Non-Vitamin K Antagonist Oral Anticoagulants Do Not Increase Cerebral Microbleeds

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Background: Atrial fibrillation (AF) is a cardiac arrhythmia that frequently induces ischemic strokes. Nowadays, non-vitamin K antagonist oral anticoagulants (NOACs) have come into widespread use for cardiogenic embolism prevention in place of warfarin. Recently, cerebral microbleeds (CMBs) have been noticed for their potential implication in cerebral small vessel disease. We hypothesized that NOACs do not have an unfavorable influence over cerebral small vessels and investigated whether NOACs increase CMBs in AF patients in a prospective manner. *Methods:* We performed baseline magnetic resonance imaging (MRI) examinations on the 69 enrolled AF patients and re-examined second round of MRI 1 year later. The enrolled patients continued the same anticoagulation therapy during the meantime. *Results:* CMBs did not develop in the 23 patients with NOACs for 1 year. Nine patients with antiplatelets also did not develop CMBs. On the other hand, 3 of 21 patients continued on warfarin and 3 of 9 with warfarin and antiplatelets had CMBs. When divided into 2 groups according to whether the CMBs developed, significant differences in the incidence of using NOACs were observed between the 2 groups ($P = .02$). A multivariate regression analysis showed that warfarin was independently related to the new development of CMBs (hazard ratio, 10.75; 95% confidence interval, 1.22-94.99; $P = .03$). *Conclusions:* This is the first report to clarify that NOACs do not increase CMBs in AF patients longitudinally in 1 year. Further consideration will be continued with a much longer follow-up in large samples. **Key Words:** NOAC—warfarin—cerebral microbleeds—atrial fibrillation.

Introduction

Atrial fibrillation (AF) is a cardiac arrhythmia that frequently induces ischemic strokes because of hemostasis or excessive blood clotting being prone to promote left atrial thrombosis. Heretofore, warfarin as an anticoagulant has been used to prevent cardiogenic embolism in AF patients. Nowadays, non-vitamin K antagonist oral anticoagulants (NOACs), formerly stood for "novel oral anticoagulants" and redefined recently as "non-vitamin K antagonist oral anticoagulants", not only rival or surpass warfarin in the efficacy but also excel in safety over warfarin[1-3] and are coming into widespread use for cardiogenic embolism prevention.

The CHA_2DS_2-VASc (1 point for congestive heart failure or left ventricular dysfunction, hypertension, age 65 to 74 years, diabetes mellitus, vascular disease [prior

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myocardial infarction, peripheral artery disease, or aortic plaque], sex category [ie, female sex] and 2 points for a prior stroke or transient ischemic attack or thromboembolism and an age ≥75 years) score[4-6] has come into general use for the risk assessment in nonvalvular AF patients because CHA_2DS_2-VASc score predicts future cardiogenic embolisms more accurately than the formerly used $CHADS_2$ score.[7] The CHA_2DS_2-VASc score makes us aware that some of its components also play a key role in focal cerebral microangiopathy.

Cerebral microbleeds (CMBs) are seen as small, from 2 to 5 mm in diameter, round foci with hypointensity on the gradient echo T2*-weighted magnetic resonance imaging (MRI).[8,9] CMBs are believed to represent perivascular accumulation of hemosiderin-containing macrophages on histopathologic examinations,[10-12] and therefore, they are considered to suggest the existence of vulnerability of the cerebral small vessels. We indicated the possibility that AF itself aggravates cerebral small vessels and significantly encompasses an increase in the CMBs as a consequence,[13] whereas only a few reports have addressed focal cerebral microangiopathy in AF patients.

The incidence of intracranial bleeding during NOAC treatment is uniformly lower than that during warfarin treatment.[1-3] Furthermore, there is a report that a hematoma that arises because of acute intracranial bleeding during dabigatran treatment tends to remain small and hard to expand.[14] We hypothesized that NOACs do not have an unfavorable influence over cerebral small vessels. Under this hypothesis, we defined that the goal in the present study was to prove that NOACs do not increase CMBs in AF patients in a prospective manner while considering the association of the CHA_2DS_2-VASc.

Methods

The entire study protocol was approved by the Ethical Review Board of the Asahikawa Medical University, and all patients gave their written informed consent for the study.

Patient Enrollment and the Longitudinal Study

A brain MRI assessment was performed on the outpatients older than 45 years with AF who visited the Cardiovascular, Respiratory, and Neurology Divisions of Asahikawa Medical University Hospital, and they were consecutively enrolled in the study. Valvular AF patients were excluded. A baseline MRI examination was performed on the patients enrolled, and 1 year later, a second round of MRI examinations were performed and analyzed changes in the number of CMBs with informed consent. The enrolled patients continued the same anticoagulation therapy for the prevention of cardiogenic embolism in the study period.

Definition of the Variables

Hypertension was defined as a systolic blood pressure of 140 mm Hg or more and/or diastolic blood pressure of 90 mm Hg or more in subjects who were not taking antihypertensive medications or continuously receiving antihypertensive treatment on an outpatient basis. Diabetes mellitus was defined as a Japan Diabetes Society hemoglobin A1c value of 6.1 or more (corresponds approximately to the National Glycohemoglobin Standardization Program hemoglobin A1c value of ≥6.5) or any continuous antidiabetic treatment on an outpatient basis. Chronic kidney disease was defined as an estimated glomerular filtration rate level of less than 60 ml/min/1.73 m^2 and/or overt albuminuria continuing longer than 3 months. Congestive heart failure was defined as that previously diagnosed by a cardiovascular specialist.

MRI Assessment

The MRI assessments were performed by trained observers who were blinded to the clinical information (J.S. and T.K.). We adopted the recommended criteria for the identification of CMBs proposed by Greenberg et al[8] to precisely assess the number of CMBs: (1) a black lesion on the T2*-weighted MRI, (2) round or ovoid lesions (rather than linear), (3) a blooming effect of the T2*-weighted MRI, (4) signals devoid of hyperintensity on the T1-weighted or T2-weighted sequences, (5) at least half of the lesion surrounded by brain parenchyma, (6) distinct from other potential mimicking conditions such as iron or calcium deposits, bone, or vessel flow voids, and (7) a clinical history excluding any traumatic diffuse axonal injury. CMBs were categorized into 2 groups: lobar (cortex, subcortex, and white matter) CMBs and deep or infratentorial CMBs. A cerebral infarction was defined as a focal lesion with a hypointense lesion with a hyperintense rim in the fluid-attenuated inversion recovery sequence images, with a corresponding hyperintensity on the T2-weighted images and corresponding hypointensity on the T1-weighted images. Cerebral infarctions with no plausible clinical history were defined as asymptomatic cerebral infarctions.

MRI Protocol

The image protocol included T1-weighted, fluid-attenuated inversion recovery, T2-weighted, and gradient echo T2*-weighted MRI. Imaging of the brain was performed on three 1.5 T MRI scanners at our hospital, the Signa Excite (General Electric Medical Systems, Waukesha, WI), Magnetom Sonata (Siemens Medical Solutions, Munich, Germany), and Achieva MR (Philips Healthcare, Bothell, WA) scanners. The gradient echo sequence parameters for the Signa Excite were as follows: 22 axial images; field of view, 220 mm; slice thickness, 5.5 mm;