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ORIGINAL ARTICLE

Ezetimibe enhances and stabilizes anticoagulant effect of warfarin

Takehiro Hashikata[1] · Minako Yamaoka-Tojo[1,2] · Ryota Kakizaki[1] · Teruyoshi Nemoto[1] · Kazuhiro Fujiyoshi[1] · Sayaka Namba[1] · Lisa Kitasato[1] · Takuya Hashimoto[1] · Shunsuke Ishii[1] · Ryo Kameda[1] · Takao Shimohama[1] · Taiki Tojo[2] · Junya Ako[1]

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Abstract Ezetimibe reduces plasma levels of low-density lipoprotein cholesterol by inhibiting Niemann–Pick C1-like protein 1 (NPC1L1). A recent study demonstrated that NPC1L1 plays an important role in absorption of fat-soluble vitamins including vitamin K. We evaluated whether the add-on treatment of ezetimibe affects anticoagulation in patients taking warfarin. Between October 2007 and March 2015, the administration of ezetimibe was started to a total of 101 outpatients who were already on oral anticoagulation with warfarin. We retrospectively analyzed blood lipid levels, prothrombin time international normalized ratio (PT-INR) and time in therapeutic INR range (TTR). Seventy-one patients (70 %) showed increase in PT-INR after ezetimibe treatment (1.96 ± 0.45 to 2.20 ± 0.61, $p < 0.001$). It was necessary to reduce the warfarin dose in 9 of 101 patients for clinical indication. There was a significant positive correlation between change in PT-INR and statin usage at baseline ($p = 0.03$). The mean value of changes in PT-INR of patients with taking statin was significantly larger than that of patients without taking statin (0.34 ± 0.54 vs. 0.06 ± 0.36, $p = 0.03$). There was an increase in the TTR (52 ± 26 to 61 ± 23 %, $p < 0.0001$) and a decrease in the frequency to change the dose of warfarin after the ezetimibe treatment [45 times of 735 examination days (6 %) to 20 times of 695 examination days (3 %), $p = 0.02$]. Our data suggest possible drug interaction between warfarin and ezetimibe. Ezetimibe may increase and stabilize the anticoagulant effect of warfarin, especially in patients taking statins.

Keywords Niemann–Pick C1-like protein 1 · Vitamin K · Ezetimibe · Warfarin · Time in therapeutic range

Introduction

Warfarin targets vitamin K epoxide reductase, thereby inhibiting the vitamin K-dependent blood coagulation proteins. A reduced functional level of factor IX, factor VII, factor X and prothrombin leads to delayed blood coagulation [1]. Therefore, the intake of vitamin K decreases the anticoagulant effect in patients with warfarin [2]. The anticoagulant effect with warfarin is monitored in the clinical laboratory with the use of prothrombin time (PT) and is corrected for the varied potencies of tissue factor used in the assay by means of a calibration factor, yielding international normalized ratio (INR). Recently, novel oral anticoagulants are well-used instead of warfarin because of their efficacy, safety and easy to use [3], however, lots of patients are prescribed warfarin for daily clinical works even now practically [4, 5].

Ezetimibe reduces the absorption of cholesterol from the gastrointestinal tract and lowers the serum low-density lipoprotein (LDL) cholesterol levels by inhibiting the Niemann–Pick C1-like 1(NPC1L1) protein [6, 7]. When added to statin therapy, ezetimibe was reported to stabilize coronary plaque as secondary prevention and improve cardiovascular outcomes accompanied by its LDL cholesterol levels lowering effect [8, 9]. Inactivating mutations

✉ Takehiro Hashikata
t_hashikata@med.kitasato-u.ac.jp

Minako Yamaoka-Tojo
myamaoka@med.kitasato-u.ac.jp

[1] Department of Cardiovascular Medicine, Kitasato University School of Medicine, Sagamihara, Japan

[2] Department of Rehabilitation, Kitasato University School of Allied Health Sciences, 1-15-1 Kitasato, Minami-ku, Sagamihara, Kanagawa 252-0373, Japan

in NPC1L1 are associated with lower levels of LDL cholesterol and a reduced risk of coronary heart disease [10]. NPC1L1 mRNA expression is enriched in the small intestine, liver and stomach in human [11]. NPC1L1 protein plays a critical role in the absorption of not only intestinal cholesterol but also fat-soluble vitamins such as vitamin D, K and E [12–14]. Previous study has demonstrated that the intestinal absorption of vitamin K is NPC1L1-dependent and inhibited by ezetimibe in vivo and PT-INR values in warfarin-treated patients increased significantly after taking ezetimibe [13]. In the present study, we aimed to evaluate the drug–drug interaction between warfarin and ezetimibe in daily clinical setting.

Methods

This was a retrospective single-center study to evaluate whether ezetimibe influences on anticoagulant effect of warfarin in daily clinical situation. Between October 2007 and May 2015, 101 dyslipidemia outpatients with maintaining oral anticoagulant therapy using warfarin, who were prescribed ezetimibe, were evaluated. All patients were analyzed at the day of additional treatment with ezetimibe (baseline) and at next medical examination day (mean follow-up days; 53 days). The exclusion criteria were as follows: (1) changing the dose of warfarin at baseline, (2) hospitalized patients, (3) prescription of ezetimibe switching from statin, (4) other medications were changed accompanied by ezetimibe prescription, (5) patients taking bucolome, and (6) insufficient data during the registration period. The study protocol was approved by the institutional review board of Kitasato University.

At the time of entry, complete medical history, physical examination, anthropometric and laboratory evaluation were obtained. The blood coagulation parameter (PT and PT-INR), the lipid profile parameter [LDL cholesterol, high-density lipoprotein (HDL) cholesterol and triglyceride], the estimated glomerular filtration rate (eGFR), aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyltransferase (γ-GTP) and total bilirubin were measured at Kitasato University Hospital. Percent time in therapeutic INR range (TTR) of warfarin was calculated with a Rosendaal method at the time of taking maintaining therapy of warfarin. Each TTR was evaluated during a period of at least 1–3 years before and after the additional treatment of ezetimibe, respectively. And we excluded the PT-INR value of the next examination day after the treatment and for evaluation of TTR.

Categorical variables are expressed as numbers and frequencies and were compared using the Chi-square test. Continuous variables are expressed as mean ± SD and were compared using the paired *t* test. Linear regression analysis was performed to determine the association between changes in the PT-INR value and other clinical parameters possibly related to NPC1L1 function. All analyses were performed using JMP 9.0 software for Windows (SAS Institute, Cary, North Carolina). A value of $p < 0.05$ was considered statistically significant.

Results

Additional treatment of ezetimibe increases the anticoagulant effect of warfarin

In this study, 101 patients were evaluated at baseline, and at the next examination day after the additional treatment with ezetimibe. During the study registration period, no medication except ezetimibe was added to or withdrawn from the patients. Ezetimibe was administered at 10 mg/day to each patient. Patient clinical characteristics at baseline are shown in Table 1. The mean age was 67 years, the mean PT-INR value was 1.96, and the mean LDL cholesterol level was 138 mg/dL. Of the patients, 71 % (72/101 patients) received statin therapy at baseline.

After additional treatment of ezetimibe, there was a significant decrease in the LDL cholesterol levels (138 ± 31 to 103 ± 29 mg/dL, $p < 0.0001$) and the HDL cholesterol levels (53 ± 14 to 51 ± 14 mg/dL, $p = 0.04$) compared to the baseline levels. The triglyceride levels, body mass

Table 1 Clinical patient characteristics at baseline

	$N = 101$
Age (years)	67 ± 10
Male, *n*	62 (61)
Body weight (kg)	61 ± 13
Body mass index (kg/m^2)	23.4 ± 3.7
Warfarin dosage (mg/day)	3.0 ± 1.1
Atrial fibrillation, *n*	38 (38)
History of arteriosclerotic vascular disease, *n*	74 (73)
Hypertension, *n*	76 (75)
Diabetes mellitus, *n*	52 (51)
Current smoking, *n*	18 (18)
Medications	
Statin, *n*	72 (71)
Beta blocker, *n*	54 (53)
ACEI/ARB, *n*	71 (70)
SAPT, *n*	47 (47)
DAPT, *n*	11 (11)

Continuous variables are expressed as mean ± SD and categorical variables as number (percentage)

ACEI angiotensin converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *S (D) APT* single (dual) anti-platelet therapy

Table 2 Comparison of clinical parameters at baseline and after the ezetimibe treatment

$N = 101$	Baseline	After ezetimibe	% of change	p value
LDL cholesterol, mg/dL	138 ± 31	103 ± 29	−25.4	<0.0001
HDL cholesterol, mg/dL	53 ± 14	51 ± 14	−3.8	0.04
Triglyceride, mg/dL	176 ± 94	165 ± 70	−6.3	0.07
PT-INR	1.96 ± 0.45	2.20 ± 0.61	+12.2	<0.0001
Aspartate aminotransferase, IU/L	27 ± 10	28 ± 15	+3.7	0.31
Alanine aminotransferase, IU/L	25 ± 13	27 ± 19	+8.0	0.21
Total bilirubin, mg/dL	0.6 ± 0.2	0.6 ± 0.3	+0.0	0.48
γ-Glutamyltransferase, IU/L	34 ± 18	37 ± 27	+8.8	0.29
eGFR, ml/min/1.73 m^2	58 ± 19	56 ± 20	−3.4	0.67

Continuous variables are expressed as mean ± SD

L (H) DL low (high) density lipoprotein, *PT-INR* prothrombin time international normalized ratio, *eGFR* estimated glomerular filtration rate

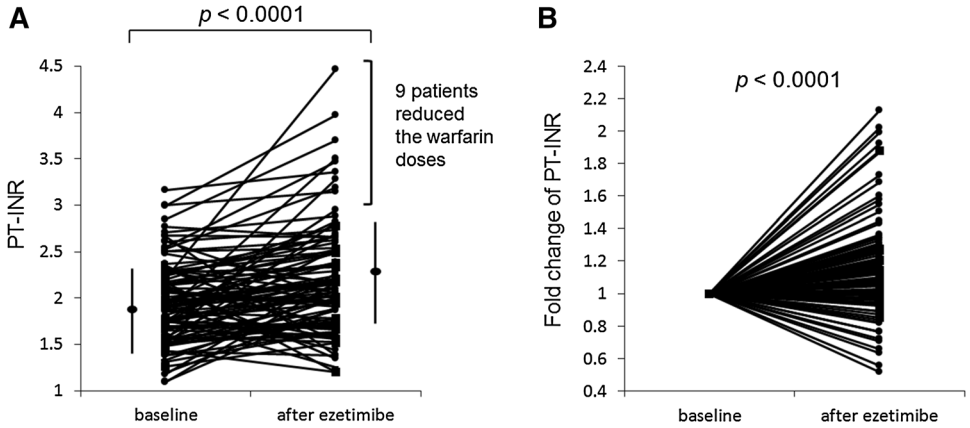

Fig. 1 Ezetimibe increases the PT-INR value in patients with warfarin. There was an increase in the PT-INR values compared to the baseline values (1.96 ± 0.45 to 2.20 ± 0.61, $p < 0.0001$). Nine of 101 patients reduced the warfarin dose for clinical indication (**a**). Fold changes of the PT-INR values were shown in **b**. p values were determined using paired t test

index, the eGFR and liver enzyme (AST, ALT, γ-GTP, total bilirubin) levels did not differ before and after treatment (Table 2). There was an increase in the PT-INR values compared to the baseline values (1.96 ± 0.45 to 2.20 ± 0.61, $p < 0.0001$) (Table 2; Fig. 1), suggesting an augmentation in the anticoagulant effect of warfarin. Nine percent of patients (9/101) were necessary to reduce the warfarin dose for clinical indication (Fig. 1a). There was no minor/major bleeding event and embolism during the study period.

Statin usage was an independent predictive factor for increase in PT-INR

Linear regression analysis was performed in evaluated patients to determine the correlation between changes in the PT-INR value and other clinical parameters. There was a significant negative correlation between changes in the PT-INR values and statin usage ($p = 0.04$); on the other hand, there was no significant correlation between changes in the PT-INR values and the improvement of dyslipidemia (Table 3). There was a significant increase in the PT-INR values after additional treatment of ezetimibe in patients with statin compared to that of patients without statin (Table 4; Fig. 2). Indeed, 17 of 29 patients (59 %) without statin therapy showed an increase in PT-INR (fold change >1.0), on the other hand, 55 of 72 (76 %) patients with statin therapy showed an increase in PT-INR (Fig. 2b, d). According to statistical analysis only in patients without statin, there was no significant increase in the PT-INR values after the treatment (Fig. 2c, d).

Of 72 patients with statin, 22 was with pravastatin, 21 was with rosuvastatin, 14 was with pitavastatin and 14 was with atorvastatin, 1 was with simvastatin. Changes in PT-INR after the treatment of ezetimibe did not differ among each statin except for simvastatin ($p = 0.67$). And there was no significant difference between the strong statin group (rosuvastatin, pitavastatin and atorvastatin, $n = 49$) and the not-strong statin group (pravastatin and simvastatin, $n = 23$) in the changes of PT-INR after taking ezetimibe ($p = 0.37$).

Ezetimibe augments the percent time in therapeutic INR range of warfarin

At the time of evaluation of TTR value, we excluded 23 patients because of insufficient examination data. Of the 78 patients, the mean TTR value of warfarin before the additional treatment of ezetimibe was 54 % in this study. There was an augmentation of the TTR value after the treatment of ezetimibe, compared with that of before the treatment (52 ± 26 to 61 ± 23 %, $p < 0.0001$) (Fig. 3). The mean PT-INR value before the treatment was lower than that of after the treatment. The frequency to change dose of warfarin before ezetimibe treatment was more frequent than that of after the treatment [45 times of 735 examination days (6 %) vs. 20 times of 695 examination days (3 %), $p = 0.02$].

Table 3 Regression analysis for change of INR after the treatment of ezetimibe

	β-coefficient (95 % CI)	p value
Age, per year	0.09 (−0.01 to 0.01)	0.40
Sex, male	0.03 (−0.10 to 0.12)	0.76
Body weight, kg	−0.02 (−0.01 to 0.01)	0.83
Body mass index, kg/m^2	0.02 (−0.03 to 0.04)	0.89
eGFR, ml/min/1.73 m^{-2}	0.03 (−0.01 to 0.01)	0.38
ΔLDL cholesterol, per mg/dl	−0.16 (−0.01 to 0.00)	0.12
ΔHDL cholesterol, per mg/dl	−0.07 (−0.01 to 0.01)	0.49
ΔTriglyceride, per mg/dl	0.00 (−0.00 to 0.00)	1.00
LDL cholesterol at baseline, mg/dl	0.03 (−0.00 to 0.00)	0.78
HDL cholesterol at baseline, mg/dl	0.06 (−0.01 to 0.01)	0.55
Triglyceride at baseline, mg/dl	−0.05 (−0.00 to 0.00)	0.63
Statin, yes	0.21 (−0.00 to 0.24)	0.04
Beta blocker, yes	0.07 (−0.07 to 0.15)	0.48
ACEI/ARB, yes	−0.02 (−0.13 to 0.11)	0.84
SAPT, yes	−0.02 (−0.12 to 0.10)	0.82
DAPT, yes	−0.08 (−0.27 to 0.11)	0.46

Δ parameter after ezetimibe—parameter at baseline, *eGFR* estimated glomerular filtration rate, *L (H) DL* low (high) density lipoprotein, *ACEI* angiotensin converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *S (D) APT* single (dual) anti-platelet therapy

Discussion

The major findings of this study are as follows: (1) in addition to LDL cholesterol lowering effect, an additional treatment with ezetimibe increased the PT-INR value in patients with warfarin; (2) there was a significant positive correlation between changes in the PT-INR and statin usage; and (3) there was an increase in the TTR and a decrease in the times to change the dose of warfarin after the ezetimibe treatment.

Warfarin is an efficacious oral anticoagulant, but drug and food interactions are frequently cited as causes of adverse events. Monitoring of PT-INR and dose adjustments of warfarin are influenced by changes in concomitant medications, diet, alcohol consumption, acute illness, liver disease and unknown factors [15]. Because Japanese patients were reported to require narrower therapeutic ranges than Westerners [16], we should pay more attention to the drug interactions of warfarin in clinical setting in Japan. Although the mechanisms of drug interactions are

Table 4 Comparison of change in clinical parameter in patients with statin and without statin

	With statin ($n = 72$)	Without statin ($n = 29$)	p value
Age, years	66 ± 10	68 ± 11	0.40
PT-INR at baseline	1.95 ± 0.46	1.97 ± 0.41	0.76
PT-INR after EZ	2.25 ± 0.63	2.06 ± 0.52	0.19
Change in PT-INR	0.34 ± 0.54	0.05 ± 0.36	0.03
Warfarin dosage, mg/day	3.0 ± 1.0	3.1 ± 1.4	0.68
LDL cholesterol at baseline, mg/dL	131 ± 27	155 ± 34	0.0003
LDL cholesterol after EZ, mg/dL	96 ± 23	123 ± 37	0.0003
% of change in LDL cholesterol, %	−26 ± 13	−21 ± 18	0.21
HDL cholesterol at baseline, mg/dL	53 ± 15	53 ± 12	0.88
HDL cholesterol after EZ, mg/dL	51 ± 15	51 ± 12	0.83
% of change in HDL cholesterol, %	−3 ± 20	−5 ± 16	0.42
Triglyceride at baseline, mg/dL	166 ± 92	200 ± 97	0.10
Triglyceride after EZ, mg/dL	163 ± 89	172 ± 92	0.52
% of change in Triglyceride	4 ± 36	−6 ± 36	0.12

Continuous variables are expressed as mean ± SD

PT-INR prothrombin time international normalized ratio, *L (H) DL-C* low (high) density lipoprotein cholesterol, *EZ* ezetimibe

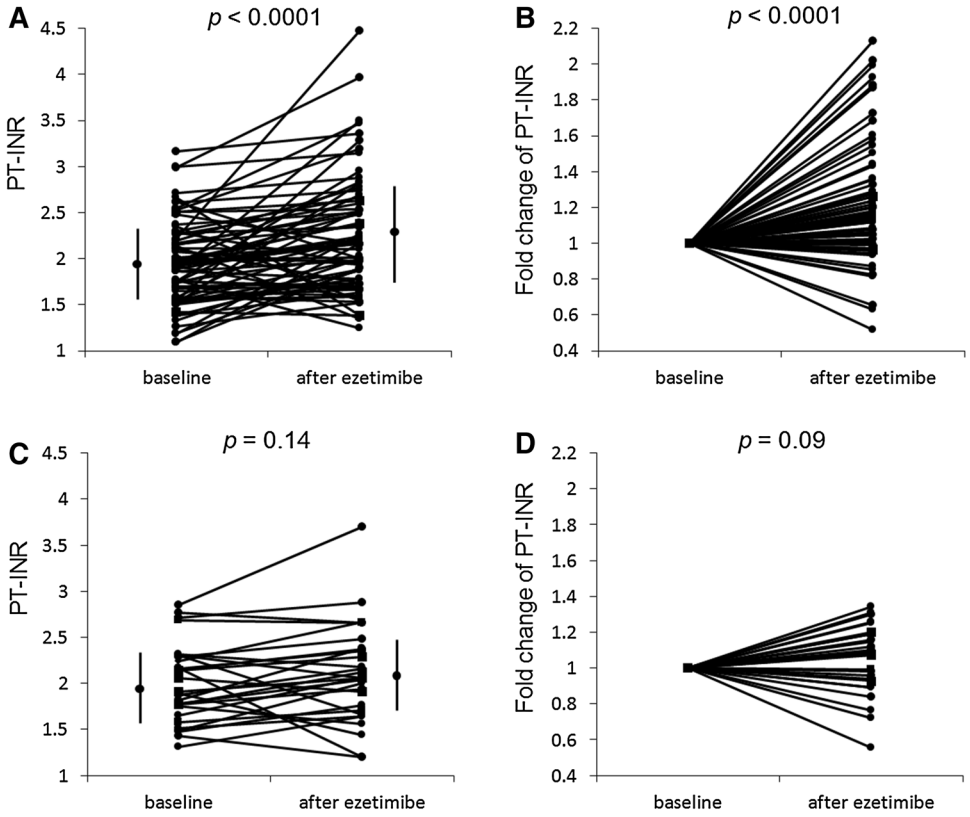

Fig. 2 The drug interaction between warfarin and ezetimibe in patients with or without statin. Each *dot* represents the PT-INR value and its fold change in patients with statin (**a**, **b**), and without statin (**c**, **d**). There was a significant increase in the PT-INR values after additional treatment of ezetimibe in patients with statin compared to that of patients without statin (0.34 ± 0.54 vs. 0.05 ± 0.36, $p = 0.03$; Table 4). Statistical analysis in patients without statin does not show significant increase in the PT-INR values after the treatment [PT-INR; 1.97 ± 0.41 to 2.06 ± 0.52, $p = 0.14$ (**c**, **d**)]. *p* values were determined using paired *t* test

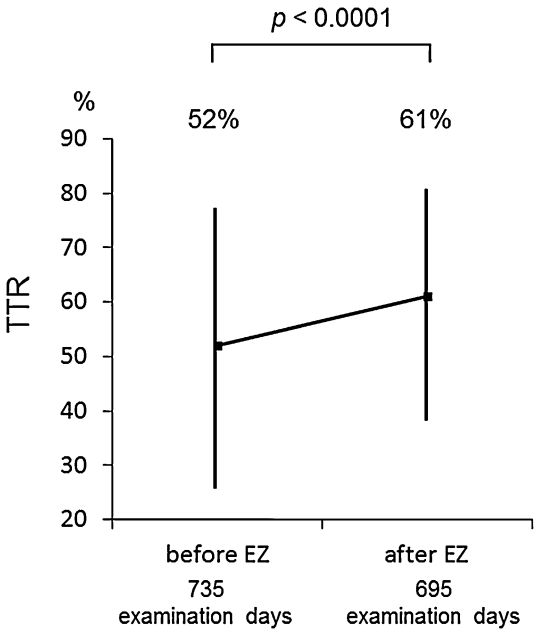

Fig. 3 Ezetimibe augments the TTR value. We evaluated 78 patients (1430 examination days) before and after the additional treatment of ezetimibe. There was an increase in the TTR value after the treatment of ezetimibe, compared with that of before the treatment (54 ± 27 to 66 ± 22 %, $p < 0.0001$). TTR of warfarin was calculated with a Rosendaal method and each TTR was evaluated during a period of at least 1–3 years before and after the additional treatment of ezetimibe, respectively. *p* values were determined using paired *t* test

not fully elucidated, there are several pharmacokinetic and pharmacodynamic factors that could influence the effect of warfarin. Warfarin is a racemic mixture of two optically active isomer, the *S* and *R* enantiomers. It is highly water soluble, rapidly absorbed from the gastrointestinal tract, highly bioavailable [17, 18]. The racemic mixture has been the subject of intense investigation in studies of the metabolism of warfarin and in the studies of drug interactions between warfarin and other drugs. The potent warfarin S-isomer is metabolized by cytochrome P-450 (CYP) 2C9. Many of the drugs including statin augments the effect of warfarin by inhibiting CYP 2C9 [19, 20]. The R-isomer of warfarin is metabolized by CYP 1A2 and CYP 3A4, several antibacterial drugs are considered to inhibit CYP 1A2 or CYP 3A4 [21–23]. The pharmacodynamics of warfarin may be influenced by medications that affect either vitamin K or the coagulation factors. The changes in dietary sources of vitamin K followed by a change in the effect of warfarin are relatively easy to understand. Ezetimibe is rapidly metabolized in the intestine via uridine 5′-diphosphate-glucuronosyltransferase enzymes to the active glucuronyl metabolite (ezetimibe-glucuronide) and appears in the portal circulation and bile within minutes [24]. Ezetimibe is not metabolized by CYP 2C9, CYP1A2 and CYP 3A4. For several drugs, including cephalosporins, levothyroxine, and clofibrate, their supposed pharmacodynamic interactions with warfarin are still uncertain [25, 26]. NPC1L1,

targeting by ezetimibe, was reported to play a critical role in vitamin K absorption in vivo [13]. Therefore, it is likely that the mechanism of this interaction between ezetimibe and warfarin was due to a decrease in dietary vitamin K intake by inhibiting NPC1L1.

Interestingly, the drug interaction between ezetimibe and warfarin more frequently appeared in patients with statin in the present study. It has been reported that the downregulation of cholesterol synthesis by statin is compensated by an increase in intestinal cholesterol absorption [27]. Tremblay et al. reported that 12-week treatment with atorvastatin increased intestinal mRNA levels of NPC1L1 by 19 % and NPC1L1 protein expression in intestinal biopsy samples by 34 % [28]. A study with miniature pigs showed that NPC1L1 expression was increased significantly in both the jejunum and the liver by combination therapy with ezetimibe and simvastatin [29]. On the basis of the results of this study, we speculated that treatment with statin increases NPC1L1 in the small intestine, possibly resulting in the increase in ezetimibe-sensitive absorption of vitamin K, Therefore, the drug interaction between ezetimibe and warfarin should be stressed. Relating to cholesterol lowering effect, multicenter trial demonstrated that ezetimibe added to statin therapy significantly reduced the LDL cholesterol level by an additional 23–26 % in patient with dyslipidemia [30]. Ezetimibe alone therapy reduced direct LDL cholesterol by a mean of 18 %, compared with an increase of 1 % with placebo [26]. Our results showed that the additional treatment with ezetimibe decreased the LDL cholesterol level by 26 % in patients with statin therapy, on the other hand, by 21 % in patients without statins during registration period ($p = 0.21$, Table 3).

In the present study, there was a statistical decrease in HDL cholesterol levels after ezetimibe treatment (53 ± 14 to 51 ± 14 mg/dL, $p = 0.04$; Table 2). However, a clinical trial demonstrated that ezetimibe increases the HDL cholesterol levels in patients with metabolic syndrome accompanied by the reduction of visceral fat [31]. The mean body mass index and the level of HDL cholesterol were within a normal range in most enrolled patients in the present study. Although the exact mechanism is unclear, such patient background might have contributed to the decrease in HDL levels.

The relationship between the intensity of treatment and the risk of an adverse event has been evaluated by examining the frequency of an event as a function of TTR [32, 33]. A strong relationship between TTR and bleeding or thromboembolic rates has been observed in several multicenter studies [33–35]. Our data demonstrated that there was an increase in TTR, and a decrease in time to change the warfarin dose after the treatment of ezetimibe. Alterations in dietary intake of vitamin K can have a significant effect on anticoagulation response to oral anticoagulants; increases in the dietary intake of vitamin K are associated with significant reductions in anticoagulation response [36, 37], whereas it has been reported that daily supplementation with vitamin K along with warfarin therapy can lead to a more stable anticoagulation in patients [38–40]. The mechanism of this phenomenon was hypothesized that higher and stable intake and thus greater body stores of vitamin K allows for steady clotting factor activation and stable control of anticoagulation of warfarin [39]. It has been reported that NPC1L1 gene variation was associated with the inter-individual variability in the response of LDL cholesterol levels to the treatment of ezetimibe [41, 42], thus the absorption of vitamin K also may have inter-individual variability due to NPC1L1 variation. Our results might suggest that ezetimibe reduces and stabilizes vitamin K absorption, leading to more stable anticoagulant effect of warfarin.

This study has several limitations. First, the present study was a single-center retrospective study with a small number of patients. Second, because we did not measure NPC1L1 expression and concentration of vitamin K, it is uncertain whether an increase and stabilization in anticoagulant effect of warfarin with the ezetimibe additional treatment depend on NPC1L1 activity. Finally, the lack of a control group made it difficult to demonstrate that the infection of warfarin's anticoagulant effect was attributable to ezetimibe treatment alone; however, it is impossible to set the control group in behalf of retrospective protocol of this study.

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Compliance with ethical standards

Conflict of interest Dr. Junya Ako received speaking honorarium from Eisai, Bayer Pharma, Tanabe Mitsubishi, Daiichi-Sankyo, MSD K.K., Boehringer Ingelheim, Kowa, and Kyowa Hakko Kirin. Dr. Minako Yamaoka-Tojo received speaking honorarium from Bayer Pharma, Tanabe Mitsubishi, Daiichi-Sankyo, MSD K.K. The other authors have nothing to disclose regarding this study.

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