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Impact of ABCB1 C3435T Polymorphism on Treatment Response of Vitamin K Antagonists: A Systematic Review and Meta-analysis

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ABSTRACT

Objective: The aim of this study was to examine the impact of ATP-binding cassette subfamily B member 1 (*ABCB1*) C3435T polymorphism on the treatment response of patients to vitamin K antagonists (VKAs). **Methods:** In this systematic review and meta-analysis, the PubMed/Medline, Embase, and Cochrane Library databases were searched for eligible articles for the period up to November 2020. Articles that reported treatment response to VKAs according to the *ABCB1* C3435T polymorphism were included in this study. **Results:** A total of 13 and 9 articles were included in the systematic review and meta-analysis, respectively. The weekly maintenance dose of warfarin was significantly lower in patients with the *ABCB1 3435CT* or *TT* polymorphism type than in those with the *ABCB1 3435CC* type (weighted mean difference [WMD], −2.53 mg/week; 95% confidence interval [CI], −3.64 to −1.43, p<0.001). However, the weekly maintenance dose of acenocoumarol was not significantly associated with the *ABCB1* C3435T polymorphism (WMD, 1.02; 95% CI, −0.61 to 2.65, p=0.22). **Conclusion:** The *ABCB1* C3435T polymorphism was significantly associated with the weekly maintenance dose of warfarin. Further research is needed to confirm the association between the *ABCB1* C3435T polymorphism and the incidence rate of bleeding events.

KEYWORDS: ABCB1, warfarin, acenocoumarol, maintenance dose, bleeding risk

In the United States, approximately 2.7-6.1 million patients had atrial fibrillation (AF) in 2010, and this number is expected to gradually increase to approximately 5.6 to 12 million by 2050.[1,2] The vitamin K antagonists (VKAs), warfarin and acenocoumarol, are prescribed for the treatment or prophylaxis of embolic AF or deep vein thrombosis (DVT). Warfarin was commonly prescribed for older individuals, those with a high risk of stroke or bleeding, and patients with many comorbidities.[3] These patients are likely to have drug-disorder or drug-drug interactions. It is necessary for patient safety and personal medication therapy to regularly monitor prothrombin time (PT) or the international normalized ratio (INR). VKAs have a narrow therapeutic range and, therefore, levels outside this range increase the risk of thromboembolism or bleeding incidences.

VKAs are drugs that interact with various medications and foods[4-6] and maintenance doses of VKAs are affected by patient age,[7] body weight,[8] clinical conditions,[9,10] and genetic factors.[8,11] According to the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines, cytochrome P450 2C9 (CYP2C9), vitamin K epoxide reductase complex subunit 1 (VKORC1), and cytochrome P450 4F2 (CYP4F2) are known to influence the warfarin dosing algorithm.[11] Similarly, the maintenance dose of acenocoumarol is also affected by *VKORC1* and *CYP2C9* genes.[12] In addition to these well-known genes, recent studies have suggested that the ATP-binding cassette subfamily B member 1 (*ABCB1*) gene affects the maintenance dose of VKAs; however, the

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results were not consistent.[13-16)]

ABCB1 encodes P-glycoprotein (P-gp), which plays an important role in the absorption and excretion of various drugs.[17)] Many drugs, including VKAs, are known substrates of P-gp[18-20)] and, therefore, the absorption or excretion of drugs can be affected by genetic variations of *ABCB1*. Consequently, pharmacokinetic parameters could be changed and the treatment response might be affected. In particular, *ABCB1* C3435T polymorphism influences the substrate specificity of P-gp.[21-23)] The aim of this systematic review and meta-analysis was to investigate the association between *ABCB1* C3435T polymorphism and the maintenance dose of VKAs, and incidence rate of bleeding events.

Methods

This study was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist[24)] and the literature review was performed independently by two authors. The two authors resolved any discordance between them by discussing the issue to draw a clinically appropriate conclusion.

Literature search

The following three databases: PubMed/Medline, Embase, and the Cochrane Library, were searched for a period up to November 2020 to identify potentially eligible articles for this study. The reference lists of the included articles in this study or other relevant articles were manually searched. The following keywords were used for the literature search: “warfarin,” “acenocoumarol,” “phenprocoumon,” “vitamin K antagonist,” “ABCB1,” “MDR1,” and “P-glycoprotein.” The first screening process was conducted to determine whether the identified articles fulfilled the inclusion and exclusion criteria for the study by reviewing the title and abstract after excluding duplicates. This was followed by a full text review for the final inclusion and exclusion decision.

Inclusion and exclusion criteria

The inclusion criteria were as follows: all article types with a design that reported the VKA maintenance dose or incidence rate of thromboembolism or bleeding events according to *ABCB1* C3435T polymorphism. The exclusion criteria were as follows: experimental articles, articles reporting other medications or other polymorphisms, interaction articles, case reports, reviews, commentaries, editorials, non-genomic articles, and irrelevant articles.

Data extraction

Data were extracted using the following pre-designed format

(1) Characteristics of data included articles in this review: purpose of the study, inclusion and exclusion criteria for patients, study design, study period, ethnicity, country, other investigated polymorphisms in the study, type of VKAs, definition of stable VKA dose, and definition of VKA resistance

(2) Characteristics of study participants: number of participants, age, body weight, height, body mass index (BMI), social habit (smoking or alcohol consumption), comorbidity, co-medications, indication of VKAs, and Hardy-Weinberg equilibrium (HWE)

(3) Response to VKAs in accordance with *ABCB1* C3435T polymorphism: total (mg) and weekly maintenance doses of VKAs (mg/week), time spent with therapeutic range (TTR), number of patients with resistance to VKAs, dosing algorithm of VKAs, incidence rate of thromboembolic or bleeding events.

Assessment of risk of bias

The Newcastle-Ottawa scale (NOS) was used to assess the risk of bias for the included articles.[25)] The NOS used to analyze cohort and case-control studies consisted of three domains and eight items. Except for comparability and comparison that could be scored with a maximum of two stars, each item could be scored with a maximum of one star based on reported contents. A total of 7-9, 4-6, and 0-3 stars was considered to indicate a “low,” “moderate,” and “high,” risk of bias, respectively.

Data conversion and synthesis

Data synthesis between the two groups was performed according to the Cochrane Handbook 6.0.[26)] The data which were reported as the median and interquartile range (IQR) were converted to means and standard deviation (SD) using the equations established by Luo *et al*.[27)] and Wan *et al*.,[28)] respectively. The meta-analysis was performed using the RevMan 5.4 program (Review Manager version 5.4, Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2020). For weekly maintenance doses of VKAs, weighted

mean difference (WMD) and 95% confidence interval (CI) were calculated. The odds ratio (OR) and 95% CI were also calculated for the incidence rate of thromboembolic or bleeding events.

Heterogeneity

The fixed effect and random effect models were used based on the assessment of heterogeneity, which was performed with reference to the I^2, characteristics of the study design, and clinical conditions of the patients. Articles included in the meta-analysis with study design characteristics and patients that were considered similar were further assessed using the fixed effect model. The random effect model was used when the characteristics of the study design and patients in the included articles in the meta-analysis were considered dissimilar.

Results

Literature search

In the first search, 818 articles were identified and one additional article was included following the manual search. After excluding 211 duplicate articles, the first screening was performed. By reviewing the titles and abstracts, the following articles were excluded: 91 experimental articles, 26 articles reporting other medications, 31 articles reporting polymorphism or non-genomic articles, 43 interaction articles, 37 unoriginal articles (case reports, reviews, commentaries, or editorials), and 358 irrelevant articles based on study participants. Subsequently, four articles each where patients were duplicated and treatment responses to VKAs were not reported in accordance with *ABCB1* C3435T polymorphism, and another polymorphism article were excluded. Finally, 13 articles were included in the final analysis (Fig. 1).[13-16, 29-37)]

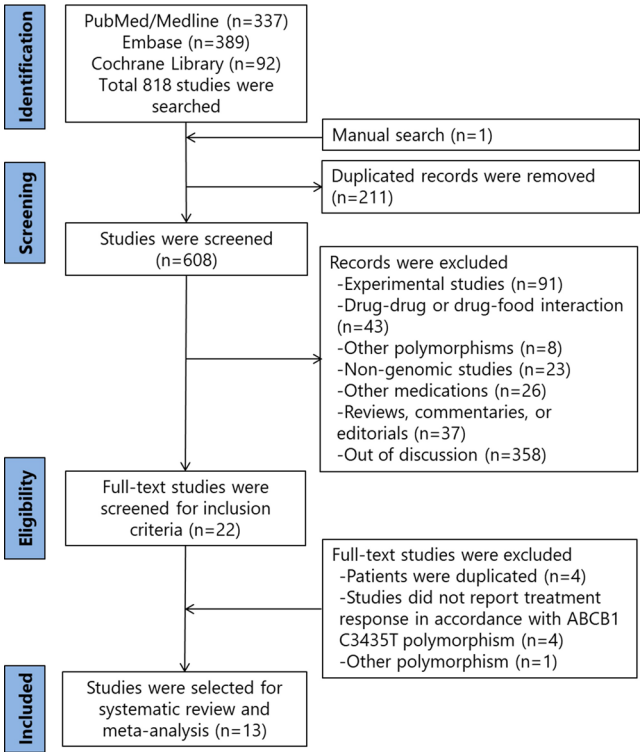

Fig. 1. Study selection process for including studies investigating impacts of *ABCB1* C3435T polymorphism on response of vitamin K antagonists (VKAs)

Characteristics of included articles and patients

Among the 13 articles, 8 and 5 investigated warfarin and acenocoumarol, respectively. The countries where the studies were conducted were Brazil, Italy, Egypt, USA, China, Sweden, Switzerland, Spain, Chile, Bulgaria, and Russia. Two articles by de Oliveira Almeida *et al*.[34)] and Rojo *et al*.[15)] did not conform to the HWE principle and Campos *et al*.[37)] did not report the HWE, whereas all other articles conformed to the HWE (Table 1). Patients were 17-88 years old with a mean BMI of 24-32 kg/m^2. The indications for VKAs were deep venous thromboembolism, AF, pulmonary thromboembolism, and heart valve prosthesis. Most studies that reported target INR targeted the INR range of 2.0-3.0.[15,30,31,33,34)] The target INR of patients with heart valve prosthesis was 2.0-3.0.[30)] Li *et al*. [13)] and Tavares *et al*. [14)] targeted the INR ranges of 1.6-2.8 and 1.8-3.2, respectively. The other studies did not report the target INR range.[16,29,32,35-37)] The comorbidities were hypertension, diabetes mellitus, heart failure, and arrhythmia.

Risk of bias analysis

Table 2 shows the results of the NOS and the studies by Ferrari *et al*.[29)] and Wadelius *et al*.[36)] assessed the risk of bias using case-control NOS, whereas the others used the cohort NOS. All the included articles reported the total score range as 5-8, and the risk of bias was considered low or moderate. The star scores for the two items, “representativeness of the exposed cohort” and “selection of the non-exposed cohort,” in the selection domain of cohort NOS were not assigned by Issac *et al*.,[31)] Kim *et al*.,[30)] Li *et al*.,[13)] and Tavares *et al*.[14)] Furthermore, Issac *et al*.[31)] excluded patients who were taking medicines known to interact with warfarin, which could result

Table 1. Characteristics of included studies and patient demographic data in this study (warfarin)

Study	Study design	Country	Type of VKAs	Note	N (M/F)	Age (years)	BMI (kg/m^2) or BW (kg)	Indication of VKAs, n (%)					HWE
								DVT	PE	AF	HVP	Others	
Campos EIF *et al*. 2018[#]	Cross-sectional	Brazil	Warfarin	Conference abstract	136 (58/78)	60.1±13.6	-	-	-	98 (72.1)	-	-	-
de Oliveira Almeida VC *et al*. 2014[#]	Prospective cohort	Brazil	Warfarin	-	116 (40/76)	42.3±14.5	27.3±5.2 kg/m^2	94 (81)	20 (17)	-	-	14 (12)	0.038
Ferrari M *et al*. 2014	Case-control	Italy	Warfarin	-	66 (34/32)	76.8±6.6	26.4±4.1 kg/m^2	-	-	54 (81.8)	12 (18.2)	-	0.13
Issac MS *et al*. 2014[#]	Cohort	Egypt	Warfarin	-	84 (41/43)	40.9±13.3	79.16±21.33 kg	12 (14.2)	-	5 (6)	-	67 (79.8)	0.216
Kim Y *et al*. 2013[#]	-	USA	Warfarin	European Americans	74 (59/15)	58.2±10.9	97.5±27.2* kg	17 (23.0)	14 (18.9)	27 (36.5)	5 (6.8)	11 (14.9)	0.926
				African Americans	59 (38/21)	55.7±11.3	95.2±23.1 kg	14 (23.7)	14 (23.7)	16 (27.1)	6 (10.2)	9 (15.3)	0.33
				Hispanic Americans	42 (23/19)	53.8±16.5	85.9±21.9 kg	9 (21.4)	6 (14.3)	14 (33.3)	5 (11.9)	8 (19.0)	0.183
				Asian Americans	21 (13/8)	58.1±9.9	78.9±17.5* kg	3 (14.3)	1 (4.8)	8 (38.1)	5 (23.8)	4 (19.0)	0.924
				Total	196 (133/63)	-	-	43 (21.9)	35 (17.9)	65 (33.2)	21 (10.7)	32 (16.3)	-
Li W *et al*. 2020[#]	-	China	Warfarin	-	214 (113/101)	72.6±11.2	24.0±3.9 kg/m^2	3 (1.4)	12 (5.6)	165 (77.1)	-	34 (15.9)	>0.05
Tavares LC *et al*. 2018[#]	Retrospective study	Brazil	Warfarin	Total	309 (155/154)	64±14	27±5 kg/m^2	-	-	-	-	-	0.899
Wadelius M *et al*. 2004	Case-control	Sweden	Warfarin	-	201 (135/66) + 24[a]	66.9 (28-88)	-	9 (4.5)		113 (56.2)	49 (24.4)	13 (6.5)	>0.05

Table 1. Continued (acenocoumarol)

Study	Study design	Country	Type of VKAs	Note	N (M/F)	Age (years)	BMI (kg/m^2) or BW (kg)	Indication of VKAs, n (%)					HWE
								DVT	PE	AF	HVP	Others	
Gschwind L *et al*. 2015[#]	Prospective observational	Swiss	Aceno-coumarol	Caucasians (n=109) Africans (n=6)	115 (62/53)	63.2±18.2	-	70 (60.9)		29 (25.2)	-	16 (13.9)	>0.05
Jiménez -Varo E *et al*. 2014[#]	Retrospective observational	Spain	Aceno-coumarol	Algorithm cohort	134 (75/59)	73±10	29 [27-33] kg/m^2	-	-	109 (81.3)	-	25 (18.7)	0.530
				Validation cohort	30 (16/14)	73±8	32±5.7 kg/m^2	-	-	26 (86.7)	-	4 (13.3)	
				Total	164 (89/75)	73±9	30 [27-33] kg/m^2	-	-	135 (82.3)	-	29 (17.7)	
Rojo M *et al*. 2020	Retrospective cohort	Chile	Aceno-coumarol	-	279 (152/127)	66.49±14.11	29.32±5.77 kg/m^2	-	-	-	-	-	<0.05
Saraeva RB *et al*. 2007	-	Bulgaria	Aceno-coumarol	-	96 (56/40)	60±12 (17-86)	80±15 kg	6 (6.3)	11 (11.5)	27 (28.1)	40 (41.7)	12 (12.5)	>0.05
Sychev DA *et al*. 2016[#]	Retrospective cohort	Russia	Aceno-coumarol	-	50 (34/16)	59±8	85.7±11.3 kg	-	-	-	-	-	0.94

[a]Twenty-four additional patients with serious warfarin bleeding were recruited (20 through the Swedish spontaneous reporting of adverse drug reactions and 4 from an ongoing national study on cerebral bleeding and warfarin); *p<0.05, presented as mean±standard deviation (SD), mean (95% confidence interval [CI]), or median (range); M=male; F=female; VKAs=vitamin K antagonists, BMI=body mass index, BW=body weight, DVT=deep venous thromboembolism, PE=pulmonary thromboembolism, AF=atrial fibrillation, HVP=heart valve prosthesis, HWE=Hardy-Weinberg equilibrium, [#]Studies were included in meta-analysis.

Table 2. Assessment of risk of bias according to Newcastle-Ottawa Scale

Study	Selection				Comparability	Outcome			Total
Cohort study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study		Assessment of outcome	Length of follow-up	Adequacy of follow-up cohorts	
Campos EIF *et al*. 2018	*	*	*	*	-	*	-	*	6
de Oliveira Almeida VC *et al*. 2014	*	*	*	*	*	*	*	*	8
Issac MS *et al*. 2014	-	-	*	*	*	*	*	*	6
Kim Y *et al*. 2013	-	-	*	*	-	*	*	*	5
Li W *et al*. 2020	-	-	*	*	*	*	*	*	6
Tavares LC *et al*. 2018	-	-	*	*	*	*	*	*	6
Gschwind L *et al*. 2015	*	*	*	*	-	*	*	*	7
Jiménez-Varo E *et al*. 2014	*	*	*	*	-	*	*	*	7
Rojo M *et al*. 2020	*	*	*	*	-	*	*	*	7
Saraeva RB *et al*. 2007	*	*	-	*	*	*	*	*	7
Sychev DA *et al*. 2016	*	*	*	*	-	*	*	*	7
Study	Selection				Comparative	Exposure			Total
Case-control study	Is the Case Definition Adequate?	Representativeness of the Cases	Selection of Controls	Definition of Controls		Ascertainment of Exposure	Same method of ascertainment for cases and controls	Non-Response rate	
Ferrari M *et al*. 2014	*	*	*	*	*	-	-	*	6
Wadelius M *et al*. 2004	*	-	*	*	-	*	*	*	6

Table 3. Weekly maintenance dose of vitamin K antagonists (VKAs) according to *ABCB1* C3435T polymorphism

Study	Note	Type of VKAs	Maintenance dose (mg/week)					
			TT type		CT type		CC type	
			Mean	N	Mean	N	Mean	N
Campos EIF *et al*. 2018	-	Warfarin	29.9±18.9	24	28.3±12.5	57	33.0±15.8	55
de Oliveira Almeida VC *et al*. 2014	-	Warfarin	55.8±38.3	54	45.5±28.7	46	39.7±26.6	16
Issac MS *et al*. 2014	-	Warfarin	49 [28-54.30]	13	42 [35-49]	46	35 [28-45.50]	25
Kim Y *et al*. 2013	European Americans	Warfarin	55.57±14.20	23	60.14±17.76	35	58.58±14.25	16
	African Americans		65.92±22.18	6	58.45±16.01	18	64.68±21.03	35
	Hispanic Americans		50.75±6.06	4	53.16±15.44	26	51.63±12.04	12
	Asian Americans		42.00±0.0	3	52.85±5.82	11	49.00±5.35	7
	Total		55.63±15.39	36	56.94±15.91	90	59.48±17.98	70
Li W *et al*. 2020	-	Warfarin	17.01±5.6	29	18.69±6.51	100	20.72±8.89	85
Tavares LC *et al*. 2018	Caucasian	Warfarin	26.8±0.7 (SE)	44	27.3±0.6 (SE)	115	30.0±0.7 (SE)	74
	non-Caucasian		25.1±2.0 (SE)*	14	29.88±1.0 (SE)*	38	35.3±1.3 (SE)*	24
	Total		26.2±0.6 (SE)*	58	28.0±0.5 (SE)*	153	30.5±0.6 (SE)*	98
Gschwind L *et al*. 2015	-	Acenocoumarol	16.17±8.46	22	14.77±5.11	57	13.72±4.90	36
Jiménez-Varo E *et al*. 2014	Algorithm cohort	Acenocoumarol	15 [11-19]	31	13 [10-18]	67	12 [8-18]	36
Saraeva RB *et al*. 2007†	≤7 mg/week, n (%) 7-28 mg/week, n (%) ≥28 mg/week, n (%)	Acenocoumarol	1 (6.3) 9 (56.3) 6 (37.5)	16	8 (15.7) 34 (66.7) 9 (17.6)	51	5 (17.2) 20 (69.0) 4 (13.8)	29
Sychev DA *et al*. 2016	-	Acenocoumarol	21.7±6.02	15	18.48±7.07	25	24.15±9.38	10

†haplotype study; *p<0.05; VKAs=vitamin K antagonists; presented as mean±standard deviation (SD) or median [range]; SE=standard error

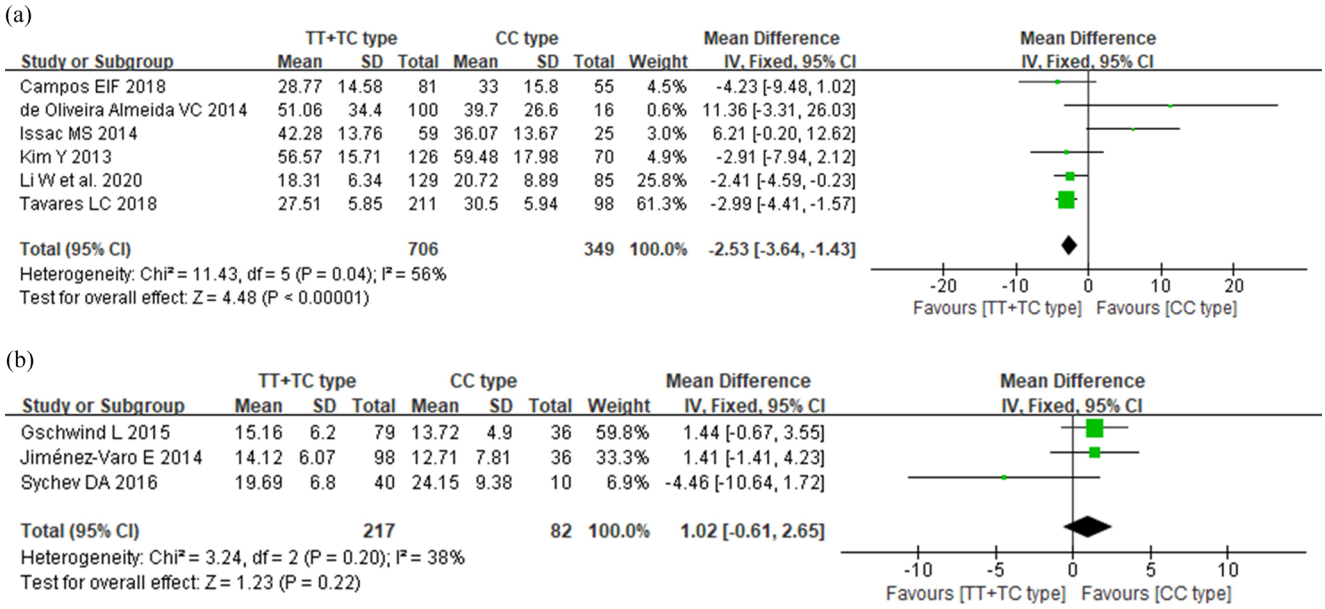

Fig. 2. Forest plots of weekly maintenance dose of (a) warfarin and (b) acenocoumarol in accordance with *ABCB1* C3435T polymorphism. (a) Mean difference of weekly maintenance dose of warfarin in accordance with *ABCB1* C3435T polymorphism (b) Mean difference of weekly maintenance dose of acenocoumarol in accordance with *ABCB1* C3435T polymorphism

in bias, because the cohort did not represent the patient population. Kim *et al.*[30] included patients who received warfarin at a dose of at least 42 mg/week for more than 1 year, which was also considered that the cohort did not represent the patients population. Li *et al.*[13] and Tavares *et al.*[14] included only patients administered stable maintenance doses of warfarin. Saraeva *et al.*[33] did not report on the item "ascertainment of exposure." For comparability, two stars were not assigned to the six articles that did not report patient characteristics that could affect VKAs treatment response, such as age, social habits, and BMI.[15,16,30,32,35,37] One star was assigned to four articles where patient characteristics were not reported according to the *ABCB1* C3435T polymorphism for comparability.[13,14,31,33] For the outcome, one star was not assigned to the study by Campos *et al.*[37] because the article did not report the follow-up period.

For the "representativeness of the cases" item in the selection analysis of the case-control NOS, one star was not assigned to Wadelius *et al.*[36] because the article did not report the characteristics of the case group. For the comparative domain, the article by Ferrari *et al.*[29] was assigned one star because the characteristics of included patients were reported according to the case-control group, but not the *ABCB1* C3435T polymorphism. The article by Wadelius *et al.*[36] was not assigned any stars because the characteristics of the included patients were not reported according to the case-control group and the *ABCB1* C3435T polymorphism. Furthermore, Ferrari *et al.*[29] did not report the exposure and was not assigned stars for the two items, "ascertainment of exposure" and "same method of ascertainment for cases and controls."

Association between *ABCB1* C3435T polymorphism and maintenance dose of VKAs

Six articles including 1055 patients reported the maintenance dose of warfarin according to the *ABCB1* C3435T polymorphism and 706 (66.9%) of the included patients had the *ABCB1 3435T* allele. Moreover, three articles including 299 patients reported the maintenance dose of acenocoumarol according to the *ABCB1* C3435T polymorphism, and 217 (72.6%) of the patients had the *ABCB1* 3435T allele (Table 3).

The result of the meta-analysis showed that the weekly maintenance dose of warfarin was significantly lower in patients with the *ABCB1 3435TT* or *TC* genotype than patients with the *ABCB1 3435CC* genotype (WMD −2.53 mg/week, 95% CI −3.64 to −1.43, p<0.001, Fig. 2a). In contrast, the weekly maintenance dose of acenocoumarol was not significantly associated with the *ABCB1* C3435T polymorphism (WMD 1.02 mg/week, 95% CI -0.61 to 2.65, p=0.22, Fig. 2b).

In the subgroup meta-analysis, the weekly maintenance

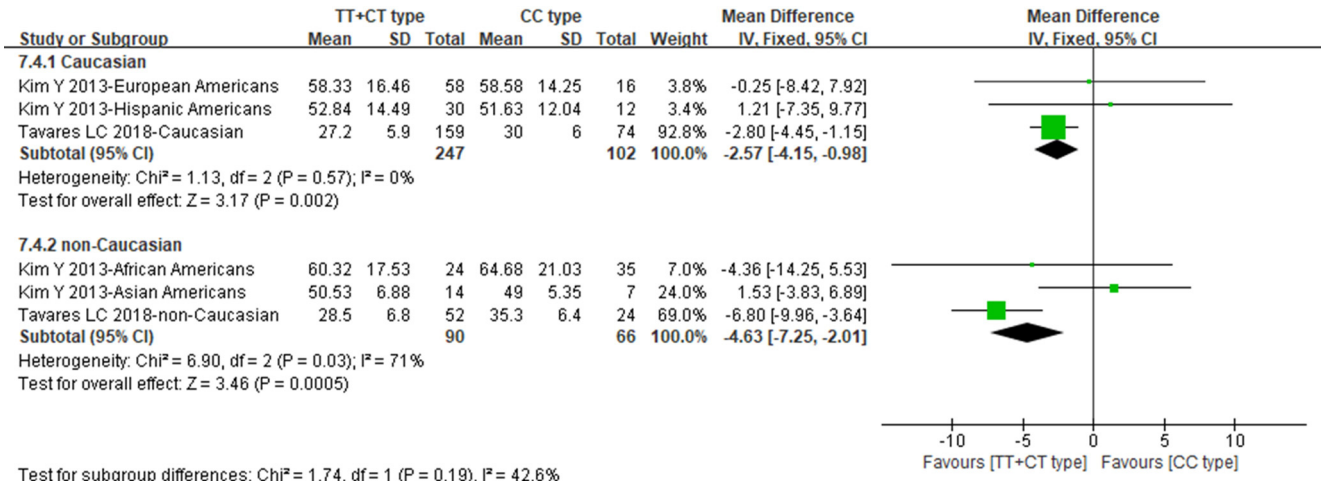

Fig. 3. Forest plots of subgroup analysis for weekly maintenance dose of warfarin in accordance with *ABCB1* C3435T polymorphism

Table 4 Treatment response of vitamin K antagonists (VKAs) according to *ABCB1* C3435T polymorphism

Study	Note	Type of VKAs	Response of VKAs		
			TT type	CT type	CC type
de Oliveira Almeida VC *et al*. 2014	Resistance rate n (%)	Warfarin	16 (29.6)	-	-
Ferrari M *et al*. 2014	TTR >85% TTR <55% n (%)	Warfarin	4 (28.6) 10 (71.4)	21 (51.2) 20 (48.8)	8 (72.7) 3 (27.3)
Gschwind L *et al*. 2015	Hazard ratio for time-to-achieve stability (95% CI)	Acenocoumarol	2.81 (1.18-6.67)*	1.12 (0.49-2.55)	1*
Rojo M *et al*. 2020	TTR (days), n	Acenocoumarol	244 [305], 107	240 [299], 135	203 [201], 37

Study	Note	Type of VKAs	Incidence rate of bleeding events					
			TT type, n (%)		CT type, n (%)		CC type, n (%)	
			Yes	No	Yes	No	Yes	No
Wadelius M *et al*. 2004	-	Warfarin	11 (14.3)	66 (85.7)	21 (18.4)	93 (81.6)	4 (11.8)	30 (88.2)
Sychev DA *et al*. 2016	-	Acenocoumarol	6 (40)*	9 (60)	13 (52)*	12 (48)	1 (10)*	9 (90)

*p<0.05; presented as median [interquartile range] or mean (95% confidence interval CI); VKAs=vitamin K antagonists; TTR=time in therapeutic range

dose of warfarin according to the *ABCB1* C3435T polymorphism in Caucasian patients was comparable to the overall weekly maintenance dose of warfarin (WMD −2.57 mg, 95% CI −4.15 to −0.98, p=0.002). However, the weekly maintenance dose of warfarin according to *ABCB1* C3435T polymorphism in non-Caucasian patients was higher than that in Caucasian patients (WMD −4.63, 95% CI −7.25 to −2.01, p=0.0005, Fig. 3).

Saraeva *et al*.[33] stratified the weekly maintenance doses of acenocoumarol as low (≤7 mg/week), medium (7-28 mg/week), and high (≥28 mg/week) and reported the number of patients according to the *ABCB1* C3435T polymorphism.

Association between *ABCB1* C3435T polymorphism and treatment response of VKAs

Three articles reported the treatment response to warfarin according to the *ABCB1* C3435T polymorphism, including two that reported on resistance[29,34] and the other that reported the incidence rates of bleeding events.[36] Similarly, the other three articles reported the treatment response of acenocoumarol according to the *ABCB1* C3435T polymorphism.[15-16,32] Two articles were about studies on resistance,[15,32] and the other was focused on the incidence rate of bleeding events[16] (Table 4).

In an article by de Oliveira Almeida *et al*., 66% of patients who were taking a weekly maintenance dose of warfarin >70 mg had *ABCB1 3435TT* genotype.[34] Although Ferrari *et al*. reported that patients with TTR <55% were more likely to have the *ABCB1* 3435T allele, which was not statistically significant.[29] In Wadelius *et al*., who reported the incidence rate of bleeding events, there was no significant association between the incidence rate of bleeding events and the *ABCB1* C3435T polymorphism.[36]

Two articles by Gschwind *et al*.[32] and Rojo *et al*.[15] reported the TTR according to the *ABCB1* C3435T polymorphism. In the article by Gschwind *et al*.,[32] the *ABCB1* 3435TT type was significantly higher in patients who rapidly reached a stable status following acenocoumarol therapy than in those with *ABCB1 3435CC* genotype (hazard ratio, 2.81; 95% CI, 1.18 to 6.67, p=0.02). Although Rojo *et al*. reported an increasing tendency of the TTR in patients with the *ABCB1* 3435T allele, and there was no statistically significant difference between TTR and the *ABCB1* C3435T polymorphism (p=0.066).[15] Sychev *et al*. reported that the *ABCB1* 3435T allele was associated with a significantly increased incidence rate of bleeding events (p=0.0366).[16]

Discussion

This study is the first systematic review and meta-analysis to show the impact of the *ABCB1* C3435T polymorphism on the weekly maintenance dose of VKAs and incidence rate of bleeding events. The results of this meta-analysis demonstrated that patients with the *ABCB1* 3435T allele required a significantly lower weekly maintenance dose of warfarin than those without this allele. However, there was no association between the *ABCB1* C3435T polymorphism and weekly maintenance dose of acenocoumarol. There was each one study in warfarin and acenocoumarol which reported the incidence rate of bleeding events according to the ABCB1 C3435T polymorphism.[16,36] With acenocoumarol, the *ABCB1* 3435T allele was significantly associated with an increased incidence rate of bleeding events, but there was no significant association between the *ABCB1* C3435T polymorphism and the incidence rate of bleeding events with warfarin therapy.

The *ABCB1* gene, which is expressed in the small intestine, liver, kidney, and blood-brain barrier plays an important role in the excretion and absorption of drugs.[20-23] Although the *ABCB1* C3435T polymorphism is a silent mutation, it affects the expression including mRNA, activity, and substrate specificity of P-gp.[20,23,38-40] In particular, for VKAs with a narrow therapeutic range, the *ABCB1* C3435T polymorphism could be an additional genetic factor affecting the response to medication treatment.

VKORC1 and *CYP2C9* are known to influence the maintenance dose of warfarin, which consequently, requires an adjustment to between 5 and 30% of the value of the calculated dose.[11] Moreover, the maintenance dose of warfarin in this meta-analysis was 2.53 mg/week, which suggest that it does not appear to have been significantly affected by *ABCB1* C3435T polymorphism. However, in clinical practice, patients respond sensitively to low doses such as those who are >70 years old,[7] with a BMI ≤25 kg/m^2,[41] low renal function,[42] and congestive heart failure.[43] The included patients in the study by Li *et al*.[13] had a mean age, BMI, and weekly warfarin maintenance dose of 72.6 years, 24.0 kg/m^2, and 19.6 mg, respectively. For these patients, the 2.53 mg/week maintenance dose of warfarin determined in this study was 12.9% of the overall weekly maintenance dose. In patients who respond with a high sensitivity to low doses of warfarin, the *ABCB1* C3435T polymorphism might be considered a factor when they require warfarin treatment or dose adjustment.

According to the Pharmacogenomics Knowledgebase (PharmGKB), the frequencies of the *ABCB1* 3435T allele are 22-38% in the African and Asian population and 42-51% in the European and Latin American population.[44] In the subgroup meta-analysis, patients with the *ABCB1* 3435T allele who were non-Caucasian were administered lower weekly maintenance doses of warfarin than those who were Caucasian. Although the frequency of the *ABCB1* 3435T allele is lower in non-Caucasian patients than it is in those who are Caucasian, this allele appears to affect the weekly maintenance dose of warfarin in those with the *ABCB1* C3435T polymorphism. Another explanatory variable was the haplotype, which consisted of *ABCB1* C1236T and G2677T for the *ABCB1* C3435T polymorphism.[44] Age, body weight and BMI have a correlation with the maintenance dose of VKAs.[7,8] Additional research is needed to examine the association between haplotype, ethnicity, age, BMI and weekly doses of VKAs.

In the present study, the weekly maintenance dose of acenocoumarol was not significantly associated with the *ABCB1* C3435T polymorphism. This might be associated

with the differences in physicochemical characteristics between warfarin and acenocoumarol. P-gp has been reported to have a higher substrate affinity for smaller molecular weight compounds.[45] Warfarin is structurally similar to acenocoumarol, but warfarin has a lower molecular weight than acenocoumarol (308.3 vs 353.3 g/mol). Thus, warfarin could be more affected by the *ABCB1* C3435T polymorphism than acenocoumarol. However, two articles that were included in the meta-analysis of weekly maintenance dose of warfarin according to the *ABCB1* C3435T polymorphism reported opposite tendencies with the other articles.[31,34] The patients included in the study by de Oliveira Almeida *et al*. did not conform to the HWE principle for the *ABCB1* C3435T polymorphism.[34] The study by Issac *et al*. reported that the weekly maintenance dose of warfarin was significantly lower in patients with the *ABCB1* 3435TT/*EPHX1* 139HH genotype than it was in those with *ABCB1* 3435CC/*EPHX1* 139HH genotype, but it was significantly higher in those with *ABCB1* 3435TT/*EPHX1* 139RH or RR genotype than in those with *ABCB1* 3435CC/*EPHX1* 139RH or RR genotype.[31] Both studies included younger patients than other studies.[31,34] Factors that could have caused the discrepancies among the results of the various studies include a lack of conformation to the HWE principle, and effect of other polymorphisms and age.

The pharmacokinetic parameters or clinical outcomes of P-gp substrate drugs could be altered by the *ABCB1* C3435T polymorphism. Many drug classes are known substrates of P-gp, including antidepressants, anticancer, antiarrhythmic, and antihypertensive agents.[46] In particular, the effects of *ABCB1* C3435T polymorphism on other types of anticoagulants and antiplatelet drugs have been reported.[47-50] Similar to the results of this study, a meta-analysis that reported a relationship between *ABCB1* C3435T polymorphism and treatment response to clopidogrel showed that the *ABCB1* 3435T allele was associated with a significantly increased incidence rate of bleeding events in the Asian population (OR 1.805, 95% CI 1.124 to 2.900, p=0.015).[49] In addition, the *ABCB1* 3435T allele was associated with a significantly reduced platelet activity (standardized mean difference with fixed effect model –0.140, 95% CI –0.272 to –0.009, p=0.036).[49] These results showed an association between the clinical outcomes of treatment with clopidogrel and the *ABCB1* C3435T polymorphism.

Another meta-analysis reported the association between pharmacokinetic parameters of new oral anticoagulants (NOACs) and the *ABCB1* C3435T polymorphism.[50] Patients with the *ABCB1* 3435CC genotype showed a significantly higher peak serum concentration of NOACs than those with the *ABCB1* 3435TT genotype (WMD –16.99 ng/mL, 95% CI –33.39 to –0.59, p=0.04) did.[50] Furthermore, the *ABCB1* 3435CC genotype was associated with a significantly lower area under the concentration time-curve from 0 h to infinity ($AUC_{0-\infty}$) than that of the *ABCB1* 3435CT or TT genotype (WMD –78.58 ng·h/mL, 95% CI –151.14 to –6.01, p=0.03).[50] The changes in pharmacokinetic parameters or clinical outcomes according to the *ABCB1* C3435T polymorphism could be a factor for dose adjustment or prediction of clinical outcomes.

A meaningful finding of this study is that the *ABCB1* gene is involved in absorption and excretion of drugs in contrast to the *CYP2C9* and *VKORC1* genes that are involved in regulating the activity and metabolism of warfarin. The results of this systematic review and meta-analysis indicate that the *ABCB1* C3435T polymorphism had a significant effect on the weekly maintenance dose of warfarin. However, this study had some limitations that are worth mentioning. Drug-drug interactions, drug-food interactions, and haplotypes were not considered. However, the results of this study included all of these potential interaction affects and showed that the *ABCB1* 3435T allele was significantly associated with a lower weekly maintenance dose of warfarin. The results of this meta-analysis could facilitate decision-making by medical specialists in clinical practice. The association between the *ABCB1* C3435T polymorphism and the incidence rate of thrombosis events was not evaluated in this study and would require further investigation.

In conclusion, the *ABCB1* 3435T allele showed a significantly lower weekly maintenance dose of warfarin than the *ABCB1* 3435CC genotype, but the weekly maintenance dose of acenocoumarol was not significantly associated with the *ABCB1* C3435T polymorphism. Furthermore, the incidence rate of bleeding events appeared to show a tendency to increase in those expressing the *ABCB1* 3435T allele, but the result was not significant. Further research is needed to confirm the association between the *ABCB1* C3435T polymorphism and the incidence rate of bleeding events.

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Conflicts of Interest

The authors have no conflicts of interest to declare with regards to the contents of this study.

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