Original Article

Atrial Fibrillation and Ischemic Stroke in Patients with Hypertension: A Multicenter Nation-Wide Study

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Background: Limited data had been reported regarding association between non-valvular atrial fibrillation [AF] and ischemic stroke in hypertensive patients as a nation-wide study in Thailand.

Objective: The primary objective of the present study was to investigate association between AF and stroke in patients with hypertension in a multicenter, nation-wide study in Thailand. Secondary objectives included 1) determine the prevalence of stroke in patients with hypertension, and 2) determining the extent of the increase in risk of ischemic stroke in patients with hypertension.

Materials and Methods: A cross-sectional study was conducted in hypertensive patients who visited 831 Thailand Ministry of Public Health [MoPH] hospitals between 2011 and 2012 to evaluate the status of standard care. Inclusion criteria were hypertensive patients aged 20 years old and older who received medical care in a MoPH hospital for at least 12 months. Main outcome measurements include AF rhythm, age, gender, cardiovascular risk factors, and ischemic stroke.

Results: Thirteen thousand two hundred seven patients with hypertension and available ECG data were included. AF was detected in 457 patients (3.46%). Five hundred thirty-six (4.1%) patients had stroke, with 503 (3.8%) having ischemic stroke. From multivariate logistic regression analysis, old age, male gender, AF, LDL-cholesterol less than 100 mg/dl, and high diastolic blood pressure were factors found to be independently associated with increased risk of ischemic stroke. Crude and multivariable adjusted odds ratio of AF and ischemic stroke was 2.32 (1.64 to 3.29) and 1.70 (1.09 to 2.65), respectively.

Conclusion: AF is an independent risk factor associated with ischemic stroke in patients with hypertension.

Keywords: Atrial fibrillation, Ischemic stroke, Hypertension

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Atrial fibrillation [AF] is a common arrhythmia and can lead to thromboembolic complications, most commonly ischemic stroke[1,2]. Annual incidence of ischemic stroke in patients with AF was approximately 5%[1,2]. Certain risk factors, such as heart failure, previous stroke, transient ischemic attack [TIA], diabetes mellitus, hypertension, and old age can increase the risk of ischemic stroke[3-5]. These immediate aforementioned factors are components of the CHADS2 score, which is a tool for assessment of stroke risk where a higher score means that the risk of ischemic stroke is higher[4]. Recently, European guidelines for management of AF recommended the use of CHA2DS2VASC score by adding vascular risk factors, and increasing the weight value of age[5]. The CHA2DS2VASC scoring system has been validated in both Western and Asian countries[6-8]. Annual risk of ischemic stroke relating to non-valvular AF in Asia was similar to rates reported from Western countries[1,2,9,10].

The rate of hemorrhagic stroke in the Asian population was higher than the rate reported from the West(11), both in patients with and without the use of oral anticoagulants[12]. Data from meta-analysis found that the Odds ratio of hemorrhagic stroke in the Asian population to be approximately four times higher than that of the Caucasian population[12]. No clear explanation for this finding has been identified. Some researchers have postulated that genetic predisposition may be responsible, especially relating to metabolism pathway of warfarin, which is a known genetic polymorphism of CYP2C9 and VKORC1[13,14]. This genetic factor has been shown to be different between Asian and Western populations[15]. Reports on stroke

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subtypes also showed the Asian population to have a higher proportion of hemorrhagic stroke, compared to that of Western countries[3,16-18].

Hypertension is a major risk factor in both ischemic and hemorrhagic stroke[19]. Increased risk of stroke from hypertension in the Asian population was consistent with reports from Western countries[20]. The majority of benefit from the treatment of hypertension is related to a reduction in stroke risk[21]. Prevalence of AF also increases in hypertensive patients[22,23]. The mechanism of stroke in patients with hypertension and AF may be related to either atherosclerotic plaque or embolic complication of AF.

Limited data has been reported regarding the association between non-valvular AF and ischemic stroke as a nation-wide study in Thailand. Data from the Thailand Stroke Registry revealed that prevalence of AF in patients admitted with stroke was 9.8%[24]. The primary objective of the present study was to investigate association between AF and stroke in patients with hypertension in a multicenter, nation-wide registry in Thailand. Secondary objectives included 1) determining the prevalence of stroke in patients with hypertension, and 2) determining the extent of the increase risk of ischemic stroke in patients with hypertension.

Materials and Methods

Study population

This is a cross-sectional survey in patients diagnosed with hypertension being treated in public hospitals under the Ministry of Public Health [MoPH] including clinics in Bangkok that registered with the Thailand National Health Security Office [NHSO] program in Thailand between 2011 and 2012. Inclusion criteria were hypertensive patients aged 20 years or older receiving medical care for at least 12 months in the hospitals participating in this survey. Patients participating in clinical trial studies were excluded.

Selection of sample of patients with hypertension both nationally and provincially was based on the two-stage stratified cluster sampling technique, proportional to the size of the population. For the area outside Bangkok, the hospital universe was defined by all hospitals that were public hospitals under the MoPH. For Bangkok, the hospital universe was defined as all hospitals and clinics that participated in the Thailand NHSO program. The present study sample was a stratified sample drawn from the subset of all MoPH hospitals in Thailand including all public and private clinics in Bangkok under the NHSO program. The first stage was the province in which were constituted 77 strata. This is followed by the second stage that involved the level of hospital in each province. Hospitals in each province were classified into five strata according to sizes, regional hospital for hospitals with more than 500 beds, provincial general hospital for 200 to 500 beds, large community hospital for 90 to 120 beds, medium community hospital for 30 to 90 beds, and small community hospital for 10 to 30 beds. The university hospitals were not included in the present study.

Data collection methods

Each site received an assigned quota of hypertensive patients to be included in the present study, as determined by the research team.

At each clinic, health care personnel, (usually a registered nurse) would invite patients with a pre-existing diagnosis of hypertension to participate in the study. Patients that agreed to participate provided written informed consent, thereby giving permission for research investigators to access, review, and collect patient data.

A standardized case report form [CRF] was used to record the required information from the patient's medical record. The data was then sent to the Medical Research Network of the Consortium of Thai Medical Schools [MedResNet] central data management unit in Nonthaburi, Thailand.

Data retrieved from patient medical records included baseline information, status of hypertensive complication, and results of laboratory testing.

The Ethical Review Committee for Research in Human Subjects of the MoPH, and the Ethical Review Board of the Royal Thai Army Medical Department approved the present study. The protocol for the present study was also approved by the institutional review boards of all participating hospitals.

Eight hundred thirty-one hospitals under the Thailand Universal Coverage Scheme were included, as follows, 25 were regional hospitals, 70 general hospitals, and 736 community hospitals. Proportion-to-size stratified cluster sampling was performed for selection of hospitals to be involved in the present study. All regional and general hospitals were included, as well as 70% of all small community hospitals, 20% of all medium size community hospitals and 10% of all large community hospitals. These selection determinations were made according to the number of registered patients at each hospital. Hypertensive patients were randomly selected according to the

proportion of registered patients at each hospital. The proportion-to-size model for each province was used to calculate the sample size of the study.

Data was collected from consecutive patients that were selected by the research team at each hospital after written informed consent was obtained. Investigators retrieved the required data from the medical record and entered it into the CRF without interviewing the patients or the doctors and without physical examination. The following patient data was collected, demographic data, weight, height, body mass index [BMI], systolic blood pressure [SBP], diastolic blood pressure [DBP], cardiovascular risk factors, blood chemistry data (fasting plasma glucose [FPG], serum creatinine, uric acid, and lipid profiles), available electrocardiogram [ECG] data and results, and complications relating to hypertension (including stroke).

Two research investigators were involved in the data retrieval and entry process. The first investigator accessed the patient data and entered it onto the CRF. The second investigator then checked the entered data and made necessary corrections before sending the CRF to central data management. The data management team sent inquiries to study sites to verify data, if needed. Data and site monitoring was performed in 10% of study sites or approximately 60 hospitals by a random selection process.

ECG interpretation

ECG data were not a prerequisite for the main study. After reviewing each patient medical record, the investigator noted in the CRF whether there were ECG data and the results of the ECG interpretation. In the present study, we focused on the presence AF rhythm in patients with hypertension.

Main outcome measurement

Main outcome measurements included AF rhythm, age, gender, cardiovascular risk factors, stroke, and type of stroke. Stroke was classified as cerebral infarction, TIA, unspecified stroke, or hemorrhagic stroke. Ischemic stroke was defined as all non-hemorrhagic stroke including TIA.

Statistical analysis

Continuous data were presented as mean ± standard deviation and categorical variables were expressed as number and percentages. Comparisons of continuous data were performed by independent samples t-test. For categorical variables, comparisons were made by Chi-square test. Odds ratio and 95% confidence interval [CI] were determined by Chi-square test for univariate analysis. Multivariate logistic regression analysis with forward LR was performed to identify independent factors associated with increased risk of ischemic stroke. A *p*-value of less than 0.05 was considered statistically significant.

Results

Of the 71,440 hypertensive patients enrolled between 2011 and 2012, 13,207 patients had ECG data in their medical record. Mean age was 63.6±11.1 years, and 4,711 (35.7%) were male. Compared to those without ECG, patients with ECG were not different in SBP, DBP, serum creatinine, FPG, total cholesterol [TC], triglyceride, high density lipoprotein [HDL]-cholesterol, and low-density lipoprotein [LDL]-cholesterol levels. However, patients with ECG data were slightly older than patients without ECG (63.6±11.1 vs. 61.1±11.2 years) and a greater proportion of male (35.7% versus 33.7%). AF was detected in 457 patients (3.46%).

Five hundred thirty-six patients had stroke (4.1%). Prevalence of each type of stroke and a comparison between patients with and without AF are shown in Figure 1. Patients with AF had increased risk for all types of stroke, however, risk of hemorrhagic stroke was not significant different between AF groups due to the small number of hemorrhagic stroke cases. Ischemic stroke was detected in 503 patients (3.8%). Prevalence of ischemic stroke increased with age and was more common in men than women (Figure 2).

Baseline characteristics and prevalence of ischemic stroke are shown in Table 1. Forest plot illustrating Odds ratio of ischemic stroke for each baseline characteristic is shown in Figure 3. In univariate analysis, prevalence of ischemic stroke

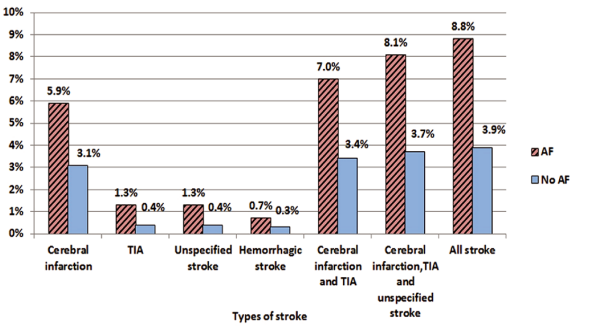

Figure 1. Prevalence of each type of stroke in patients with and without atrial fibrillation [AF].

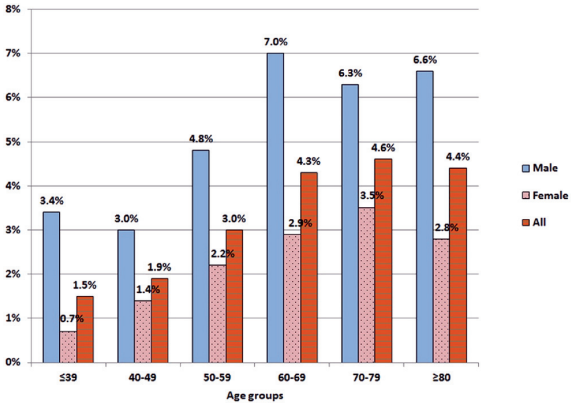

Figure 2. Prevalence of ischemic stroke in men and women by age groups.

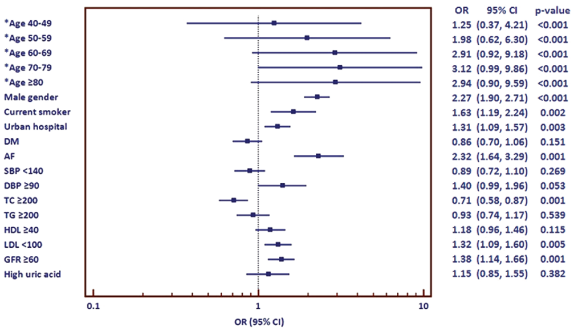

Figure 3. Factors from bivariate analysis that affect stroke.

was influenced by the following factors, age, gender, AF, current smoker, patients treated at regional or general hospitals, high DBP, TC less than 200 mg/dl or LDL-cholesterol less than 100 mg/dl, and glomerular filtration rate [GFR] less than 60 ml/minute. Factors found to be independently associated with increased risk of ischemic stroke from multivariate analysis were old age, male gender, AF, LDL less than 100 mg/dl, and high DBP (Table 2). AF was the most important factor associated with ischemic stroke.

Discussion

The results of the present study showed a prevalence of stroke of 4.1%, and a prevalence of AF of 3.46% in hypertensive patients. AF increases the risk of ischemic stroke approximately 2.3 times, compared to those without AF.

Hypertension increases the risk of both ischemic and hemorrhagic stroke[19]. Hypertension, especially in those with poorly controlled blood pressure, is associated with atherosclerosis and changes in vascular structure that predisposes patients to thrombosis, which can lead to ischemic stroke[25]. Atherosclerosis of the carotid arterial system in patients with hypertension can also result in emboli from atherosclerotic plaque[26]. High blood pressure can cause loss of autoregulation of the intracranial arterial system potentially resulting in hemorrhagic stroke[27]. Hypertension is a risk factor that increases risk of ischemic stroke in patients with AF[4,5]. The present study found that the prevalence of

Table 1. Baseline characteristics of patients with and without ischemic stroke (n = 13,207)

Baseline variables	n	Mean ± SD or n (%)	Prevalence of ischemic stroke (%)
Age (years)	13,207	63.6±11.1	
Gender	13,207		
Male		4,711 (35.7)	5.9
Female		8,796 (64.3)	2.6
Current smoker	13,207		
Yes		750 (5.7)	5.9
No		12,457 (94.3)	3.7
Type of hospital	12,800		
General		5,258 (41.1)	4.4
Community		7,542 (58.9)	3.4
Diabetes mellitus	13,207		
Yes		3,653 (27.7)	3.4
No		9,554 (72.3)	4.0
SBP (mmHg)	13,197	130.8±16.3	
≥140		2,789 (21.1)	4.2
<140		10,408 (78.9)	3.7
DBP (mmHg)	13,187	75.4±10.8	
≥90		741 (5.6)	5.1
<90		12,446 (94.4)	3.7
TC (mg/dL)	11,635	190.7±44.1	
≥200		4,432 (38.1)	3.1
<200		7,203 (61.9)	4.3
TG (mg/dL)	11,882	158.2±92.8	
≥200		2,622 (22.1)	3.6
<200		9,260 (77.9)	3.8
HDL (mg/dL)	11,268	47.8 ± 13.7	
≥40		3,157 (28.0)	4.2
<40		8,111 (72.0)	3.6
LDL (mg/dL)	11,539	113.5±37.4	
≥100		7,145 (61.9)	3.4
<100		4,394 (38.1)	4.4
GFR (ml/minute)	12,248	66.7±23.9	
≥60		7,384 (60.3)	3.4
<60		4,864 (39.7)	4.6
Uric acid (mg/dL)	5,392	6.15±1.95	
High		2,257 (41.9)	3.5
Normal		3,135 (58.1)	3.0

SD = standard deviation; DM = diabetes mellitus; AF = atrial fibrillation; SBP = systolic blood pressure; DBP = diastolic blood pressure; TC = total cholesterol; TG = triglyceride; HDL = high density lipoprotein cholesterol; LDL = low density lipoprotein cholesterol; GFR = glomerular filtration rate by epidemiology collaboration formula

Table 2. Multivariate analysis of factors that had independent association with ischemic stroke

Factors	OR_{crude}	$OR_{adjusted}$	95% CI	*p*-value
Age (every 10 years)		1.22	1.11 to 1.34	<0.001
Male gender	2.27	2.12	1.73 to 2.60	<0.001
AF	2.32	1.70	1.09 to 2.65	0.019
LDL <100	1.32	1.28	1.04 to 1.57	0.019
DBP ≥90	1.40	1.51	1.00 to 2.29	0.05

OR = odds ratio; CI = confidence interval; AF = atrial fibrillation; LDL = low density lipoprotein cholesterol; DBP = diastolic blood pressure

ischemic stroke in hypertensive patients was 4.1%. This finding was comparable to reports from both Western and Asian countries, although a trend toward higher prevalence of stroke in Asia has been identified[28]. Some researchers have suggested that genetic differences may be responsible for the differences in stroke prevalence between Asia and the West[20].

Prevalence of ischemic stroke in hypertensive patients increased with age and was more common in men than women. The results from the present study were similar to results from previous reports[20,21]. The present study showed that AF doubles the risk of ischemic stroke in hypertensive patients. Limited data is available from previous reports regarding the extent of increased risk of stroke in hypertensive patients with AF. Previous studies demonstrated that AF increased the risk of stroke approximately five times, compared to patients without AF[1,2,9,10]. However, the populations in these studies had diagnosis of hypertension in only about 25% of subjects. Stroke in patients with hypertension and AF may be attributed in part by hypertension and in part by AF. The Framingham Study showed that hypertension itself increased stroke by a risk ratio of 3.4; whereas, AF increased stroke by a risk ratio of 4.8[2]. Therefore, in patients with hypertension and AF, the proportion of increased risk of stroke from AF in addition to risk of stroke contributed by hypertension, may not be as much as the effect of AF in the increased risk of stroke in those without hypertension. This is consistent with findings from the present study. The authors showed that, in the hypertensive population, AF increased risk of stroke by approximately two times as compared to those without AF.

Regarding subtypes of stroke, the proportion of hemorrhagic stroke in the present study was 6.7%. This results differs from previous reports on stroke subtype in the Asian population that found a proportion of hemorrhagic stroke of approximately 15% to 20%, which was higher than rates found in Western population[16-18]. In the present study, AF increased the risk of all types of strokes, including doubling the risk of hemorrhagic stroke. However, this increase in risk was not statistically significant due to the small number of hemorrhagic stroke cases.

Factors other than AF that were found to be independently associated with ischemic stroke were older age, male gender, low LDL-cholesterol, and high DBP. Association of ischemic stroke with age, gender, and blood pressure has been reported in many previous studies in both Western and Asian countries[20,28,29]. DBP control has been emphasized together with SBP. It has been estimated that a difference in DBP of 10 mmHg, could double the risk of stroke mortality[21,30]. The relationship between ischemic stroke and low LDL-cholesterol may be difficult to interpret. A limitation of cross-sectional studies just like ours would be a lack of data regarding medications like statins. Patients with ischemic stroke would likely receive statins to lower LDL-cholesterol more often than patients without ischemic stroke, and would, therefore, have a lower level of LDL-cholesterol.

Limitations of the present study include the following, 1) when the survey was developed, there was no initial intent to study ECG finding. When the decision was made to include ECG data in the present study, we included only patients with ECG data and interpretations in their medical record. As such, only 18.5% of patients had ECG data. 2) Data regarding important medications, such as antihypertensives, antithrombotics, and statins were not collected. 3) Stroke was determined by data and documentation contained in the medical record only, no imaging data were evaluated to validate the diagnosis of stroke. 4) Interval from the occurrence of stroke and the survey was unknown. Given the cross-sectional design of the present study, the identified risk factor associations cannot be proved. Information was lacking regarding whether AF was presented before or after stroke.

In conclusion, prevalence of stroke in hypertensive patients was 4.1%. AF was found to be an independent factor associated with increased risk of stroke. The risk of ischemic stroke doubled in patients with AF, as compared to those without.

What is already known on this topic?

AF and hypertension increases risk of stroke. Data is scarce in Asian population.

What this study adds?

AF is an independent risk factor for ischemic

stroke in patients with hypertension with the crude and multivariable adjusted Odds ratio of AF and ischemic stroke was 2.32 (1.64 to 3.29) and 1.70 (1.09 to 2.65), respectively.

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Potential conflicts of interest

The authors declare no conflict of interest.

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