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ORIGINAL ARTICLE

Increased Risk of First-Ever Stroke in Younger Patients With Atrial Fibrillation Not Recommended for Antithrombotic Therapy by Current Guidelines: A Population-Based Study in an East Asian Cohort of 22 Million People

Kuan-Cheng Chang, MD, PhD; Yu-Chen Wang, MD; Po-Yen Ko, MD; Hung-Pin Wu, MD; Yu-Wei Chen, MD; Chih-Hsin Muo, MS; Fung-Chang Sung, PhD; Tsai-Chung Li, PhD; and Chung Y. Hsu, MD, PhD

Abstract

Objective: To assess the risk of first-ever ischemic stroke in younger patients with atrial fibrillation (AF) who have none of the CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, previous stroke/transient ischemic attack, vascular disease, age 65-74 years, sex category [female sex]) risk factors (excluding female sex) by using the National Health Insurance research database in Taiwan.

Patients and Methods: From 22,842,778 insured people, we identified 24,612 hospitalized patients with newly diagnosed AF between January 1, 2002, and December 31, 2004, as the AF group and randomly selected 98,448 age- and sex-matched persons without AF as the non-AF group. Both groups were followed up until December 31, 2010, to estimate ischemic stroke incidences in relation to other stroke risk factors.

Results: During a follow-up period of 89,468 person-years, the stroke rate was higher in patients with AF than in those without AF (5.79 per 100 person-years vs 2.25 per 100 person-years). The higher prevalence of CHA_2DS_2-VASc comorbidities (heart failure, hypertension, diabetes, coronary artery disease, and peripheral artery disease) in patients with AF further increased the stroke risk. In 790 patients with AF aged 30 to 55 years who had none of the CHA_2DS_2-VASc comorbidities at baseline and retained a "low risk," that is, those with a CHA_2DS_2-VASc score of 0 in men and 1 in women during follow-up, the stroke rate remained considerably higher than that in their non-AF counterparts (1.00 per 100 person-years vs 0.25 per 100 person-years), with a sex-adjusted hazard ratio of 4.09 (95% CI, 2.97-5.62).

Conclusion: This study finds an increased risk of stroke in younger patients with AF who are not recommended for prevention of thromboembolism by current guidelines. Better stroke risk stratification tools are needed to prioritize younger patients with AF for thromboprophylactic therapy in this population.

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Atrial fibrillation (AF), the most common type of sustained cardiac arrhythmia, is an independent predictor of stroke.[1-4] However, it is not uncommon for patients with AF to carry other stroke risk factors, such as old age, hypertension, diabetes, hyperlipidemia, and heart diseases (coronary artery disease, congestive heart failure, valvular heart diseases, and others).[5] These comorbidities contribute to increase stroke risk beyond AF.[6] To prevent stroke in patients with AF, antithrombotic medications are efficacious in reducing stroke risk, with anticoagulation being substantially more effective than antiplatelet therapy.[7-14] Adverse effects associated with antithrombotic therapy for stroke prevention in patients with AF, particularly bleeding complications caused by oral anticoagulation, led to the development of stroke risk stratification tools to prioritize patients with AF for thromboprophylactic therapy.[6,15-19]

A common scheme for stratifying stroke risk in patients with AF is the $CHADS_2$ (recent congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and previous stroke/transient ischemic attack [doubled risk weight]) scoring scheme.[16] This scoring system has been

From the Division of Cardiology, Department of Medicine, China Medical University Hospital, Taichung, Taiwan (K.-C.C., Y.-C.W., P.-Y.K., H.-P.W.); Graduate Institute of Clinical Medical Science (K.-C.C., Y.-C.W., C.Y.H.), Department of Public Health (C.-H.M., F.-C.S., C.Y.H.), and

Affiliations continued at the end of this article.

assessed for its classification of a large proportion of patients in the "intermediate risk" category with the need to refine selected thromboembolic risk factors.[20] To complement $CHADS_2$ scoring, CHA_2DS_2-VASc (recent congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, previous stroke/transient ischemic attack, vascular disease, age 65-74 years, sex category [female sex], and previous stroke [doubled risk weight]) scoring has been proposed to identify patients with AF with truly low risk of stroke.[6] Olesen et al[21] reported a relatively lower thromboembolism rate (0.78 per 100 person-years) in the low-risk group defined by the CHA_2DS_2-VASc score compared with that (1.67 per 100 person-years) in the low-risk group defined by the $CHADS_2$ score after 1-year follow-up in a non—anticoagulated cohort of patients with AF. However, patients with AF who have none of the CHA_2DS_2-VASc risk factors and are not recommended for antithrombotic therapy are frequently patients of younger age. Considering the longer poststroke life span and greater socioeconomic burden with stroke at younger age, the merit of a more rigorous stroke prevention measure for young patients with AF appears to be overlooked by $CHADS_2$ and CHA_2DS_2-VASc scores. Gattellari et al[22] reported that the outcomes of stroke in younger patients with AF were worse, with a higher mortality rate and longer length of hospital stay, than those in their non-AF counterparts. With the availability of new oral anticoagulants, a recent Markov decision analysis model suggests that treatment with these drugs should even be considered in patients with a stroke risk of 0.9% per year.[23] Therefore, it is important to reassess the stroke risk in younger patients with AF who have none of the CHA_2DS_2-VASc risk factors and are not recommended for thromboprophylactic therapy by current guidelines.[24,25] In the present study, we sought to assess the risk of first-ever stroke in younger patients with AF who had none of the CHA_2DS_2-VASc risk factors (excluding female sex) in a cohort of 22,842,778 patients covered by a universal health insurance program, the National Health Insurance (NHI) in Taiwan. This large-scale population-based study provides information derived from clinical practice in the real world to emphasize the importance of AF as a stroke risk factor in younger patients with AF who lack conventional risk factors as defined by the CHA_2DS_2-VASc scheme.

PATIENTS AND METHODS

Data Source and Study Cohort

An insured population of more than 22 million people, that is, more than 99% Taiwan population, in the NHI program was established by the National Health Research Institute for the period of 1996 to 2010. This NHI database includes information on birth date, sex, institution codes, type and date of care for inpatient services, diagnoses based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*), and health care expenditure. The information on medication use and personal health behaviors, such as physical activity, smoking, and alcohol consumption, was not available in this NHI data set. The NHI prevents coding errors and misdiagnosis by regularly monitoring disease coding and by auditing claims submitted for reimbursement by hospitals that contract with the NHI to offer inpatient services to NHI participants. The stringent surveillance program ensures the reliability of the diagnostic coding.[26] Hence, the consistent information could allow us to assess the risk of first-ever stroke in patients with AF who had none of the CHA_2DS_2-VASc comorbidities (heart failure, hypertension, diabetes, coronary artery disease, and peripheral artery disease).[27] Retrospective analysis was performed on a cohort of 22,842,778 eligible patients in the period of 2002 to 2004. Patients with AF newly diagnosed between January 1, 2002, and December 31, 2004, with an inpatient claim of the *ICD-9-CM* code 427.31 based on an electrocardiographic documentation of AF rhythm comprised the AF group. The date of their first diagnosis of AF was defined as the entry date. Patients with significant valvular heart diseases, such as any degree of mitral stenosis and aortic valve or mitral valve diseases, were excluded from the present study. The comparison group consisted of randomly selected insured people without a history of AF in 2002 to 2004, matched with the AF group across age strata (every 5 years), sex, and the entry year and entry month with a sample size 4-fold of the AF group. Patients with a history of stroke (*ICD-9-CM* codes 430-438) before the entry date were excluded from both the AF and non-AF groups. With a sample

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