Recurrent Stroke and Bleeding Events after Acute Cardioembolic Stroke—Analysis Using Japanese Healthcare Database from Acute-Care Institutions

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Background: To understand the reality of patients who experienced a cardioembolic stroke (CES) is important because of the high incidence of recurrent stroke and the need to account for bleeding risk in relation to the need for anticoagulation treatment. We elucidated the current real-world medical care in patients who had a CES and identified the risk factors for recurrent stroke. *Methods and Results:* The study comprised 9804 patients who were diagnosed with CES between April 2008 and September 2013 as identified in a healthcare database used by acute-care institutions in Japan. We analyzed the incidence and risk factors of stroke and bleeding events in CES patients. The incidence of stroke was 10.3% during the median observation period of 68 days, mainly consisting of recurrent CES (8.5%). The incidence of bleeding events and intracranial bleeding was 10.3% and 7.0%, respectively. The recurrence of ischemic stroke was significantly lower, and brain hemorrhage was significantly higher in the anticoagulation treatment group. The factors related to an increased risk of stroke were a history of cerebral infarction or transient ischemic attack, diabetes, and increase of CHA_2DS_2-VASc and $CHADS_2$ scores. The risk factors for bleeding events were hypertension, renal dysfunction,

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and use of proton pump inhibitors (PPIs). *Conclusions:* The patients who experienced CES had a high rate of recurrent stroke or CES, mainly consisting of recurrent CES. Although anticoagulation may be beneficial for reducing recurrence of ischemic stroke, careful management is required given consideration of increased risk of brain hemorrhage during anticoagulation treatment, especially for patients with hypertension, renal dysfunction, and use of PPIs. **Key Words:** Cardioembolic stroke—bleeding event—healthcare database—risk factors.

Introduction

As Japan faces a rapidly aging society, it also anticipates it will face an increase in the rate of strokes with the rise in the number of older people. Cerebral infarction accounts for 75.9% of strokes and cardioembolic stroke (CES) accounts for 27.7% of cerebral infarction.[1] It has been reported that the number of CES is increasing recently and that the incidence is especially high in elderly people.[1,2] CES is characterized as being severe with a poor prognosis, and it tends to recur compared with other forms of cerebral infarction.[1,2] Indeed, the consequences are more frequent and severe after a CES, with 60% of these patients requiring nursing care, being bedridden, or dying, among other outcomes.[3] The Hisayama Study reported a recurrence rate of 75.2% at 10 years.[4] The devastating impact on patients and families, along with the substantial economic cost for medical and long-term nursing care, are pressing issues. Therefore, the primary and secondary prevention of CES is very important to avoid these personal and societal burdens.

Atrial fibrillation (AF) has been reported in more than 70% of patients who developed CES.[1] These patients should be treated with anticoagulant and antiplatelet therapy in relation to their risk of embolism, according to the Japanese guidelines for these treatment modalities in cardiovascular disease.[5]

There are limited data in Japan on the current status of the incidence and treatment of CES, and despite some data from epidemiological studies,[4,6-8] the picture is unclear. A healthcare database has been used to investigate CES and its treatment in Europe and the United States,[9,10] and several healthcare databases are becoming available for such epidemiological studies in Japan.[11,12] A merit of using a healthcare database for such studies is the capacity to understand current practices in a shorter period of time than required for a traditional prospective study. Therefore, it is anticipated that this approach will be used increasingly for clinical research. Moreover, the Pharmaceuticals and Medical Devices Agency in Japan has issued guidelines for epidemiological studies using a healthcare database.[13]

We conducted the present study using a Japanese healthcare database to investigate the current treatment strategies for CES and understand the patients who require further treatment to prevent recurrent stroke. A validation analysis was conducted first to ensure that the definitions of the events were sufficiently robust to capture stroke, systemic embolism (SE), and intracranial bleeding events.

Methods

EBM provider, a healthcare database developed and managed by Medical Data Vision Co., Ltd. (Tokyo, Japan), was used for this study. EBM provider is a healthcare database comprising 100 acute-care institutions that participate in the Diagnosis Procedure Combination (representing 8% of these institutions) in Japan with a balanced regional distribution. Patients who suffer a CES most commonly go directly to an acute-care institution in Japan.

Patients who met the criteria for CES during the period of April 1, 2008, to September 30, 2013, and whose inpatient and outpatient medical information was available were included in the statistical analysis for this study. CES was defined based on International Statistical Classification of Diseases, Tenth Revision (ICD-10), code with specific diagnosis and treatment episodes related to CES, and the index date of the event was the date of the first Diagnostic Procedure Combination code for CES in the healthcare database. Table 1 and Table S1 in the Supplementary Material provide further details. In this study, we evaluated AF-related stroke, SE, and bleeding events considered to be associated with CES. Antithrombotic treatment also was evaluated in this study.

The definition of each event is shown in Table S1 of the Supplementary Material. We first conducted a validation study for stroke, SE, and bleeding events, and then conducted the investigation of risk factors. The details of the validation study have been reported elsewhere.[14] Briefly, 2 cardiovascular specialists and 1 neurologist confirmed the presence or absence of events for all recorded medical procedures and laboratory data, for which it was possible to define the medical insurance claims (e.g., drugs, treatments, tests), targeting patients who were treated in a medical institution where these data could be obtained. Then, the positive predictive value (PPV) was calculated. The definition for each event was decided among the authors before the validation study and was limited to conditions that could be extracted from the electronic health record regardless of the presence or absence of laboratory data.[14] PPV was defined as the rate