Impact of gene polymorphisms in drug-metabolizing enzymes and transporters on trough concentrations of rivaroxaban in patient with atrial fibrillation

（心房細動患者におけるリバーロキサバンのトラフ濃度に及ぼす薬物代謝酵素および薬物トランスポーター遺伝子多型の影響）

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Abstract

Rivaroxaban is excreted from the body via multiple pathways involving glomerular filtration, drug metabolizing enzymes, and transporters. In this study, we aimed to examine the impact of single nucleotide polymorphisms (SNPs) in P-glycoprotein, breast cancer resistance protein, cytochrome P450 (CYP) 3A5, and CYP2J2 on the pharmacokinetics of rivaroxaban. Eighty-six patients with non-valvular atrial fibrillation (NVAF) undergoing AF catheter ablation were enrolled in this study. In these analyses, the dose-adjusted plasma trough concentration ratio (C_{0h}/D) of rivaroxaban was used as the pharmacokinetic index. The median (quartile range) rivaroxaban C_{0h}/D was 3.39 (2.08–5.21) ng/mL/mg (coefficient of variation: 80.5%). The C_{0h}/D did not differ significantly among *ABCB1* c.3435C>T, c.2677G>A/T, c.1236C>T, *ABCG2* c.421C>A, *CYP3A5*3*, and *CYP2J2*7* genotypes. Stepwise selection multiple linear regression analysis showed that the estimated glomerular filtration rate (eGFR) was the only independent factor influencing the C_{0h}/D of rivaroxaban (R^2 = 0.152, P < 0.001). There was a significant correlation between the C_{0h} of rivaroxaban and prothrombin time (PT) (*rho* = 0.357, P = 0.001). In patients with NVAF, pharmacokinetic genotype tests are unlikely to be useful for prediction of the C_{0h} of rivaroxaban.

Keywords: rivaroxaban, *ABCB1*, *ABCG2*, *CYP3A5*3*, *CYP2J2*7*

Introduction

Direct oral anticoagulants (DOACs) are increasingly used in clinical practice to prevent venous thrombosis or thrombus formation in non-valvular atrial fibrillation (NVAF) [1]. The usage of rivaroxaban, a factor Xa (FXa) inhibitor, increased from 0.13% to 13.87% from 2011 to 2014 in the United States of America (USA) [2]. Rivaroxaban has been shown to have efficacy similar to that of warfarin for prevention of stroke or systemic embolism in patients with NVAF [3]. In addition, fatal bleeding and intracranial hemorrhage (ICH) occur less frequently in patients receiving rivaroxaban than in those receiving warfarin [3]. Although DOACs do not require routine coagulation monitoring, serious bleeding events have been occasionally reported in patients taking these drugs [4]. Rivaroxaban was among the top 10 drugs involved in emergency department visits for adverse drug events in the United States in 2013–2014 [5]. In addition, interindividual variability of the pharmacokinetics of rivaroxaban in patients with NVAF has been shown to be large [6-9].

Rivaroxaban bioavailability ranges from 66–100%, depending on the dose and whether or not the dose is administered with a meal [10]. After being absorbed from the gut lumen, rivaroxaban is excreted from the body via multiple pathways [10]. Rivaroxaban is highly bound to plasma proteins (primarily to albumin), with the free fraction typically accounting for only 5–8% of the total. Approximately one-third of the dose is eliminated as unchanged active drug in the urine via a process thought to involve P-glycoprotein (P-gp, gene code *ABCB1*) and breast cancer resistance protein (BCRP, gene code *ABCG2*). The remaining two-thirds of the dose is subjected to metabolic degradation via cytochrome P450 (CYP) 3A4/5, CYP2J2, and CYP-independent mechanisms. No pharmacologically active

metabolites have been described. The interindividual pharmacokinetic variability of rivaroxaban depends on many factors, such as drug dose, age, kidney function, co-administered drugs, and comorbidities. Measurement of plasma concentrations of rivaroxaban is not routinely recommended but may be beneficial in elderly and frail patients, extremely overweight patients, and patients with impaired kidney function or bleeding due to overdosing [11].

Interindividual genetic variations in drug metabolizing enzymes and transporters influence the pharmacokinetics and pharmacodynamics of various drugs [12]. Several polymorphisms, such as c.3435C>T, c.2677G>A/T, and c.1236C>T, have been identified in the *ABCB1* gene [13]. *ABCB1* limits the absorption of xenobiotics from the gut lumen and is involved in biliary and renal secretion of its substrates. However, no consensus has been reached regarding the functional consequences of these polymorphisms in the transporter's function. *CYP3A5*3* polymorphisms affect the pharmacokinetics of drugs that serve as a substrate for this drug-metabolizing enzyme [14]. Although the *ABCG2* 421C>A polymorphism affects drug efficacy and safety, the effects of this variant on the pharmacokinetics of most BCRP substrates are generally relatively modest [15]. Kaspera et al. reported that the amount of CYP2J2 in liver microsomes with the *CYP2J2*7* allele was decreased to 39% compared with that in liver microsomes from other individuals [16].

However, to date, no clinical studies have addressed the contributions of all of the above polymorphisms to plasma concentrations of rivaroxaban in the same patient population. Therefore, in this study, we investigated the impact of the single nucleotide polymorphisms

(SNPs) *CYP3A5*3*, *ABCB1* c.3435C>T, c.2677G>A/T, c.1236C>T, *ABCG2* c.421C>A, and *CYP2J2*7* on plasma concentrations (C_{0h}/D) of rivaroxaban in Japanese patients with NVAF.

2. Methods

2.1 Patients

Eighty-six patients with NVAF undergoing AF catheter ablation admitted to the Hirosaki University Hospital from June 2018 through February 2020 were enrolled in this study. All patients had been taking rivaroxaban after breakfast at least 1 week prior to hospitalization. Rivaroxaban was skipped only in the morning of the day of AF ablation. Adherence was confirmed by the nurse via the empty press through pack on the day before AF ablation. Blood collection for plasma concentration measurement at trough was performed in the morning of the day of AF ablation. These blood samples were stored at -30℃ until analysis. The dose of rivaroxaban (10 or 15 mg once daily) was determined by medical indication in Japan as 10 mg once daily in patients with creatinine clearance (CCr) [17] between 15 and 50 mL/min and 15 mg once daily in those with CCr [17] greater than or equal to 50 mL/min. Patients taking drugs or foods that obviously affected rivaroxaban pharmacokinetics, such as amiodarone and verapamil, during the study were excluded [18]. Body surface area (BSA) and estimated glomerular filtration rate (eGFR) were calculated using the following formulas:

$$\text{BSA } (m^2) = \text{body weight (kg)}^{0.425} \times \text{height (cm)}^{0.725} \times 0.007184 \text{ [19]}$$

eGFR (mL/min) = 194 × serum creatinine (mg/dL)$^{-1.094}$ × age (years old)$^{-0.287}$ × body surface area (m^2) (× 0.739 if female) / 1.73 [20].

PT was determined using Tronborel S (Siemens Healthcare Diagnostics Products, Marburg, Germany) on a CS-5100 (Sysmex, Kobe, Japan) according to the manufacturer's instructions. The study protocol was approved by the Ethics Committee of Hirosaki University Graduate School of Medicine (project identification code: 2018-011), and all patients provided written informed consent before the study. The study was conducted in accordance with the *Basic & Clinical Pharmacology & Toxicology* policy for experimental and clinical studies [21].

2.2 Analytical method of plasma concentration

Blood samples were centrifuged at 3,500 rpm for 10 min at 4℃, and separated plasma was stored at -30℃ until analysis. Plasma concentrations of rivaroxaban were measured by ultra-performance liquid chromatography (UPLC) tandem mass spectrometry using an ACQUITY UPLC System (Waters, MA, USA). Plasma (100 μL) was mixed with 150 μL of acetonitrile and 10 μL of internal standard (500 ng/mL apixaban). The mixture was vortexed for 30 s and centrifuged at 13,500 rpm for 5 min at room temperature. Supernatant (100 μL) was diluted with 100 μL MilliQ water (total volume: 200 μL). The sample was transferred to an autosampler vial, and 5 μL was then injected into an ACQUITY UPLC Phenyl column (1.7 μm, 75 mm × 2.1 mm) at 40℃. The mobile phase consisted of (A) MilliQ with 0.1% formic acid and (B) acetonitrile with 0.1% formic acid at a flow rate of 0.4 mL/min. Gradient conditions were as follows: 0–1.0 min, held in 5% B; 1.0–6.0 min, linear from 5% to 95% B;

6.0–7.0 min, held in 5% B; 7.0–7.1 min, linear from 95% to 5% B; 7.1–10.0 min, held in 5% B. The analyte and internal standard were ionized and detected using Xevo TQD (Waters). Positive electrospray ionization was performed in the multiple reaction monitoring mode. Ion transitions of rivaroxaban and internal standard were m/z 436.1→144.9 and 460.0→443.0, respectively. Cone voltage and collision energies were 40 V and 30 eV, respectively, for both agents. The calibration curve was linear in the range of 5－200 ng/mL. If the plasma concentration of the analyte exceeded the upper limit of the calibration curve, the analyte was diluted twice and measured. The calibration curve showed good linearity with $R^2 > 0.99$. The intra- and interday accuracy values (CV%) were all within ± 15%, and precision values (CV%) were all less than 15% in each calibration curve range.

2.3 Genotyping

DNA was extracted from peripheral blood samples with a QIAamp Blood Kit (Qiagen, Hilden, Germany) and was stored at -30℃ until analysis. The *CYP3A5*3* (c.6986A>G, rs776746), *ABCB1* c.3435C>T (rs1045642), c.2677G>A/T (rs2032582), c.1236C>T (rs1128503), *ABCG2* c.421C>A (rs2231142), and *CYP2J2*7* (c.-76G>T, rs890293) genotypes were determined by real-time PCR using TaqMan SNP Genotyping Assays from Thermo Fisher Scientific (Waltham, MA, USA). Cycle conditions were as follows: 95℃ for 3 min, followed by 40 cycles of 95℃ for 15 s and 60℃ for 15 s, except for *CYP2J2*7* genotyping. Heating at 50℃ for 2 min was added as an initial step, followed by cycling at 95℃ for 10 min and 40 cycles of 95℃ for 60 s and 60℃ for 15 s for *CYP2J2*7* genotyping.

Genotypes were detected using a CFX-Connect Real-Time PCR system (Bio-Rad Laboratories Inc., Hercules, CA, USA).

2.4 Statistical procedures

Shapiro-Wilk test was used to assess distribution. Allele frequencies of polymorphisms were evaluated according to the Hardy-Weinberg equilibrium using χ^2 tests. The Kruskal-Wallis test or Mann-Whitney U test was used to determine differences in continuous values between groups. Spearman's rank correlation coefficient test was used to assess correlations in continuous values between groups, and all results were expressed as Spearman's *rho* values. Stepwise multiple linear regression analysis was performed to determine the effects of all factors in a univariate analysis. For each patient, each genotype was replaced with dummy variables (1 and 0, 0 and 1, and 0 and 0, respectively). The percent variation that could be explained by the multiple regression equation was expressed as a coefficient of determination (R^2). Results with p values of less than 0.05 were considered statistically significant. Statistical analysis was performed with SPSS 26.0 for Windows (SPSS IBM Japan Inc., Tokyo, Japan).

3. Results

The clinical characteristics of the patients with NVAF taking rivaroxaban are listed in Table 1. There were no patients with serious renal dysfunction (eGFR < 30 mL/min) or hepatic dysfunction (Child-Pugh score > 2). The distributions of *CYP3A5*3*, *ABCB1* c.3435C>T,

c.2677G>A/T, c.1236C>T, *ABCG2* c.421C>A and *CYP2J2*7* genotypes were in agreement with the Hardy-Weinberg equilibrium (P = 0.083, 0.134, 0.875, 0.292, and 0.651) [22, 23].

The daily dose (D), trough concentration (C_{0h}), and dose-adjusted C_{0h} (C_{0h}/D) of rivaroxaban are listed in Table 2. The majority of patients had taken rivaroxaban 15 mg. The coefficients of variation of C_{0h} and C_{0h}/D were very large.

Correlation between the C_{0h}/D of rivaroxaban and clinical characteristics of patients with NVAF are listed in Table 3. The C_{0h}/D of rivaroxaban was correlated with eGFR and aspartate aminotransferase. In contrast, no correlations were observed with any drug-metabolizing enzyme and transporter genotypes (Figure 1a–f). In addition, there were no significant differences in the C_{0h}/D of rivaroxaban between *ABCB1* haplotypes (Figure 2). eGFR was an independent factor influencing the C_{0h}/D of rivaroxaban in stepwise selection multiple linear regression analysis (P < 0.001). The determination coefficient (R^2) for the C_{0h}/D of rivaroxaban was 0.152. eGFR was also an independent factor influencing the C_{0h} of rivaroxaban, similar to the above analyses (P = 0.001). The correlation between the C_{0h} of rivaroxaban and PT is shown in Figure 3. A significant correlation was observed ~~with PT~~between these parameters (*rho* = 0.357, P = 0.001).

4. Discussion

This was the first study to comprehensively assess the influence of major pharmacokinetics-related polymorphisms on the pharmacokinetics of rivaroxaban in patients with NVAF. Pharmacogenomics of FXas is a relatively new area of research [24].

eGFR showed a definite correlation with the C_{0h}/D of rivaroxaban. However, eGFR alone could not fully explain the effects on C_{0h}/D. One-third of the oral total dose is excreted into the urine as unmodified rivaroxaban, for which the mean ratio between active renal secretion and glomerular filtration is 4:1 [25]. Therefore, it is necessary to consider effects other than renal function on the C_{0h}/D of rivaroxaban. However, the effects of P-gp, BCRP, CYP3A5, and CYP2J2, other than gene polymorphisms, on the C_{0h}/D of rivaroxaban were not evaluated in this study. Ketoconazole, a strong CYP3A4 inhibitor, P-gp/BCRP inhibitor, and potential CYP2J2 inhibitor, has been reported to increase blood levels of rivaroxaban in healthy volunteers [26]. Therefore, drug-drug interactions are considered to be more important than these gene polymorphisms with regard to the impact on the C_{0h}/D of rivaroxaban.

In this study, the *ABCB1* c.2677G>A/T, c.3435C>T, and c.1236C>T genotypes did not affect the C_{0h}/D of rivaroxaban. A recent case report suggested that patients who are homozygous for the *ABCB1* haplotype (c.2677G>T; T/T and c.3435C>T; T/T) may have higher plasma levels, C_{max} values, half-lives, and increased risk of bleeding complications [27]. In contrast, another study suggested that the combined *ABCB1* haplotype (1236T/T-2677T/T-3435T/T) did not have any significant effect on the pharmacokinetics of rivaroxaban [28]. Therefore, it was unclear whether the *ABCB1* polymorphism affected the pharmacokinetics of rivaroxaban. Moreover, Sennesael et al. evaluated the in vitro effects of these gene polymorphisms on rivaroxaban transport activity [29]. As a result, these gene polymorphisms had no significant influence on the intracellular accumulation of rivaroxaban when compared with the wild-type protein. Our results were consistent with these findings.

Thus, these *ABCB1* genotypes are unlikely to contribute to interindividual variability in rivaroxaban C_{0h}.

PT showed a definite correlation with the C_{0h} of rivaroxaban. Although the correlation between PT and plasma concentration of rivaroxaban is known to vary depending on the reagents used for the PT test [30, 31], Tromborel S, which was used in this study, is known to correlate well with the plasma concentration of rivaroxaban estimated by anti-FXa activity assays within the therapeutic range [32]. Kubitza et al. reported that renal clearance and total body clearance of rivaroxaban are decreased in patients with increasing renal impairment, leading to increased plasma concentrations, increased inhibition of FXa activity, and prolongation of PT [25]. Our results are consistent with the findings of this previous study. Although further studies are necessary to clarify the relationships between high rivaroxaban trough concentrations and bleeding tendency with increasing PT, rivaroxaban may affect PT according to factor Xa or thrombin activity [33].

There are still several limitations to this single-center study. First, the number of patients with renal dysfunction in this study was small. Genotyping of pharmacokinetic factors, such as CYP and P-gp, may be useful for individualization of the rivaroxaban dosage in these patients [27~~20~~]. Therefore, it is necessary to evaluate the effects of drug-metabolizing enzyme and transporter polymorphisms on the pharmacokinetics of rivaroxaban in patients with severe renal impairment. Second, the patients in this study were Japanese only. To the best of our knowledge, the contributions of CYP3A4 and CYP3A5 to total rivaroxaban metabolism by CYP3A are still unclear. Although the *CYP3A4*22* allele is associated with

reduced CYP3A4 activity in vivo [34], no *CYP3A4*22* allele carriers were found in a prior Japanese population [35], and we did not analyze this polymorphism. A previous study also showed that the C_{0h}/D of apixaban, an FXa inhibitor that serves as the substrate for CYP3A4/5, in patients with NVAF was lower in those with the *CYP3A5*1/*1* genotype than in those with the *CYP3A5*3* allele [36]. Although the C_{0h}/D of rivaroxaban was not influenced by *CYP3A5* gene polymorphisms in our study, there were only 4 patients with the *CYP3A5*1/*1* genotype. In addition, the allele frequency of *CYP3A5*3* exhibits interethnic variability [37]. However, the allele frequency of *CYP2J2*7* is low in humans, and that in the Japanese population is only about 6.2% [38]. In this study, none of the patients were homozygous for the *CYP2J2*7* genotype. Therefore, the effects of *CYP2J2* SNPs on the C_{0h}/D of rivaroxaban were not fully considered. However, the rates of contribution of CYP3A4/5 and CYP2J2 to clearance pathways are approximately 18% and 14% of total clearance [10]. At this time, gene polymorphisms in drug metabolizing enzymes and transporters have not been reported to have any apparent effects on the pharmacokinetics of rivaroxaban [24]. Therefore, gene polymorphisms in these drug metabolizing enzymes may have limited effectiveness against the C_{0h}/D of rivaroxaban.

5. Conclusions

In patients with normal renal function and/or without drug-drug interactions, pharmacokinetic genotype tests are unlikely to be useful for prediction of the C_{0h}/D of rivaroxaban. In the future, additional studies will be necessary to clarify the impact of gene

polymorphisms in drug metabolizing enzymes and transporters on trough concentrations in patients with NVAF with abnormal clearance of rivaroxaban.

Conflicts of interest

Dr. Kinjo received research funding from The Center of Innovation Program from Japan Science and Technology Agency. Dr. Tomita received research funding from Boehringer Ingelheim, Bayer, Daiichi-Sankyo, and Pfizer and Speakers' Bureau/Honoraria from Boehringer Ingelheim, Bayer, Daiichi-Sankyo, and Bristol-Myers Squibb. Dr. Niioka received Speakers' Honoraria from Daiichi-Sankyo. The remaining authors have nothing to disclose.

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Figure Legends

Figure 1. Comparison of C_{0h}/D among drug-metabolizing enzyme and transporter genotypes. (a) *CYP3A5*3*; (b) *CYP2J2*7*; (c) *ABCG2* c.421C>A; (d) *ABCB1* c.1236C>T; (e) *ABCB1* c.2677G>A/T; (f) *ABCB1* c.3435C>T; C_{0h}/D, dose adjusted-trough concentration; CYP, cytochrome P450. The values above the upper limits of the Y-axis are shown with a scale break line. Medians [quartile ranges] for each genotype were as follows: *CYP3A5*3* (A/A versus A/G versus G/G = 4.77 [3.83–7.36] versus 3.58 [2.21–5.13] versus 2.99 [1.94–5.34]), *CYP2J2*7* (G/G versus G/T = 3.26 [2.11–5.14] versus 4.31 [2.39–8.60]), *ABCG2* c.421C>A (C/C versus C/A versus A/A = 3.35 [2.25–5.14] versus 3.47 [1.88–5.39] versus 1.89 [0.99–3.49]), *ABCB1* c.1236C>T (C/C versus C/T versus T/T = 4.37 [2.49–4.91] versus 3.09 [2.11–5.72] versus 3.06 [2.18–5.30]), *ABCB1* c.2677G>A/T (G/G versus G/A or G/T versus A/A or T/T or A/T = 4.17 [2.16–6.05] versus 3.17 [1.31–5.11] versus 3.35 [2.45–5.41]), *ABCB1* c.3435C>T (C/C versus C/T versus T/T = 3.76 [2.12–5.14] versus 3.43 [1.89–5.72] versus 2.87 [2.45–5.14]).

Figure 2. Comparison of C_{0h}/D between ABCB1 haplotypes. C_{0h}/D, dose adjusted-trough concentration; TT-TT-TT, *ABCB1* 1236TT-2677TT-3435TT haplotype. The values above the upper limit of the Y-axis are shown with a scale break line. Medians [quartile ranges] for Other and TT-TT-TT were 3.47 [1.94–5.16] and 2.99 [2.52–5.30].

Figure 3. Relationship between prothrombin time and trough concentration.

Table 1. Patient characteristics.

	Mean ± SD	Range
Age (years)	62.4 ± 10.6	(31 - 82)
Body weight (kg)	69.6 ± 12.7	(47.1 - 103)
AST (U/L)	27 ± 13	(16 - 109)
ALT (U/L)	29 ± 25	(12 - 210)
T-Bil (g/dL)	0.7 ± 0.4	(0.3 - 3.2)
Alb (g/L)	4.2 ± 0.3	(3.2 - 4.8)
eGFR (mL/min)	72.3 ± 16.7	(36.5 - 118.2)
PT (sec)	12.0 ± 1.1	(10.3 - 19.2)
		n
Sex (male : female)		73 : 13
Genotypes		
*CYP3A5*3* (A/A : A/G : G/G)		3 : 40 : 43
*CYP2J2*7* (G/G : G/T : T/T)		78 : 8 : 0
ABCG2 c.421C>A (C/C : C/A : A/A)		45 : 37 : 4
ABCB1 c.1236C>T (C/C : C/T : T/T)		16 : 46 : 24
ABCB1 c.2677G>A/T		20 : 16 : 25
(G/G : G/A : G/T : A/A : A/T : T/T)		: 4 : 10 : 11
ABCB1 c.3435C>T (C/C : C/T : T/T)		39 : 33 : 14

AST, aspartate aminotransferase; ALT, alanine aminotransferase; T-Bil, serum total bilirubin;
Alb, serum albumin; eGFR, estimated glomerular filtration; PT, prothrombin time; SD, standard deviation

Table 2. Distributions of C_{0h} and C_{0h}/D of riaroxaban in steady state.

Daily dose	No. patients			Median	Quartile range	%CV
10 mg	6	C_{0h}	(ng/mL)	51.3	(38.2 - 65.5)	54.3%
		C_{0h}/D	(ng/mL/mg)	5.13	(3.82 - 6.55)	
15 mg	80	C_{0h}	(ng/mL)	47.2	(29.5 - 77.7)	83.7%
		C_{0h}/D	(ng/mL/mg)	3.15	(1.96 - 5.18)	
Total	86	C_{0h}	(ng/mL)	48.9	(29.8 - 77.6)	81.9%
		C_{0h}/D	(ng/mL/mg)	3.39	(2.08 - 5.21)	80.5%

C_{0h}, trough concentration; C_{0h}/D, dose-adjusted trough concentration; SD, standard deviation; %CV, coefficient of variation

Table 3. Correlation between C_{0h}/D and clinical characteristics in patients with NVAF.

Explanatory variable	Spearman's *rho*	*P* value
Age (years)	0.110	0.313
Body weight (kg)	0.042	0.703
AST (U/L)	0.233	0.031
ALT (U/L)	0.008	0.943
T-Bil (g/dL)	0.133	0.221
Alb (g/L)	-0.092	0.397
eGFR (mL/min)	-0.307	0.004

C_{0h}/D, dose-adjusted trough concentration; AST, aspartate aminotransferase; ALT, alanine aminotransferase; T-Bil, serum total bilirubin; Alb, serum albumin; eGFR, estimated glomerular filtration

Figure 1

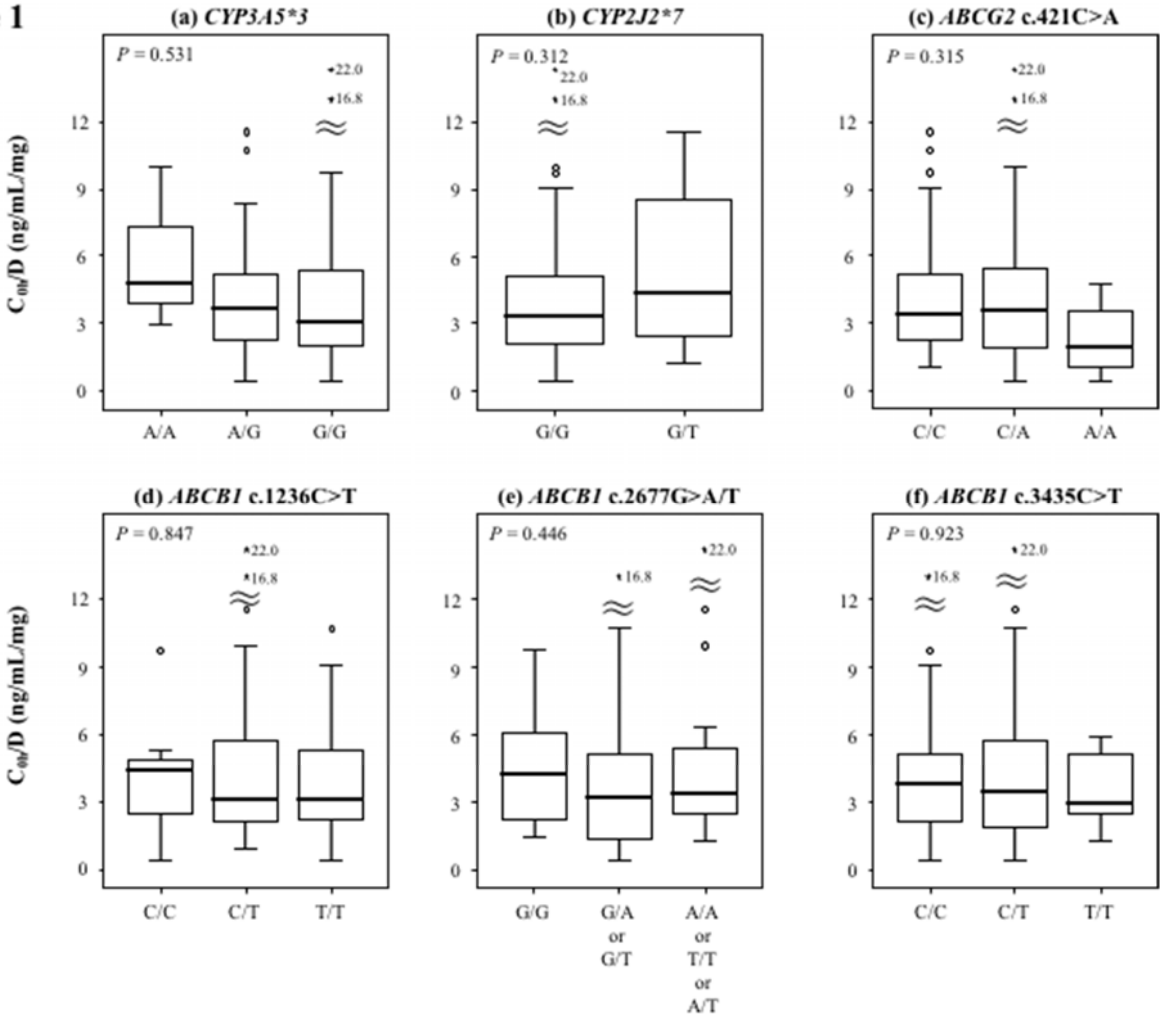

(a) CYP3A5*3
P = 0.531
(b) CYP2J2*7
P = 0.312
(c) ABCG2 c.421C>A
P = 0.315
(d) ABCB1 c.1236C>T
P = 0.847
(e) ABCB1 c.2677G>A/T
P = 0.446
(f) ABCB1 c.3435C>T
P = 0.923
C0h/D (ng/mL/mg)
22.0
16.8
0
3
6
9
12
A/A
A/G
G/G
G/T
C/C
C/A
A/A
C/T
T/T
G/A or G/T
A/A or T/T or A/T

Figure 2

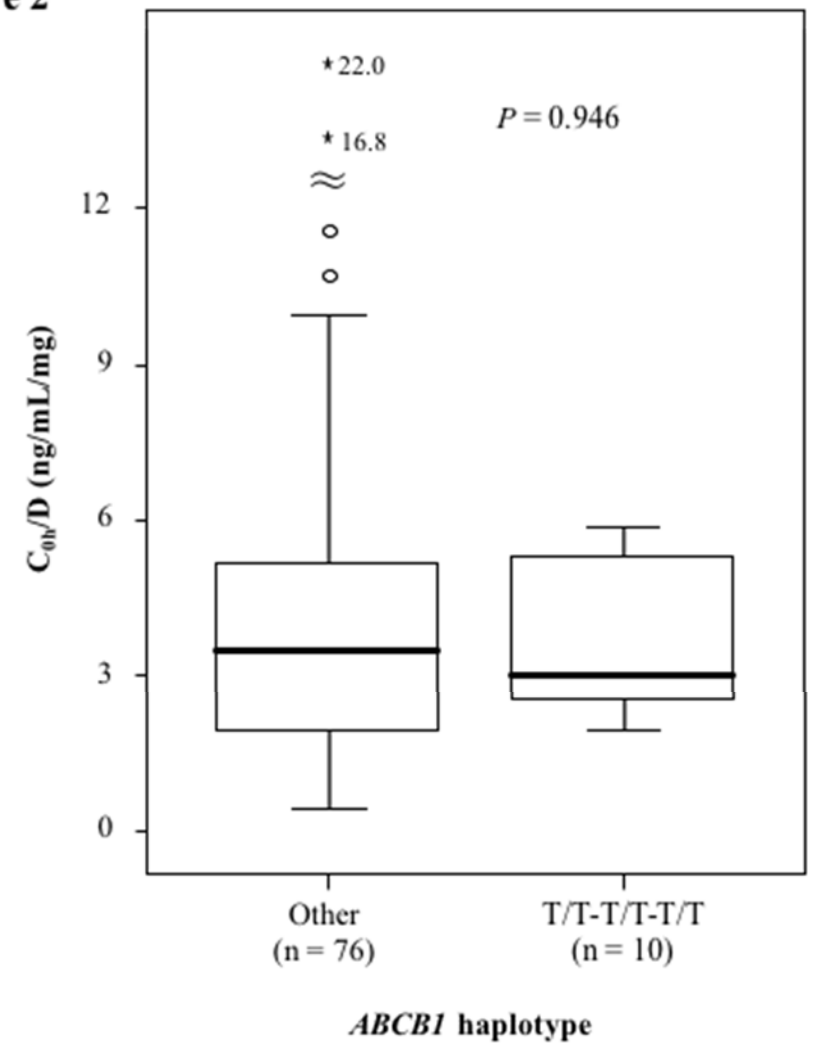
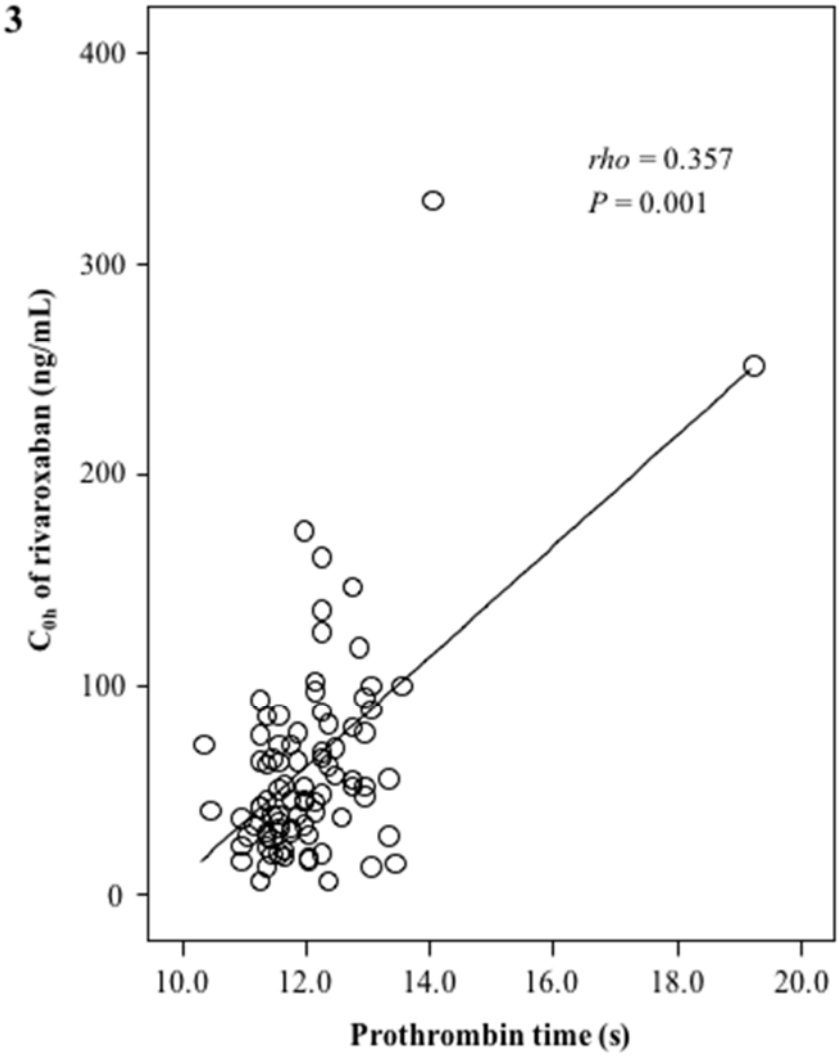

22.0
16.8
P = 0.946
12
9
6
3
0
C0h/D (ng/mL/mg)
Other
(n = 76)
T/T-T/T-T/T
(n = 10)
ABCB1 haplotype

Figure 3


400
300
200
100
0
rho = 0.357
P = 0.001
C0h of rivaroxaban (ng/mL)
10.0
12.0
14.0
16.0
18.0
20.0
Prothrombin time (s)