ABO Blood Type and Response of Activated Partial Thromboplastin Time to Dabigatran in Nonvalvular Atrial Fibrillation Patients

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Background: The association between ABO blood type and the activated partial thromboplastin time (aPTT) under dabigatran therapy in nonvalvular atrial fibrillation (NVAF) patients is unclear.

Methods and Results: Between 2011 March and 2015 May, data on ABO blood type and aPTT under dabigatran were obtained for 396 NVAF patients (baseline aPTT, 166). The prevalence of blood type O tended to increase or significantly increase according to baseline aPTT, aPTT under dabigatran, and their difference (ΔaPTT) (P=0.054, 0.001, and 0.012, respectively).

Conclusions: In these NVAF patients, a high aPTT value under dabigatran therapy was associated with blood type O.

Key Words: Anticoagulation; Atrial fibrillation; Dabigatran

Low plasma levels of von Willebrand factor (vWF) in patients with blood type O, because of a low clearance rate of vWF, have been reported. vWF is the carrier protein for factor VIII (FVIII) and protects it from proteolysis. Consequently, low vWF concentrations cause a short half-life and low plasma concentrations of FVIII. Thus, FVIII activity in subjects with blood type O has been reported as 20–30% lower than in those with other blood types.

In 2011, dabigatran etexilate was approved in Japan for stroke prevention in patients with nonvalvular atrial fibrillation (NVAF). Although dabigatran etexilate should not theoretically require routine monitoring, assessment of plasma drug concentration is required under the suspicion of overdose, or the occurrence of bleeding, renal insufficiency, emergency surgery, or trauma. For this purpose, the activated partial thromboplastin time (aPTT) is frequently used in daily clinical practice in Japan, because of its moderate sensitivity (at least to some extent) and its availability.

aPTT is prolonged when there is inhibition of the intrinsic pathway of the coagulation cascade, which specifically includes factors XII, XI, IX, and VIII, and shares factors I, II, V, and X with the extrinsic pathway. Given this mechanism, it can be hypothesized that aPTT under dabigatran might be prolonged in patients with blood type O, because of low FVIII activity. In the present study, we retrospectively investigated the association between ABO blood type and aPTT under dabigatran therapy in Japanese NVAF patients.

Methods

Data Collection
Dabigatran was prescribed for 881 NVAF patients between March 25, 2011 and May 31, 2015. NVAF was defined as AF without mitral stenosis and/or prosthetic valve (mechanical or biological). We recorded background details and distribution of aPTT (reagent: Platerin LS II [Kyowa Hakko Kirin Co, Tokyo, Japan]; analyzer: Coagtron-180 [Kyowa Hakko Kirin Co]). When we could obtain 2 or more measurements of aPTT, we used the maximum. The data collection was part of the Shinken Database, a prospective, hospital-based cohort of cardiovascular diseases in an urban area of Japan, for which the Ethics Committee at the Cardiovascular Institute granted ethical permission.

At the Cardiovascular Institute, ABO blood type is routinely
Results

Characteristics of the Patients (Table)
The study group included 321 men (81.1%; mean age, 63.0 years). CHADS2 score was ≥2 in 36.1% of patients. A low dose of dabigatran (220 mg/day) was administered to 267 (67.4%) patients. Significant differences in patients' backgrounds were not observed among the ABO blood types.

Distribution of ABO Blood Type According to aPTT (Figure)
The prevalence of blood type O tended to increase according to the increment in baseline aPTT level (n=166): 0% at baseline aPTT ≤23 s, 30–40% in 28–43 s, and 100% in ≥44 s (P for trend 0.054). Similarly, the prevalence of blood type O increased according to the increment in aPTT under dabigatran, which

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Table. Patients Characteristics According to ABO Blood Type

| Characteristic                      | Total (n=396) | O (n=121) | A (n=156) | B (n=82) | AB (n=37) | P value |
|-------------------------------------|---------------|-----------|-----------|----------|-----------|---------|
| Dose of dabigatran                 |               |           |           |          |           |         |
| 300 mg/day                          | 129 (32.6)    | 43 (35.5) | 47 (30.1) | 27 (32.9)| 12 (32.4)| 0.822   |
| 220 mg/day                          | 267 (67.4)    | 78 (64.5) | 109 (69.9)| 55 (67.1)| 25 (67.6)|         |
| Age, years                          | 63±11.4       | 61.6±11.7 | 63.8±11.4| 63.8±11.5| 62.1±10.7| 0.369   |
| ≥75                                 | 203 (51.3)    | 67 (55.4) | 81 (51.9)| 34 (41.5)| 21 (56.8)| 0.220   |
| 65–74                               | 132 (33.3)    | 38 (31.4) | 46 (29.5)| 37 (45.1)| 11 (29.7)|         |
| <65                                 | 61 (15.4)     | 16 (13.2) | 29 (18.6)| 11 (13.4)| 5 (13.5) |         |
| Body weight, kg                     | 67.3±12.2     | 66.8±13.1 | 67.8±11.8| 67.3±12.8| 67.7±9   | 0.858   |
| CHADS2 score                        |               |           |           |          |           |         |
| ≥2 points                           | 143 (36.1)    | 45 (37.2) | 56 (35.9)| 32 (39.0)| 10 (27.0)| 0.229   |
| 1 point                             | 147 (37.1)    | 47 (38.8) | 50 (32.1)| 30 (36.6)| 20 (54.1)|         |
| 0 point                             | 106 (26.8)    | 29 (24.0) | 50 (32.1)| 20 (24.4)| 7 (18.9) |         |
| Creatinine clearance, ml/min        | 83.2±25.7     | 83.3±26.0 | 83.3±25.9| 82.3±26.9| 84.2±22.2| 0.981   |
| <50                                 | 30 (7.6)      | 10 (8.3)  | 12 (7.7) | 7 (8.5)  | 1 (2.7)  | 0.694   |
| Mitral regurgitation                | 17 (4.3)      | 2 (1.7)   | 7 (4.5)  | 6 (7.3)  | 2 (5.4)  | 0.261   |
| Aortic regurgitation                | 3 (0.8)       | 0 (0.0)   | 1 (0.6)  | 1 (1.2)  | 1 (2.7)  | 0.385   |
| Aortic stenosis                     | 5 (1.3)       | 2 (1.7)   | 2 (1.3)  | 1 (1.2)  | 0 (0.0)  | 0.891   |
| Tricuspid regurgitation             | 12 (3.0)      | 3 (2.5)   | 7 (4.5)  | 2 (2.4)  | 0 (0.0)  | 0.474   |
| Myocardial infarction               | 10 (2.5)      | 4 (3.3)   | 3 (1.9)  | 3 (3.7)  | 0 (0.0)  | 0.590   |
| Dilated cardiomyopathy             | 10 (2.5)      | 4 (3.3)   | 5 (3.2)  | 0 (0.0)  | 1 (2.7)  | 0.437   |
| Hypertrophic cardiomyopathy        | 17 (4.3)      | 5 (4.1)   | 6 (3.8)  | 5 (6.1)  | 1 (2.7)  | 0.811   |
| Hypertension                       | 214 (54.0)    | 64 (52.9) | 80 (51.3)| 44 (53.7)| 26 (70.3)| 0.215   |
| Diabetes mellitus                  | 49 (12.4)     | 9 (7.4)   | 27 (17.3)| 9 (11.0) | 4 (10.8) | 0.092   |
| History of cerebral infarction or transient ischemic attack | 15 (3.8) | 3 (2.5) | 9 (5.8) | 2 (2.4) | 1 (2.7) | 0.427   |
| P-glycoprotein inhibitor use       | 17 (4.3)      | 8 (6.6)   | 4 (2.6)  | 3 (3.7)  | 2 (5.4)  | 0.406   |
| Patients with baseline aPTT         | 166 (41.9)    | 57 (47.1) | 57 (36.5)| 36 (43.9)| 16 (43.2)| 0.340   |
| Baseline aPTT, s                    | 30.7±4.3      | 31.4±4.5  | 31±4.5   | 29.9±3.9 | 29.1±3.1 | 0.133   |
| aPTT under dabigatran, s           | 49.5±10.2     | 52.1±10.6 | 48.0±9.5 | 48.5±10.3| 49.5±10.4| 0.006   |
| 300 mg/day                          | 50.2±10       | 54.1±10.9 | 47.7±8.5 | 48.4±9.3 | 50.4±10.2| 0.015   |
| 220 mg/day                          | 49.1±10.3     | 51±10.3   | 48.1±10  | 48.5±10.9| 49.1±10.7| 0.279   |
| ΔaPTT, s                            | 19.0±9.2      | 20.7±10.8 | 18.2±8.7 | 17.7±7.0 | 19.0±9.0 | 0.370   |
| 300 mg/day                          | 20.7±10.5     | 23.4±11.8 | 17.8±10.4| 18.7±7.8 | 21.0±10.0| 0.522   |
| 220 mg/day                          | 18.5±8.7      | 19.5±10.3 | 18.2±8.4 | 17.4±8.6 | 18.5±9.2 | 0.810   |

Categorical and consecutive data are presented as n (%) and mean±standard deviation, respectively. ΔaPTT was calculated by aPTT under dabigatran–baseline aPTT. aPTT, activated partial thromboplastin time.

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checked when patients are hospitalized with any reason. Of the 881 NVAF patients under dabigatran therapy, both the ABO blood type and aPTT under dabigatran in the outpatient clinic in the morning were available for 396 patients, who comprised the study group.

Statistical Analysis

Study patients were divided into 4 ABO blood type categories, and their background, baseline aPTT (n=166), aPTT under dabigatran, and ΔaPTT (aPTT under dabigatran–baseline aPTT) were compared. The categorical and consecutive data are presented as number (%) and mean±standard deviation, respectively. The chi-square test and 1-way ANOVA were used for group comparison. Simple and multiple linear regression analyses were performed to examine the relationship between ABO blood type and aPTT values; in the multivariate model, patients' clinical variables were selected by a stepwise method. Statistical analyses were performed using SPSS for Windows version 19.0 software. Statistical significance was set at a 2-sided P-value <0.05.
Figure. Distribution of ABO blood type according to the activated partial thromboplastin time (aPTT). P values for trend were calculated by Cochran-Armitage methods. In (C), ΔaPTT was calculated as aPTT under dabigatran–baseline aPTT. AM, in the morning.
was sampled in the morning (n=396): <30% at aPTT ≤43 s, 30–40% in 44–71 s, and >60% in ≥72 s (P for trend 0.001). Similar trends could be observed in the relationship between the prevalence of blood type O and ΔaPTT (aPTT under dabigatran in the morning–baseline aPTT): <40% at ΔaPTT ≤27 s, 40–60% in 28–35 s, and >60% in ≥36 s (P for trend 0.012).

By simple linear regression analysis of aPTT under dabigatran, the partial regression coefficient of blood type O (vs. non-O blood types) was 3.41 (95% confidence interval 1.59–5.92; P=0.001). In the multiple linear regression model adjusted for all variables in the Table (except baseline aPTT and ΔaPTT), the partial regression coefficient of blood type O (vs. non-O blood types) was 3.28 (95% confidence interval 1.44–5.74; P=0.001).

**Discussion**

Our data showed that, in NVAF patients under dabigatran therapy, the prevalence of blood type O tended to increase according to the baseline aPTT, and significantly increase according to the aPTT under dabigatran and ΔaPTT, which, we believe, supports our hypothesis.

However, in our data not all patients with blood type O showed a high baseline aPTT value and/or a high response of aPTT to dabigatran. Therefore, it is assumed that the coagulation disability in FVIII does not always exist in patients with blood type O; rather, clinically significant coagulation disability may be scarce because the numbers of patients with high baseline aPTT (≥44 s, n=2), high aPTT under dabigatran (≥72 s, n=12), and high ΔaPTT (≥36 s, n=7) were small in our population.

**Study Limitations**

First, our database consisted of a cohort at a single cardiovascular hospital, and most of them were indicated for catheter ablation. So selection bias should be considered. Second, we did not measure coincident FVIII with aPTT. Third, the aPTT under dabigatran in the present study is not exactly the peak or the trough. Given these limitations, the results should be ascertained in a larger, multicentre study with rigid indications.

**Conclusions**

In a group of NVAF patients, a high aPTT value under dabigatran therapy was associated with blood type O, indicating an intrinsic pathway disability in blood type O patients.

**Disclosures**

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