Genetic and Non-Genetic Factors Affecting the Quality of Anticoagulation Control and Vascular Events in Atrial Fibrillation

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Background: Warfarin has a narrow therapeutic window. We hypothesized that genetic factors related to warfarin metabolism (*CYP2C9*) and activity (*VKORC1*) would show stronger associations than modifiable factors with the quality of anticoagulation control and risks for thromboembolism and hemorrhage. *Methods:* In this retrospective cohort analysis, clinical and genetic data were collected from 380 patients with atrial fibrillation (AF) who were followed for an average observation period of 4 years. We evaluated the factors associated with time in therapeutic range (TTR, international normalized ratio [INR]: 2-3) and vascular events (either thromboembolic or hemorrhagic), including both genetic (*CYP2C9* and *VKORC1* genotype) and modifiable factors (anticoagulation service and warfarin dose assessment interval). *Results:* The genotypic frequency of *CYP2C9**3* (rs1057910) was 9.5% and that of *VKORC1* 1173C>T (rs9934438) was 16.3%. TTR showed dependence on *VKORC1* polymorphism: TTR was higher in carriers of the *VKORC1* 1173C>T than of the *VKORC1* TT genotype (61.7 ± 16.0% versus 56.7 ± 17.4%, $P = .031$). Multivariate testing showed that the *VKORC1* genotype and anticoagulation service were independently related to labile INRs (TTR <65%). Vascular events were observed in 66 patients (18.4%) during the study period. A Cox proportional hazard model showed that the use of anticoagulation service and patients' characteristics, such as AF-thromboembolic risk (CHA_2DS_2-VASc score: Congestive heart failure, Hypertension, Age 75 years or older, Diabetes mellitus, previous Stroke or transient ischemic attack, Vascular disease, Age 65 to 74 years, female) and consequence (neurologic disability), but not genetic factors, were independently associated with vascular events. *Conclusions:* Both genetic factor (*VKORC1* genotype) and clinical efforts (anticoagulation service) influenced the quality of

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Received November 25, 2016; revision received February 14, 2017; accepted February 18, 2017.

Grant support: This research was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (HC15C1056).

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1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2017.02.022

anticoagulation control. However, clinical events were more strongly associated with patient characteristics and clinical efforts than with genetic factors. **Key Words:** Atrial fibrillation—*CYP2C9*—*VKORC1*—warfarin—polymorphism—stroke.

Introduction

The incidence of anticoagulation-associated intracranial hemorrhage is increasing with increasing warfarin use.[1] Warfarin has a narrow therapeutic window, and the hemorrhagic or thrombotic consequences of over- or underdosing may be devastating. Even in clinical trials of atrial fibrillation (AF) with carefully selected and monitored patients, the proportion of time in therapeutic range (TTR), defined by an international normalized ratio (INR) of 2-3, is less than two-thirds.[2] Although AF-related strokes occur on the suboptimal use of warfarin, adverse bleeding events may occur in 8 of every 100 patients treated annually with the drug.[3]

Several genetic and clinical factors contribute to the interindividual variation in warfarin maintenance dose requirements.[4] Single nucleotide polymorphisms in genes affecting warfarin metabolism (cytochrome-P450 2C9, *CYP2C9*) and response (vitamin K epoxide reductase complex 1, *VKORC1*) wield important influences. Variations in genes encoding *CYP2C9* and *VKORC1* enzymes account for 10%-15% and 20%-35%, respectively, of variation in warfarin dose requirements. Age, height, and body weight account for 10%-20%, drug interactions for 5%-10%, and other factors (generally unknown) for up to 40%.[4] Genetic factors may influence time to stabilization of the INR, as well as the warfarin dose requirement. Dose prediction algorithms, derived by multiple linear regression analysis of genetic and clinical factors, indicate the relative contributions of each factor.[4] However, the role of genotype in warfarin maintenance is unsettled. Previous prospective randomized studies exploring the potential clinical utility of genotype-guided dosing have found either negative result for improvement of anticoagulation control[5] or improvement, but only during the initiation of warfarin treatment.[6]

Besides warfarin pharmacogenetics, several factors may also be involved in long-term intraindividual variation of the quality of anticoagulation therapy. For example, the assessment scheme based on clinical variables (the SAMe-TT_2R_2 score) has been introduced to predict the quality of anticoagulation control with warfarin.[7] Clinical efforts, such as frequent warfarin dose assessment and anticoagulation service by a pharmacist, may improve the quality of anticoagulation therapy and reduce thromboembolic and hemorrhagic risks.

We hypothesized that anticoagulation service has greater influence on the effectiveness of anticoagulation control and thromboembolic or hemorrhagic risks than do genetic factors associated with warfarin dosing. To test this, we investigated the factors associated with labile INR and clinical events, evaluating both genetic and clinical factors in the long-term follow-up data of AF patients receiving long-term warfarin treatment with a target INR range of 2.0-3.0 and with good compliance.

Patients and Methods

Patient Selection

This retrospective cohort study was based on data from consecutive patients who visited a university medical center in Seoul, Korea. Four hundred seventy-nine patients who visited an outpatient clinic or were admitted to the hospital in the neurology department between January 1996 and May 2013 were initially reviewed. Among the patients, 380 patients were included in this study if (1) they had non-valvular AF, (2) they were eligible to take warfarin to prevent thromboembolism (i.e., $CHADS_2$ score), (3) their genetic testing results were available, and (4) they were followed for more than 6 months. The exclusion criteria were (1) irregular medication (>20% missed doses or >10% extra doses),[8] (2) active cancer or severe systemic illness, including hepatic or renal disease, (3) chronic alcoholism, and (4) regular consumption of food, beverages, or medication that could interfere with the effects of warfarin, such as green liquor and herbal medication.[9-11] Compliance with warfarin treatment was regularly monitored and patients received dietary instructions from a pharmacist at an anticoagulation service. Ninety-nine patients were excluded because of the presence of heart valve disease (n = 13), irregular use of medication (n = 19), active cancer (n = 9), follow-up duration of less than 6 months (n = 39), refusal to take warfarin (n = 8), and chronic alcoholism (n = 2). Patients with target INR ranges of 1.5-2.5 or 2.5-3.5 (n = 9) were also excluded. Patients taking an antiplatelet agent in addition to warfarin were not excluded from this study. The detailed patients' selection and characteristics were described in our previous study.[12] The local institutional review board approved the study and all participants gave informed consent before the study began.

Workup

After stabilization, dose maintenance within the therapeutic INR range was achieved by periodic testing of the INR. Dose assessment was performed every 1-3 months. Once a patient was enrolled, we obtained a medical history,