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Characteristics and outcomes of ischemic stroke in patients with known atrial fibrillation or atrial fibrillation diagnosed after stroke

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ABSTRACT

Background: It is unclear whether ischemic stroke patients with known atrial fibrillation (KAF) had different outcomes than those with atrial fibrillation diagnosed after stroke (AFDAS). We aimed to explore the characteristics and outcomes in ischemic stroke patients with KAF or AFDAS.

Methods: Consecutive patients hospitalized between 2000 and 2012 for first-ever stroke along with atrial fibrillation, either diagnosed before or during the stroke hospitalization, were identified from a nationwide claims database in Taiwan. The outcome of interest was a composite outcome of ischemic stroke, intracranial hemorrhage, or death within one year. Univariable and multivariable Cox regression analyses were used to determine the effect of KAF versus AFDAS on the composite outcome.

Results: We identified 1161 patients, of whom 481 (41.4%) had KAF and 680 (58.6%) had AFDAS. Age, sex, and stroke severity were similar between groups. However, patients with KAF had a higher prevalence of underlying heart diseases than those with AFDAS (67.2% versus 39.0%, $p < 0.001$). In univariable analysis, patients with KAF had a higher risk of the composite outcome than those with AFDAS (hazard ratio [HR]: 1.42, 95% confidence interval [CI]: 1.13–1.79, $p = 0.003$). In multivariable analysis, KAF was no longer independently associated with the composite outcome.

Conclusions: As compared to ischemic stroke patients with AFDAS, those with KAF had a higher prevalence of underlying heart diseases. Whether AF was known before or diagnosed after stroke was not an independent predictor of the composite outcome.

1. Introduction

Atrial fibrillation (AF) is the most common cardiac rhythm disorder, and its prevalence is expected to rise as the global population ages [1]. Compared to those without AF, patients with AF have a five times higher risk of stroke [2]. Furthermore, patients with AF and a history of previous stroke carry the highest risk of recurrent ischemic stroke, with a 15% risk during the first year after stroke (2.5 times higher than in those without a previous stroke) [3]. It is thus important to provide an adequate strategy of secondary prevention for stroke patients with AF.

Use of adjusted-dose vitamin K antagonist (warfarin) could reduce all stroke by >60% in patients with AF [4]. At this point in time, several direct oral anticoagulants have not only demonstrated at least non-inferiority to warfarin for the prevention of stroke, but also carried a lower risk of bleeding side effects as compared to warfarin [5]. Physicians may thus be more willing to use cardiac monitoring to identify AF in stroke patients and to administer anticoagulants to stroke patients with AF. These changes in clinical practice might contribute to the significant rise in the prevalence of AF among patients with ischemic stroke and transient ischemic attack because such an increasing trend could not solely be explained by age or other patient factors [6,7].

Recently, AF newly diagnosed after stroke (AFDAS) has been proposed to be a distinct entity from AF already known before stroke (KAF) in the pathophysiology, and possibly might have different clinical characteristics [8]. Although current stroke guidelines did not separate AFDAS and KAF regarding the treatment strategies [9,10], it remained unclear whether outcomes, such as recurrent stroke or mortality, are similar among ischemic stroke patients with KAF and AFDAS. Using an insurance claims database representative of the population of Taiwan, we aimed to explore the characteristics and one-year outcomes in ischemic stroke patients with KAF or AFDAS.

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2. Methods

2.1. Data source

In 1995, Taiwan launched its mandatory, single-payer National Health Insurance (NHI) program, which provides universal coverage for inpatient care, outpatient care, dental care, and prescription medications for its residents. This retrospective study used a subset of the claims data of NHI enrollees, the Longitudinal Health Insurance Database 2000 (LHID2000), which contains all the original claims data from 1997 to 2013 of one million subjects randomly sampled in the year 2000 from the 23.8 million enrollees of the NHI program. Because all patient identifiers in the LHID2000 have been encrypted to protect privacy, this study was exempt from a full review by the Institutional Review Board of Ditmanson Medical Foundation Chia-Yi Christian Hospital (CYCH-IRB No. 106035) and informed consent was deemed unnecessary.

2.2. Study population

Adult patients hospitalized between 2000 and 2012 with a principal discharge diagnosis of ischemic stroke (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 433.x and 434.x) were identified. The above codes have been used to ascertain a diagnosis of ischemic stroke with a sensitivity of 94.5% to 97.3% and a positive predictive value of 88.4% to 97.8% [11,12]. The first hospitalization for stroke in each patient during this period was designated as the index hospitalization. Transfers from the index hospitalization to other acute care hospitals were merged and treated as the same hospitalization. The date of admission was defined as the index date. Patients with a prior stroke, defined as having an ICD-9-CM code of 430 to 434, 436, or 438 in previous inpatient or outpatient claims records from 1997 until before the index hospitalization were excluded. Only patients with atrial fibrillation (ICD-9-CM code 427.31) listed in the secondary discharge diagnoses were included.

2.3. Independent variables

Baseline demographics, including age and sex, were obtained from the LHID2000. We gathered all diagnosis codes from the inpatient and outpatient claims in the one-year baseline period, and secondary diagnosis codes from the index hospitalization. Patients were diagnosed with a specific comorbidity if a corresponding ICD-9-CM code (Supplemental Table 1) was listed in the index hospitalization claims, in at least one prior inpatient claim, or in at least 2 prior outpatient claims [13]. In addition, patients who were prescribed lipid-lowering drugs, identified by the Anatomic Therapeutic Chemical (ATC) code C10, were considered to have hyperlipidemia [13]. Patients were assigned to the AFDAS group if the ICD-9-CM code for AF (427.31) had never been listed in any prior inpatient claims or outpatient claims and to the KAF group otherwise.

A modified version of the Charlson comorbidity index (CCI) was used to summarize comorbidity and was dichotomized into low (<2) or high (≥2) comorbidity [14]. The $CHADS_2$ [15] and CHA_2DS_2-VASc [16] scores for each patient were calculated. Treatment with intravenous tissue plasminogen activator during the index hospitalization was identified using ATC code B01AD02. Antithrombotic use for stroke prevention was determined using ATC codes B01AA, B01AE, and B01AF for oral anticoagulants and ATC code B01AC for antiplatelet agents.

Because clinical stroke scales were not available in the claims data, a validated proxy for stroke severity, the stroke severity index (SSI), was used to estimate patient stroke severity. The SSI is made up of seven items including airway suctioning, bacterial sensitivity test, general ward stay, intensive care unit stay, nasogastric intubation, osmotherapy, and urinary catheterization, which can be readily extracted from the index hospitalization claims [17]. The SSI highly correlated with admission National Institutes Health Stroke Scale (NIHSS) with a Pearson correlation coefficient of 0.742 [17] and can be converted to the NIHSS using the equation: estimated NIHSS = 1.1722 × SSI − 0.7533 [18]. It provided better case-mix adjustment of mortality models in patients with ischemic stroke when a clinical stroke scale was unavailable [18,19]. The estimated NIHSS was then categorized as mild (≤5), moderate (6–13), or severe (>13) stroke in accordance with a prior study [20], in which the NIHSS was used to predict stroke outcome.

2.4. Outcome variables

The outcome of interest was a composite outcome of ischemic stroke, intracranial hemorrhage, or death within one year after the index date. Ischemic stroke (433.x, 434.x, 436) and intracranial hemorrhage (430, 431, 432.x) were defined as an admission to an acute care hospital with a corresponding ICD-9-CM code as the principal discharge diagnosis. Mortality status was ascertained per a validated algorithm [21]. In addition, out-of-hospital death was assumed if a patient was disenrolled from the NHI program because the main reason for disenrollment is death [19]. The other reasons for disenrollment, which include moving overseas, being jailed for 2 months or more, and being missing for 6 months or more, are very unlikely for stroke survivors. All patients were observed until the occurrence of the composite outcome or until one year after the index date, whichever came first.

2.5. Statistical analysis

We reported continuous variables with means and standard deviations, and categorical variables with counts and percentages. Baseline characteristics of patients in the KAF and AFDAS groups were compared by Chi-square tests or Fisher's exact tests for categorical variables and *t*-tests or Mann–Whitney *U* tests for continuous variables. The Kaplan-Meier method was used to plot survival curves stratified by AF groups, and differences in time to the composite outcome were assessed using the log-rank test. Univariable Cox regression analysis was performed to assess the association between each independent variable and the composite outcome. All independent variables except for the $CHADS_2$ and CHA_2DS_2-VASc scores were entered in a multivariable Cox regression analysis with forward selection procedure to identify factors associated with the composite outcome. All variables with $p < 0.15$ were included in the model. After fitting the model, the proportional hazards assumption was assessed with the Schoenfeld test.

Because using two outpatient claims for ascertaining comorbidities might be too stringent and consequently lead to under-identification of comorbidities, we conducted a sensitivity analysis in which comorbidities were verified using one inpatient or one outpatient claim.

Two-tailed *p* values <0.05 were considered statistically significant. Statistical analyses were performed using Stata 15 (StataCorp, College Station, Texas).

3. Results

The study population consisted of 1161 patients (Supplemental Fig. 1), of whom 481 (41.4%) had been diagnosed with AF before stroke (KAF group) and 680 (58.6%) were diagnosed with AF after stroke (AFDAS group). Table 1 gives the characteristics of patients. Mean age and sex were not different between the two groups. Patients with KAF were more likely to have hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, congestive heart failure, and peripheral artery disease, and hence a greater burden of comorbidity and higher $CHADS_2$ and CHA_2DS_2-VASc scores. Underlying heart diseases (coronary artery disease or congestive heart failure) were more prevalent in the KAF group than in the AFDAS group (67.2% versus 39.0%, $p < 0.001$). Stroke severity was similar in both groups; however, patients with KAF had a marginally lower chance to receive oral anticoagulant for

Table 1
Patient characteristics.

Characteristics	Total ($n = 1161$)	KAF ($n = 481$)	AFDAS ($n = 680$)	*P*
Demographics				
Age, mean (SD)	73.6 (10.6)	73.6 (10.6)	73.6 (10.6)	0.985
Female	571 (49.2)	248 (51.6)	323 (47.5)	0.173
Risk factors				
Hypertension	818 (70.5)	364 (75.7)	454 (66.8)	0.001
Diabetes mellitus	344 (29.6)	158 (32.8)	186 (27.4)	0.043
Hyperlipidemia	342 (29.5)	161 (33.5)	181 (26.6)	0.012
CAD	400 (34.5)	222 (46.2)	178 (26.2)	<0.001
CHF	365 (31.4)	228 (47.4)	137 (20.1)	<0.001
PAD	66 (5.7)	37 (7.7)	29 (4.3)	0.013
Prior TIA	50 (4.3)	25 (5.2)	25 (3.7)	0.209
Modified CCI ≥ 2	404 (34.8)	234 (48.6)	170 (25.0)	<0.001
Stroke severity				0.305
Mild (eNIHSS ≤ 5)	418 (36.0)	163 (33.9)	255 (37.5)	
Moderate (eNIHSS 6–13)	221 (19.0)	100 (20.8)	121 (17.8)	
Severe (eNIHSS > 13)	522 (45.0)	218 (45.3)	304 (44.7)	
Treatments				
IV tPA	59 (5.1)	23 (4.8)	36 (5.3)	0.695
OAC	484 (41.7)	185 (38.5)	299 (44.0)	0.061
Antiplatelet	617 (53.1)	270 (56.1)	347 (51.0)	0.086
Risk scores				
$CHADS_2$, mean (SD)	1.9 (1.1)	2.2 (1.1)	1.7 (1.0)	<0.001[a]
CHA_2DS_2-VASc, mean (SD)	3.6 (1.6)	4.0 (1.5)	3.3 (1.5)	<0.001[a]
Outcomes within one year				
Ischemic stroke	96 (8.3)	46 (9.6)	50 (7.4)	0.178
ICH	13 (1.1)	4 (0.8)	9 (1.3)	0.575[b]
Mortality	209 (18.0)	102 (21.2)	107 (15.7)	0.017
Composite	296 (25.5)	143 (29.7)	150 (22.1)	0.003

Data are numbers (percentage) unless specified otherwise.
AFDAS: atrial fibrillation diagnosed after stroke; AMI: acute myocardial infarction; CAD: coronary artery disease; CHF: congestive heart failure; CCI: Charlson comorbidity index; eNIHSS: estimated National Institutes of Health Stroke Scale; ICH: intracranial hemorrhage; IV: intravenous; KAF: known atrial fibrillation; NIHSS: National Institutes of Health Stroke Scale; OAC: oral anticoagulant; PAD: peripheral artery disease; SD: standard deviation; TIA: transient ischemic attack; tPA: tissue plasminogen activator.
[a] Mann–Whitney *U* tests.
[b] Fisher's exact test.