

# Age Threshold for Increased Stroke Risk Among Patients With Atrial Fibrillation



## A Nationwide Cohort Study From Taiwan

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### ABSTRACT

**BACKGROUND** Recent studies from Asia have suggested that the risk of ischemic stroke for patients with atrial fibrillation (AF) with a “low-risk” congestive heart failure, hypertension, age  $\geq 75$ , diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65 to 74, female (CHA<sub>2</sub>DS<sub>2</sub>-VASc) score of 0 (for males) or 1 (for females) might be higher than that for non-Asians.

**OBJECTIVES** This study hypothesized that the age threshold (65 years) used in the CHA<sub>2</sub>DS<sub>2</sub>-VASc system for initiating oral anticoagulants (OACs) might be lower in Taiwanese AF patients than in non-Asians.

**METHODS** We used the National Health Insurance Research Database in Taiwan to study 186,570 nonanticoagulated AF patients. There were 9,416 males with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 0 and 6,390 females with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1. Their risk of ischemic stroke was analyzed with stratification on the basis of age.

**RESULTS** The annual risks of ischemic stroke for males (score 0) and females (score 1) were 1.15% and 1.12%, respectively, and continuously increased from younger to older age groups, with an increment in stroke risk evident for patients  $>50$  years of age. At a cutoff of 50 years, patients could be further stratified into 2 subgroups with different stroke risks ( $>50$  years of age: 1.78%/year; vs.  $<50$  years of age: 0.53%/year). This observation was consistent for males (1.95%/year vs. 0.46%/year, respectively) and females (1.58%/year vs. 0.64%/year, respectively) with AF. In a subgroup analysis, the annual risks of ischemic stroke for males and females with AF 50 to 54 years of age were 1.47% and 1.07%, respectively.

**CONCLUSIONS** For Taiwanese patients 50 to 64 years of age, the annual stroke risk was 1.78%, which may exceed the threshold for OAC use for stroke prevention. The annual risk of ischemic stroke for AF patients  $<50$  years of age was 0.53%, which was truly low-risk, and OACs could be omitted. Whether resetting the age threshold to 50 years could refine current clinical risk stratification for Asian AF patients deserves further study. (J Am Coll Cardiol 2015;66:1339-47)  
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## ABBREVIATIONS AND ACRONYMS

**AF** = atrial fibrillation

**CI** = confidence interval

**ESC** = European Society of  
Cardiology

**ICD-9-CM** = International  
Classification of Diseases-Ninth  
Revision-Clinical Modification

**NHI** = National Health  
Insurance

**NHIRD** = National Health  
Insurance Research Database

**NOACs** = non-vitamin K  
antagonist oral anticoagulants

**OACs** = oral anticoagulants

**ROC curve** = receiver  
operating characteristic curve

**A**trial fibrillation (AF) is the most common, sustained cardiac arrhythmia and increases the risk of ischemic stroke by 4- to 5-fold (1). The risk of AF-associated stroke is not homogeneous and depends on the patient's age and comorbidities. This has resulted in clinical scores to aid risk stratification for patients with AF.

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The CHA<sub>2</sub>DS<sub>2</sub>-VASc score (congestive heart failure, hypertension, age  $\geq 75$ , diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65 to 74, female) has been validated as useful for stroke risk prediction in several independent cohorts (2-7), and current European and American guidelines

recommend use of the CHA<sub>2</sub>DS<sub>2</sub>-VASc scheme to assess stroke risk (8,9). Compared to the CHADS<sub>2</sub> system (congestive heart failure, hypertension, age  $\geq 75$ , diabetes mellitus, and prior stroke or transient ischemic attack), previous studies have demonstrated that the CHA<sub>2</sub>DS<sub>2</sub>-VASc score reliably identifies "truly low-risk" patients, even among those with a low CHADS<sub>2</sub> score (4,5). In the Danish nationwide cohort study, the annual risk of ischemic stroke was 0.66% for male patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 0 and 0.82% for female patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1 (2). A low risk of ischemic stroke for male patients with AF and a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 0 was also evident in Swedish (0.2% risk per year) and American (0.04% risk per year) cohorts (10,11). Given the low risk of ischemic stroke, current major guidelines suggest that oral anticoagulants (OACs) could be omitted for males with AF and a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 0 and for females with AF and a score of 1 (8,9).

What is the risk of ischemic stroke for these "low-risk" patients in Asia? In a previous nationwide study from Taiwan, the annual risk of ischemic stroke was 1.15% for male AF patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 0, which was higher than that reported from Western countries (12). In the recent study by Siu et al. (13), which enrolled 9,727 Hong Kong AF patients from a hospitalized cohort, the annual stroke rate was as high as 2.41% among 395 patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 0 (13). Thus, stroke risk among Asian patients with AF and a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 0 (males) or 1 (females) might be higher than that seen among Caucasians, and such patients may still require OACs for effective stroke prevention because the threshold for initiating anticoagulation can be lowered to a stroke rate of 0.9%/year with the better safety profile of non-vitamin K antagonist OACs (NOACs) (14).

By its current definition, the CHA<sub>2</sub>DS<sub>2</sub>-VASc score assigns 1 point for patients older than 65 years of age, although the setting of the threshold for age has not been previously well studied for Asians. In the present study, we aimed to investigate the risk of ischemic stroke in male patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 0 and female patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1 stratified on the basis of age. We hypothesized that the threshold age (65 years) used in the CHA<sub>2</sub>DS<sub>2</sub>-VASc system might have to be lowered in Taiwanese AF patients.

## METHODS

**DATABASE.** This study used the National Health Insurance Research Database (NHIRD) released by the Taiwan National Health Research Institutes. The National Health Insurance (NHI) system is a mandatory universal health insurance program that offers comprehensive medical care coverage to all Taiwanese residents. NHIRD consists of detailed health care data from >23 million enrollees, representing >99% of Taiwan's population. In this cohort dataset, patients' original identification numbers were encrypted to protect patients' privacy, but the encrypting procedure was consistent, so that a linkage of claims belonging to the same patient was feasible within the NHI database and could be followed continuously. The large sample size of this database provided a good opportunity to study the risk of ischemic stroke in "low-risk" patients with AF and a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 0 (for males) and 1 (for females), stratified by age.

**STUDY COHORT.** The study protocol for the present study was similar to that of our previous studies (12,15). From January 1, 1996, to December 31, 2011, a total of 354,649 AF patients  $\geq 20$  years of age were identified from the NHIRD as the study population. AF was diagnosed using International Classification of Diseases-Ninth Revision-Clinical Modification (ICD-9-CM) code 427.31. To ensure accuracy of diagnosis, we defined patients with AF only when it was a discharge diagnosis or was confirmed more than twice in the outpatient department (12,15,16). Diagnostic accuracy of AF using this definition in NHIRD has been validated previously (17,18). The CHA<sub>2</sub>DS<sub>2</sub>-VASc score was calculated for each patient by assigning 1 point each for age between 65 and 74 years, history of hypertension, diabetes, recent cardiac failure, vascular disease (myocardial infarction or peripheral artery disease), and female sex, and 2 points each for a history of a stroke, transient ischemic attack, or  $\geq 75$  years of age (19). From the study population, we excluded patients who received treatments with warfarin or any antiplatelet agent,

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