Incidence and prediction of ischemic stroke among atrial fibrillation patients with end-stage renal disease requiring dialysis

Tze-Fan Chao, MD,[*†] Chia-Jen Liu, MD,[‡§] Kang-Ling Wang, MD,[*†] Yenn-Jiang Lin, MD,[*†] Shih-Lin Chang, MD,[*†] Li-Wei Lo, MD,[*†] Yu-Feng Hu, MD,[*†] Ta-Chuan Tuan, MD,[*†] Fa-Po Chung, MD,[*†] Jo-Nan Liao, MD,[*†] Tzeng-Ji Chen, MD,[¶] Gregory Y.H. Lip, MD,[‖] Shih-Ann Chen, MD[*†]

From the [*]Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, [†]Institute of Clinical Medicine and Cardiovascular Research Center, National Yang-Ming University, Taipei, Taiwan, [‡]Division of Hematology and Oncology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, [§]Institute of Public Health and School of Medicine, National Yang-Ming University, Taipei, Taiwan, [¶]Department of Family Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, and [‖]University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, United Kingdom.

BACKGROUND Renal dysfunction is a significant risk factor for ischemic stroke in atrial fibrillation (AF). However, the incidence of ischemic stroke and how to predict its occurrence among AF patients with end-stage renal disease (ESRD) are unclear.

OBJECTIVE The purpose of this study was to compare the $CHADS_2$ and CHA_2DS_2-VASc scores for stroke risk stratification in AF patients with ESRD.

METHODS A total of 10,999 AF patients with ESRD undergoing renal replacement therapy who were not receiving oral anticoagulants or antiplatelet agents were identified from Taiwan's National Health Insurance Research Database. The study endpoint was occurrence of ischemic stroke.

RESULTS The median (interquartile) $CHADS_2$ and CHA_2DS_2-VASc scores for the study cohort were 3 (2–5) and 5 (4–7), respectively. During follow-up, 1217 patients (11.7%) experienced ischemic stroke, with an incidence rate of 6.9 per 100 person-years. In Cox regression models, the $CHADS_2$ and CHA_2DS_2-VASc scores both were significant predictors of ischemic stroke. C-indexes for $CHADS_2$ and CHA_2DS_2-VASc were 0.608 and 0.682, respectively ($P < .001$). CHA_2DS_2-VASc improved the net reclassification index by 4.8% compared with $CHADS_2$ ($P < .0001$). Among 1409 patients with a $CHADS_2$ score of 0 or 1, the CHA_2DS_2-VASc score ranged from 1 to 4, with event rates ranging from 2.1 to 4.7 per 100 person-years.

CONCLUSION The CHA_2DS_2-VASc score was useful in predicting ischemic stroke in AF patients with ESRD undergoing dialysis and was superior to the $CHADS_2$ score. The net clinical benefit balancing stroke reduction against major bleeding with anticoagulation in these high-risk patients remains to be defined.

KEYWORDS Atrial fibrillation; End-stage renal disease; Ischemic stroke; $CHADS_2$ score; CHA_2DS_2-VASc score

ABBREVIATIONS ACC = American College of Cardiology; **AF** = atrial fibrillation; **AHA** = American Heart Association; **AUC** = area under the curve; **CI** = confidence interval; **ESC** = European Society of Cardiology; **ESRD** = end-stage renal disease; **ICD-9-CM** = International Classification of Diseases, Ninth Revision, Clinical Modification; **ICH** = intracranial hemorrhage; **NHIRD** = National Health Insurance Research Database; **NHI** = National Health Insurance; **NRI** = net reclassification index; **ROC** = receiver operating characteristic; **TIA** = transient ischemic attack

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is responsible for approximately 15% to 20% of ischemic strokes. Indeed, AF-related strokes are associated with a much poor prognosis, with greater than 50% of the survivors having a severe deficit, and recurrences as high as 12% per year.[1,2] Renal dysfunction has been identified as an important risk factor for new-onset AF, and the prevalence of AF was about 27% in patients with end-stage renal disease (ESRD) undergoing long-term dialysis.[3] Importantly, renal

impairment has been shown to increase the risk of AF-related strokes.[4–8] Also, the risks of stroke and systemic thromboembolism were substantially increased among patients with ESRD undergoing renal replacement therapy compared to those without chronic kidney disease (hazard ratio 1.83).[5] Despite their high risk of stroke, patients with ESRD were excluded from clinical trials of thromboprophylaxis in AF.

A key step in the prevention of AF-related stroke is effective risk stratification. The $CHADS_2$ score is commonly used for stratifying stroke risk of AF patients.[9,10] More recently, the European Society of Cardiology (ESC) recommended use of the CHA_2DS_2-VASc score, an approach also recommended by the Asia Pacific Heart Rhythm Society and the 2014 American College of Cardiology/American Heart Association (ACC/AHA) guidelines.[11–14] The CHA_2DS_2-VASc score extends the older $CHADS_2$ score by considering additional common stroke risk factors, such as vascular disease and female gender.[11] Because data on stroke rates in AF patients with ESRD undergoing dialysis are limited, the value of using the $CHADS_2$ and CHA_2DS_2-VASc scores in this patient population is uncertain.[9,11]

The objective of the present study was to compare the $CHADS_2$ and CHA_2DS_2-VASc scores for stroke risk stratification in AF patients with ESRD undergoing renal replacement therapy.

Methods

We conducted a nationwide cohort study, retrieving data on all patients with AF and ESRD undergoing renal replacement therapy from Taiwan's National Health Insurance Research Database (NHIRD) released by the Taiwan National Health Research Institutes (NHRI). The National Health Insurance (NHI) system is a mandatory universal health insurance program that offers comprehensive medical care coverage to all residents of Taiwan. NHIRD consists of detailed health care data from >23 million enrollees, representing $>99\%$ of Taiwan's population. In this cohort dataset, the patients' original identification numbers were encrypted to protect their privacy, but the encrypting procedure was consistent, such that a linkage of the claims belonging to the same patient was feasible within the NHI database and could be followed continuously. Numerous scientific research papers have already been published using data from NHIRD (http://nhird.nhri.org.tw/en/Research.html). The large sample size of this database provided a good opportunity to study the risk of ischemic stroke among AF patients and ESRD undergoing dialysis.

Study cohort

From January 1, 1996, to December 31, 2011, a total of 14,163 AF patients aged ≥ 20 years and with ESRD requiring renal replacement therapy were identified from the NHIRD as the study population. AF was diagnosed using the International Classification of Diseases (ICD), Ninth Revision, Clinical Modification (ICD-9-CM) codes (427.31). To ensure the accuracy of diagnosis, we defined

patients has having AF only when it was a discharge diagnosis or it was confirmed more than twice in the outpatient department.[15] The diagnostic accuracy of AF using this definition in NHIRD has been validated previously.[16,17] Diagnosis of ESRD requiring renal replacement therapy was confirmed by both specific ICD-9-CM codes and inclusion in the Registry for Catastrophic Illness Patient Database (RCIPD), a subpart of the NHIRD. Among the study population, patients who received treatment with warfarin or any antiplatelet agent, including aspirin, clopidogrel, dipyridamole, and ticlopidine, were excluded. The reasons for exclusion of patients who received antithrombotic drugs included the following. (1) The goal of the present study was to validate the usefulness and to compare the accuracies of $CHADS_2$ and CHA_2DS_2-VASc schemes for stroke risk stratification in AF patients with ESRD. This issue ideally should be studied in a nonanticoagulated cohort. (2) The detailed data about international normalized ratio and time in the therapeutic range for warfarin users were not recorded in NHIRD, and the lack of these parameters would significantly confound the analysis about the risk of ischemic stroke. Finally, a total of 10,999 patients were enrolled into the study cohort. A flow chart of the enrollment of the study cohort is shown in Figure 1.

Information about important comorbid conditions of each individual was retrieved from the medical claims based on the ICD-9-CM codes. We defined patients as having a certain disease only when it was a discharge diagnosis or if it was confirmed more than twice in the outpatient department. The diagnostic accuracies of important comorbidities in NHIRD, such as hypertension, diabetes mellitus, heart failure, myocardial infarction, hyperlipidemia, and chronic obstructive pulmonary disease, have been validated previously.[18,19]

Calculation of scores and definitions of clinical end-points

The $CHADS_2$ score was calculated for each patient by assigning 1 point each for age ≥ 75 years, hypertension, diabetes mellitus, and heart failure, and 2 points each for a previous stroke or transient ischemic attack (TIA).[9] The CHA_2DS_2-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 gender, and 2 points each for a history of a stroke, TIA, or age ≥ 75 years.[11]

The principal clinical end-point was the occurrence of ischemic stroke, with concomitant imaging studies of the brain, including computed tomography or magnetic resonance imaging. We also determined how the CHA_2DS_2-VASc score could refine stroke risk stratification in patients with a $CHADS_2$ score of 0 to 1. The accuracy of diagnosis of ischemic stroke in Taiwan's NHIRD has been reported to be approximately 94%.[18] Another validation study also demonstrated that the diagnostic accuracy of ischemic stroke in