested AD patients treated with APT are associated with higher risk of ICH compared with non-AD patients without APT. The ICH risk was higher in the elderly and male patients.

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