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Clinical Study

Anticoagulation-related reduction of first-ever stroke severity in Chinese patients with atrial fibrillation

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ABSTRACT

Atrial fibrillation (AF) is an independent risk factor for ischemic stroke and warfarin related anticoagulation has been recommended as an effective treatment for stroke prevention. We aimed to determine whether pre-stroke oral anticoagulation therapy would reduce initial stroke severity in AF patients with first-ever ischemic stroke. We identified consecutive patients who developed first-ever ischemic stroke and were eligible for anticoagulation therapy from the China National Stroke Registry. Multivariate logistic analysis was used to assess the association between warfarin usage and initial stroke severity, measured by the National Institutes of Health Stroke Scale (NIHSS) and the Glasgow Coma Scale (GCS). Of 9519 patients, 1140 (11.98%) had AF, including 440 (38.6%) without known AF before presentation, 561 (49.2%) with known AF but not taking warfarin, and 139 (12.2%) with known AF who were taking warfarin. Compared to patients with known AF but not on warfarin, the odds ratio (OR) of having a major stroke (NIHSS $\geqslant$4) was lower in patients with known AF who were on warfarin (OR = 0.68; 95% confidence interval [CI] 0.57–0.84). The OR of developing a severe coma (GCS 3–8) was also reduced in the warfarin group (OR = 0.71; 95% CI 0.56–0.91). In conclusion, pre-stroke warfarin therapy lowered the severity of the first-ever ischemic stroke in patients with known AF. Considering its efficacy in stroke prevention and the significant under-usage of warfarin in China, the primary prevention of stroke in AF patients should be reinforced.

1. Introduction

Atrial fibrillation (AF) is an independent risk factor accountable for approximately 15% of all ischemic strokes (IS) [1]. Randomized trials have shown that vitamin K antagonists (for example, warfarin) are highly effective in preventing stroke in AF patients, with a risk reduction of more than 60% [2]. In recent years, Hylek et al. [3] reported that oral anticoagulation therapy reduced stroke severity as measured by the modified Rankin Scale at discharge in patients with AF, and O'Donnell and co-workers [4] demonstrated that therapeutic warfarin was associated with reduced initial severity of stroke at presentation. However, neither of these studies distinguished patients with first-ever IS from patients with recurrent strokes, nor did they exclude patients with contraindications of anticoagulation therapy from the target population.

To determine whether pre-stroke oral anticoagulation therapy is associated with reduced initial stroke severity in AF patients with first-ever IS who are eligible for anticoagulation therapy, we completed a study based on data from the China National Stroke Registry (CNSR).

2. Methods

2.1. Patients and procedures

The CNSR is a national hospital-based and prospective registry sponsored by the Ministry of Health. The primary objective of the registry is to evaluate the quality of care during acute hospitalization of all stroke patients. The registry collects data on many performance measurements related to the delivery of stroke care around China. A total of 132 hospitals representing 27 provinces and four municipalities (Taiwan and Macao are not included) in mainland China have been selected as registry hospitals. Among them, 100 are tertiary hospitals and 32 are secondary urban

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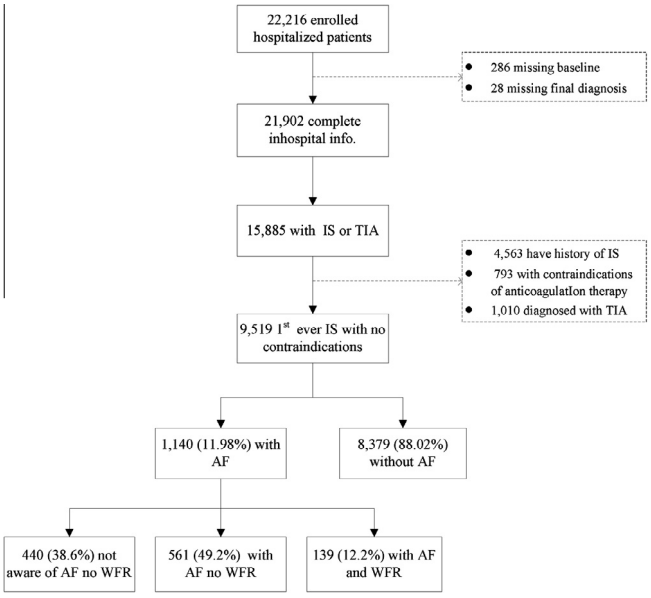

Fig. 1. Screening flowchart for patients with first-ever ischemic stroke categorized by atrial fibrillation and warfarin usage. AF = atrial fibrillation, IS = ischemic stroke, TIA = transient ischemic attack, WFR = warfarin.

hospitals. Approval for the CNSR was obtained from the central Institutional Review Boards, and written informed consent was required before admission from the patient or their legally proxy.

Patients enrolled in the registry would have met the following criteria: ⩾18 years of age, and suffering from IS, transient ischemic attack (TIA), intracranial hemorrhage (ICH), or subarachnoid hemorrhage, confirmed by brain CT scan or MRI within 14 days after the onset of symptoms. Trained research coordinators at each institute reviewed medical records daily to identify and enroll qualified consenting patients.

A standardized data collection form was used by all sites. Trained research coordinators interviewed the patients and family to obtain pre-hospital care, pre-stroke modified Rankin Scale score, and baseline National Institutes of Health Stroke Scale (NIHSS) and Glasgow Coma Scale (GCS) scores. Other data extracted from the medical records included patient demographics, medical history, medication use, IS subtypes, ICH and causes, vascular malformation, coagulopathy, disease status (such as NIHSS score, neuroimaging studies), complications in hospital, disease management in different hospital settings, and discharge status. Patients were contacted by telephone at 3, 6, 12, 18 and 24 months after discharge by trained research personnel at Beijing Tiantan Hospital. Throughout the study period, all data elements were manually checked by a research specialist from an independent research organization. A professional data processing company was responsible for the computer data entry. Beijing Translational Medicine Research Center, an independent research organization, performed the data analysis. Other details of the design and rationale of the CNSR are described elsewhere [5].

For the current analysis, we identified consecutive patients who presented with first-ever IS defined as acute cerebral ischemia without a medical chart-confirmed history of previous IS. Patients diagnosed with ICH or subarachnoid hemorrhage or those with a history of IS were excluded. Patients with contraindications to warfarin usage were also excluded. Other contraindications included metastatic cancer, dementia, cirrhosis, renal failure requiring dialysis, previous gastrointestinal bleed, and peptic ulcer diseases. Warfarin usage was determined by checking the prescriptions filled by the patient or their caregiver. The target population was divided into four groups based on the presence of AF (determined by history, positive admission 12 lead electrocardiogram, or Holter results) and the pre-stroke usage of warfarin. The groups were no AF; unaware of AF (no history of AF but newly diagnosed with AF at admission); AF and not on warfarin; and AF taking warfarin. The baseline characteristics of these four groups included age, sex, marital status, body mass index, educational level (elementary or below [⩽6 years education], middle school [6–9 years] and high school or above [>9 years]), health insurance type (urban or governmental, rural, commercial or other and self-payment) and geographic regions (eastern, central, or western according to the geographic location of the hospitals from which the patients were recruited). Data on risk factors and comorbidities of stroke included currently smoking (continuous or accumulated smoking for at least 6 months and ⩾1 cigarette per day and had smoked at least once in the 30 days before the stroke), heavy drinking (⩾5 standard alcoholic drinks per day), hypertension (defined as history of hypertension or hypotensive drug use), hyperlipidemia (history of dyslipidemia or lipid-lowering drug use), congestive heart failure (with definitive diagnosis on record), coronary heart disease (including silent myocardial ischemia, angina pectoris, myocardial infarction, and ischemic cardiomyopathy), peripheral vascular diseases (defined as peripheral vascular or lymph diseases including thromboangiitis obliterans, arteriosclerotic obliterans, arterial embolism, polyarteritis, Raynaud's syndrome, varicose veins or deep venous thrombosis) and diabetes mellitus (both type 1 and 2).

The international normalized ratio (INR) was measured at admission. Stroke severity was assessed by the NIHSS [6,7] and the GCS [8] on admission by local certified neurologists or physicians. The NIHSS score was categorized as minor stroke (NIHSS <4) or major stroke (NIHSS ⩾4) [9], and the GCS score was classified as minor or moderate coma (GCS 9–15) or severe coma (GCS 3–8) [8]. Data from eligible patients for current analysis were obtained from the CNSR database after all information had been entered.

2.2. Statistical analysis

For descriptive analysis, proportions were used for categorical variables, and means with standard deviations were used for continuous variables. For baseline characteristics, the group of patients was compared with each of the other groups by analysis of variance for continuous data (age) and by chi-squared test for categorical data. The variable of AF subtype was categorized as no AF (reference category), unaware of AF, AF not on warfarin and AF taking warfarin. The multivariate models in this analysis included age, sex, marital status, comorbidities, pre-stroke drug administration, personal educational level and health insurance type. The AF group variable was included as an independent variable in each multivariate logistic regression model, with no AF as the reference category. A 95% confidence interval (CI) that did not contain 1.0 was considered statistically significant. All analyses were conducted with a commercially available software package (SAS version 9.1.3, SAS Institute Inc., Cary, NC, USA).

3. Results

During the study period, 22,216 patients were consecutively recruited into the CNSR. From these patients, 15,885 had either IS or TIA. After excluding 4563 (28.73%) patients with a history of IS, 793 (4.99%) patients with contraindications to anticoagulation therapy, and 1010 (6.36%) patients with TIA, a total of 9519 patients were included in the analysis. Among these patients, 1140 (11.98%) had AF, including 440 (38.6%) unaware of AF before