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Predictive value of clinical examination parameters for cardiovascular adverse events during treatment of chronic myeloid leukemia with tyrosine kinase inhibitors

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Original article

Running head: Prediction of CAE during treatment with TKI

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Abstract

Treatment of chronic myelogenous leukemia (CML) requires management of long-term use of tyrosine kinase inhibitors (TKIs). Although cardiovascular adverse events (CAEs) caused by off-target effects of TKIs can be life-threatening, the optimal method of monitoring for CAEs has not been established. Here, we comprehensively evaluated the clinical utility of various cardiovascular parameters, including ankle-brachial blood pressure index (ABI), cardiac ankle vascular index (CAVI), and carotid ultrasonography and electrocardiogram measurements, for monitoring and predicting CAEs in 74 patients with CML receiving TKIs. Based on concordance statistics, the predictive value of established risk factor models was significantly improved by addition of both ABI and CAVI, as follows: model 1 (hypertension, smoking history, and dyslipidemia), 0.680 vs. 0.817 ($p = 0.041$); model 2 (hypertension, dyslipidemia, and diabetes mellitus), 0.685 vs. 0.830 ($p = 0.047$); and model 3 (age, hypertension, dyslipidemia and diabetes mellitus) 0.737 vs. 0.818 ($p = 0.044$). However, no single cardiovascular parameter independently improved the predictive value of established risk factor models. In conclusion, addition of combined assessment of ABI and CAVI to assessment of established risk factors can improve prediction of future CAEs and may enable better clinical management of patients

with CML receiving TKIs.

Keywords:

Ankle-Brachial Index, Cardiac Ankle Vascular Index, Peripheral arterial disease, Peripheral arterial occlusive diseases, TKI-induced vascular events

1. Introduction

Since the launch of tyrosine kinase inhibitors (TKIs), the prognosis of patients with chronic myeloid leukemia (CML) has drastically improved [1-5]; however, many patients need to receive TKI drugs long-term, with the number who can discontinue TKI treatment currently limited [6-12]. Therefore, it has become important to manage off-target adverse effects, particularly cardiovascular adverse events (CAEs), which are often life-threatening during long-term administration of TKIs [13].

Although many analyses of risk factors for CAEs during TKI treatment for CML have been conducted [14-17], prediction of CAEs remains challenging and no effective prediction method has been identified. The onset of CAEs due to TKIs is greatly influenced by comorbidities in each patient, and the incidence is elevated in patients at high risk of cardiovascular disease [14-17]; however, it develops even in young patients who are not at risk [18, 19], thus it is possible that a mechanism other than canonical thrombus formation pathogenesis is involved.

The cardiac ankle vascular index (CAVI) can be used to quantitatively evaluate vascular wall stiffness of the aorta, femoral artery, and tibial artery, by measuring blood pressure and heart-femoral pulse wave velocity (PWV) [20, 21]; PWV can be influenced by

blood pressure and is, therefore, an unstable index, while, CAVI is more reproducible and less influenced by blood pressure than brachial-ankle PWV [20-23].

Regular cardiovascular evaluation monitoring tests, including electrocardiogram and measurement of ankle-brachial blood pressure index (ABI), are recommended for patients on long-term TKI therapy [16]; however, the predictive value of these examinations for CAEs have been not sufficiently investigated. In addition, to our best knowledge, the predictive value of CAVI and carotid ultrasonography (US) associated during TKI therapy have yet to be evaluated.

Herein, we describe a comprehensive investigation of the clinical usefulness, and value for monitoring and prediction, of various cardiovascular examination parameters for CAEs during TKI treatment for CML.

2. Methods

2.1. Study Population

We retrospectively analyzed data from outpatients with chronic (CML-CP) or accelerated (CML-AP) phase CML, who were receiving TKI treatment (imatinib, nilotinib, dasatinib, bosutinib, or ponatinib) and in whom cardiovascular evaluation tests were performed in our

hospital outpatient clinic between 1 June 2017 and 30 December 2018. The closing date for follow-up and evaluation of CAEs occurrence was 30 September 2020. Cardiovascular evaluation tests included measurement of ABI and CAVI, electrocardiography, and carotid US. Measurement of ABI and CAVI was conducted using a vascular screening system (Vasera VS 1500, Fukuda Denshi Co., Ltd., Tokyo, Japan). Electrocardiography was performed using a recording system (ECG-2550, NIHON KOHDEN Corporation, Tokyo, Japan) and carotid US was conducted using an Ultrasound Color Doppler (SSA-790A Aplio XG, Canon Medical Systems Corporation, Tochigi, Japan). Corrected QT interval was calculated using Bazett's formula.

This study was approved by the Ethical Committee of Osaka City University Graduate School of Medicine and conducted according to the Declaration of Helsinki and Ethical Guidelines for Medical and Health Research Involving Human Subjects of Japan.

2.2. Definitions

In our study, CAEs were defined as cardiomyopathy, cardiac failure, ischemic heart disease, ischemic cerebrovascular disease, peripheral arterial occlusive disease (PAOD), pulmonary hypertension, and cardiac arrhythmias [16, 24]. Hypertension, hyperlipidemia, diabetes

mellitus, chronic kidney disease (CKD), and smoking history were determined by medical records or by measurements and test results at the time of the visit. CKD was defined as stage 3a (G3a) or higher (eGFR < 60 ml/min). CAEs before the onset of CML were excluded. ABI values of 1.00–1.40, 0.91–0.99, and ≤ 0.90 were defined as normal, borderline, and abnormal, respectively. A CAVI value of ≥ 9.0 was defined as abnormal. CAVI was measured at the same time as ABI. Patients with ABI ≤ 0.9, who may have a severe atherosclerotic femoral artery lesion, can have falsely low CAVI scores; in such cases, since the CAVI value was only displayed as a reference value, it was excluded from our analysis [21]. PAOD was defined as an ABI of ≤ 0.9, with diagnostic imaging and physical findings supporting the diagnosis. Carotid US pathological findings were defined as > 50% stenosis and/or echolucent unstable plaque, which was considered a high risk of stroke [25]. QTc values of ≥ 430 for male and ≥ 450 for female were defined as QTc prolongation.

2.3. Statistical analysis

Continuous variables were compared by Mann-Whitney *U* test, and statistical comparisons between categorical groups were performed using the Fisher exact test. Analysis of

predictive power was limited to CAEs that occurred after cardiovascular examinations. Univariate logistic regression analysis was used to identify cardiovascular examination parameters useful to predict CAEs.

In addition, we applied concordance (c-) statistics, including receiver operating characteristic (ROC) curve analysis, to examine the incremental effects of cardiovascular examinations on the predictive value for CAEs of established base models, comprising known risk factors, including hypertension, smoking history, and dyslipidemia (model 1); hypertension, dyslipidemia, and diabetes mellitus (model 2); or age, hypertension, dyslipidemia, and diabetes mellitus (model 3).

P-values < 0.05 were considered statistically significant and all statistical analyses were performed using IBM SPSS statistics version 26 (IBM, New York, NY, USA) and EZR version 1.41 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [26].

3. Results

3.1. Patients' characteristics

A total of 74 patients (CML-CP n = 72, CML-AP n = 2) were included in this study. A summary of patient characteristics is provided in Table 1. Median duration from diagnosis

of CML disease until cardiovascular assessments was 7.95 years. Median TKI treatment duration was 7.84 years. At the time of cardiovascular evaluation, 15 (20.3%) patients were receiving imatinib, 22 (29.7%) nilotinib, 22 (29.7%) dasatinib, 11 (14.9%) bosutinib, and 4 (5.4%) patients were receiving ponatinib.

3.2. CAEs

In 16 of 74 patients, 18 CAEs occurred before and after cardiovascular examination, as follows: PAOD (n = 4), angina (n = 2), cerebral infarction (n = 2), cerebrovascular severe stenosis and/or occlusion (n = 2), subarachnoid hemorrhage (n = 1), pulmonary hypertension (n = 1), aortic dissection (n = 1), and atrial fibrillation (n = 5) (Table 2). Of the 18 CAE, 9 (50%), 4 (22.2%), 3 (16.7%), and 2 (11.1%) occurred while patients were taking nilotinib, dasatinib, imatinib, and bosutinib, respectively. All but one patient had cardiac risk factors. Cardiovascular risks and management of them are summarized in Table 2. Management of risk factors such as comorbidities, except for smoking and CKD, was performed in seven patients. Only four patients received antithrombotic medication.

Further, 10 CAEs occurred in 10 patients during the follow-up period after cardiovascular examination, as follows: PAOD (n = 4), angina (n = 1), cerebral infarction

(n = 1), cerebrovascular severe stenosis and occlusion (n = 1), pulmonary hypertension (n = 1), and paroxysmal atrial fibrillation (n = 2).

3.3. Comparisons of patient characteristics and cardiovascular examination parameters between patients who had CAE and those who did not from the initiation of TKI therapy to the evaluation

Of the 18 events, eight had already occurred at the time of cardiac evaluation. In the comparison of cases with (n=8) and without (n=66) CAE at that time, the proportion of patients who showed QTc prolongation was significantly greater in the CAE than the non-CAE group (87.5% vs. 28.6%, p = 0.002). The proportion of patients who showed abnormal ABI, CAVI, and carotid US findings did not significantly differ between the two groups (Supplemental Table).

3.4. Predictive value of combined assessment of cardiovascular examination parameters for CAEs

To evaluate the predictive value for CAEs of established risk factors in combination with cardiovascular test parameters we conducted an analysis limited to the 10 cases in whom

CAEs occurred after cardiovascular evaluation. The results indicated that the proportion of female patients was significantly higher among those who experienced CAEs than those who did not experience CAEs (70.0% vs. 32.8%, $p = 0.036$), and the proportion of patients with diabetes mellitus was also greater in the CAE group than the non-CAE group (50.0% vs. 10.9%, $p = 0.008$).

In univariate logistic analysis, female sex and diabetes mellitus were significant risk factors for CAEs [odds ratio (OR) 4.78; 95% confidence interval (CI) 1.12–20.4, $p = 0.034$ and OR 8.14; 95% CI 1.88–35.3, $p = 0.005$, respectively] (Table 3). Dyslipidemia showed marginal statistical significance as a risk factor for CAEs (OR 3.83; 95% CI 0.967–15.2, $p = 0.056$).

ABI ≤ 0.9 and ABI < 1.0 were both significant risk factors for CAEs (OR 20.3; 95% CI 3.73–111, $p = 0.0005$ and OR 4.33; 95% CI 1.08–17.4, $p = 0.039$, respectively). ABI and CAVI were applied as a composite indicator and abnormality of either ABI or CAVI (ABI $\leq$ 0.9 or CAVI ≥ 9.0) was a significant risk factor for CAEs (OR 11.1; 95% CI 2.13–57.3, $p = 0.0042$). Further, ABI < 1.0 or CAVI ≥ 9.0 were also significant risk factors for CAEs (OR 6.67; 95% CI 1.31–34.0, $p = 0.023$). Absolute QTc value was a significant risk factor for CAEs; however, the number of patients with QTc prolongation was not significant (OR

1.05; 95% CI 1.01–1.10, p = 0.011 and OR 2.05; 95% CI 0.531–7.91, p = 0.30, respectively).

Next, we used c-statistics, including ROC curve analysis, to evaluate the incremental effects of cardiovascular examination parameters on predictive value for future CAEs. Addition of ABI and CAVI parameters (ABI ≤ 0.9 or CAVI ≥ 9.0) had a significant incremental effect on the area under the ROC curve (AUC) of base models, generated using established risk factors, including: hypertension, smoking history, and dyslipidemia (model 1) (AUC, 0.680 vs. 0.817, P = 0.041); hypertension, dyslipidemia, and diabetes mellitus (model 2) (AUC, 0.685 vs. 0.830, P = 0.047); and age, hypertension, dyslipidemia, and diabetes mellitus (model 3) (AUC, 0.737 vs. 0.818, P = 0.044) (Table 4).

4. Discussion

In this study, we found that combined assessment of ABI and CAVI, in addition to established risk factors, provided improved predictive value for future CAE in patients with CML receiving TKIs.

It is established that the incidence of CAEs has increased due to the increase of atherosclerosis in patients at high risk, according to the general cardiovascular scoring

system [14-17].

CAVI was developed to evaluate artery stiffness and is an established powerful index for assessment of systemic arteriosclerosis. Further, CAVI is associated with coronary artery disease, diabetes mellitus, and smoking [22, 27]; however, CAVI alone was insufficient to predict the onset of CAE in our study, indicating the influence of mechanisms other than atherosclerosis. Indeed, CAEs occur even in young patients who are not at cardiovascular risk [18, 19].

In a previous report on ABI examination, 26% and 35.7% of patients receiving nilotinib as first- and second-line therapy, respectively, showed pathological ABI [28]; however, ABI alone was insufficient to predict CAEs in our study. This is likely because the incidence of PAOD can influence the predictive value of ABI and the ABI test is highly specific for detection of arterial occlusion and stenosis of the lower limbs, but does not become abnormal in the early stages of arteriosclerosis.

In addition, the pathogenesis of CAE caused by TKI treatment is complex. TKIs are thought to cause CAE by changing the functions of cells, including vascular endothelial cells, platelets, and immune cells (T cells, mast cells, and macrophages). Further, CAE pathogenesis also depends on the type of TKI [29-35], manifesting differently among

patients receiving different TKI drugs [13, 24]. Therefore, there may be value in developing specific monitoring and prevention methods, depending on the type of TKI used, or routine monitoring using other inspection methods to capture different types of CAE.

In this study, the prevalence of QTc prolongation was significantly higher among patients who experienced CAE from the start of TKI therapy to the cardiovascular evaluation than among those who did not. Any change in the QT interval can reflect abnormalities in the two phases of the cardiomyocyte electrical cycle [36]. In addition, QTc prolongation is associated with arrhythmia, myocardial infarction, left ventricular dysfunction, and stroke [37-39]. We therefore speculate that this is the reason why the prevalence of QTc prolongation was significantly higher among patients who experienced CAE after the initiation of TKI therapy.

There were some limitations of this study, including the retrospective nature of the analysis and the relatively small cohort size. In addition, the effects of previous TKI administration histories on the incidence of CAE were not analyzed. Moreover, CAVI values can be inaccurate in cases with abnormal ABI. Therefore, we excluded CAVI values of patients with ABI $\leq$ 0.9 from the analysis. Hence, the limitations of each test, due to the nature of the examinations, can be compensated for by the other, and we speculate that this

underlies our finding that the combination of ABI and CAVI had good predictive power.

In conclusion, the results of our study suggest that assessment of combined ABI and CAVI, in addition to existing routine approaches, may be useful for monitoring of CAE associated with TKI treatment. Establishment of more useful and noninvasive monitoring and/or predictive procedures for the early detection of CAE in patients with CML undergoing TKI treatment is necessary.

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Conflicts of interest:

MN received honoraria from Novartis and payment (honoraria) to spouse (Please refer to H. Nakamae disclosure). HN received honoraria from Pfizer Japan Inc. and Takeda Pharmaceutical Co., Ltd., and research funding and honoraria from Novartis, Bristol Myers Squibb, and Otsuka Pharmaceutical. HK received honoraria from Novartis, and honoraria and research funding from Takeda Pharmaceutical Co., Ltd. YN received honoraria from

Pfizer Japan Inc., and honoraria and research funding from Novartis. MHino received honoraria from Pfizer Japan Inc., Bristol Myers Squibb, Novartis, Takeda Pharmaceutical Co., Ltd, and Otsuka Pharmaceutical, research funding from Pfizer Japan Inc. Takeda Pharmaceutical Co., Ltd and Novartis, and donations made to the university that were not limited to specific research purposes from Pfizer Japan Inc. and Otsuka Pharmaceutical. MHa and AH have no conflicts of interest.

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Table 1. Patient characteristics

Characteristic	N＝74
Age (years), median (range)	63.5 (21–91)
Sex, Male/Female, n	46/28
BMI (kg/m^2), median (range)	23.8 (16.0–38.8)
Hypertension, n (%)	37 (50.0%)
Smoking history, n (%)	28 (37.8%)
Diabetes mellitus, n (%)	12 (16.2%)
Dyslipidemia, n (%)	24 (32.4%)
CKD (≥ stage G3a), n (%)	28 (37.8%)
CML disease status at evaluation	
Non-HR, n (%)	1 (1.4%)
HR, not MR3.0, n (%)	3 (4.1%)
MR3.0, n (%)	7 (9.5%)
MR4.0, n (%)	18 (24.3%)
MR4.5, n (%)	45 (60.8%)

Cardiac risk factors evaluated at the cardiovascular examinations are shown. Abbreviations: BMI: body mass index; CKD: chronic kidney disease; CML: chronic myeloid leukemia; HR: hematologic response; MR: molecular response.

Table 2. Characteristics of patients who experienced cardiovascular adverse events (CAE)

No.	Sex	Age (years)	Disease status at CAE	Manifestation of CAE	CAE after evaluation	TKI therapy at CAE	History of TKI therapy	Treatment at CAE	**Cardiac risk factors at CAE
1	M	66	MR4.5	Subarachnoid hemorrhage	No	IM	IM	Statin	HL, smoking
2	M	71	MR4.5	Cerebral artery severe stenosis	No	NIL	IM, NIL	None	CKD
3	M	90	MR4.5	Aortic dissection	No	IM	IM	None	CKD
4	M	51	MR3.0	pAf	No	IM	IM	None	CKD
5	M	61	MR3.0	Angina pectoris	No	NIL	NIL	None	Smoking
6	F	68	MR4.5	pAf	No	DAS	DAS	None	HL
7	F	79	MR4.5	Af	No	NIL	NIL	SU, DPP-4 inhibitors, statin, Ca-blocker	DM, HL, HT
		84	MR4.5	PAOD	Yes	NIL	NIL	Glinide, β-blocker, aldosterone antagonists, loop diuretic, DOAC	CKD, DM, HL, HT
8	F	62	MR4.5	Cerebral infarction	No	NIL	NIL	DPP-4 inhibitors, Ca-blocker, ARB, PGE1 derivative	DM, HT, smoking
		66	MR4.5	PAOD	Yes	DAS	DAS	DPP-4 inhibitors, Ca-blocker, ARB, PGE1 derivative	DM, HL, HT, smoking
9	F	75	MR4.5	Cerebral artery	Yes	NIL	NIL	None	CKD

				stenosis and occlusion					
10	F	66	Unknown	PAOD	Yes	DAS	DAS	Metformin, statin, β-blocker, aspirin	DM, HL, HT, smoking
11	F	72	MR4.5	pAf	Yes	NIL	IM, NIL	α-GI, statin	DM, HL, HT
12	M	41	MR4.0	pAf	Yes	NIL	NIL	None	None
13	M	75	Unknown	Cerebral infarction	Yes	*DAS	IM	None	HT, smoking
14	M	69	MR4.0	Angina pectoris	Yes	BOS	DAS, NIL, BOS	DPP-4 inhibitors, metformin, statin, Ca-blocker, aspirin	DM, HL, HT, smoking
15	F	88	MR4.5	PAOD	Yes	NIL	NIL, DAS, IM, NIL	Statin	HL, HT
16	F	53	MR4.0	Pulmonary hypertension	Yes	BOS	IM, NIL, DAS, BOS	None	CKD

Abbreviations: MR: molecular response; Af: atrial fibrillation; pAf: paroxysmal atrial fibrillation; PAOD: peripheral arterial occlusive disease; TKI: tyrosine kinase inhibitor; IM: imatinib; NIL: nilotinib; DAS: dasatinib; BOS: bosutinib; SU: sulfonylurea; DPP-4: dipeptidyl peptidase 4; PGE1: prostaglandin E1; DOAC: direct oral anticoagulant; α-GI: alpha-glucosidase inhibitor; ARB: angiotensin II receptor blocker; HT: hypertension; HL: hyperlipidemia; DM: diabetes mellitus; CKD: chronic kidney disease; smoking: smoking including smoking history. *Cerebral infarction occurred while dasatinib treatment was interrupted due to an adverse event. **Cardiac risk factors at the time of CAE are shown.

Table 3. Predictive value of various parameters for CAE

Patient characteristic	OR	OR 95% CI	p value	AUC
Age (years)	1.04	0.987–1.10	0.14	0.642
Sex (female)	4.78	1.12–20.4	0.034*	0.686
BMI (kg/m^2)	1.06	0.916–1.24	0.41	0.601
Hypertension	2.64	0.627–11.1	0.19	0.616
Smoking history	1.11	0.284–4.34	0.88	0.513
Diabetes mellitus	8.14	1.88–35.3	0.005*	0.695
Dyslipidemia	3.83	0. 967–15.2	0.056	0.659
CKD (≥ stage G3a)	0.669	0.158–2.83	0.58	0.545
Duration of CML disease (years)	1.01	0.863–1.18	0.91	0.509
Treatment duration of TKI (years)	1.00	0.823–1.20	0.96	0.502
Cardiovascular examinations				
Carotid US pathological findings	2.03	0.452–9.09	0.36	0.563
ABI ≤ 0.9	20.3	3.73–111	0.0005*	0.727
ABI < 1.0	4.33	1.08–17.4	0.039*	0.656
CAVI ≥ 9.0	4.70	0.716–30.8	0.11	0.679
ABI ≤ 0.9 or CAVI ≥ 9.0	11.1	2.13–57.3	0.0042*	0.767
ABI < 1.0 or CAVI ≥ 9.0	6.67	1.31–34.0	0.023*	0.712
QTc value (ms)	1.05	1.01–1.10	0.011*	0.738
QTc prolongation	2.05	0.531–7.91	0.30	0.586

Abbreviations: CAE: cardiovascular events; OR: odds ratio; BMI: body mass index; CKD: chronic kidney disease; CML: chronic myeloid leukemia; TKI: tyrosine kinase inhibitor; US: ultrasonography; ABI: ankle-brachial index; CAVI: cardiac ankle vascular index; QTc: collected QT. *$p < 0.05$.

Table 4. Value of ABI, CAVI, and established risk models, alone and in combination, for prediction of CAE in patients with CML on TKI therapy

Risk factors		AUC	P value vs. base model
Base model 1 (HT, DL, Smoking history)	**(Model 1 only)**	**0.680**	
	+ ABI ≤ 0.9	0.768	0.37
	+ ABI <1.0	0.716	0.49
	+ ABI ≤ 0.9 or CAVI ≥ 9.0	0.817	0.041*
	+ ABI <1.0 or CAVI ≥ 9.0	0.766	0.085
	+ Carotid US pathological findings	0.733	0.31
	+ QTc prolongation	0.684	0.95
Base model 2 (HT, DL, DM)	**(Model 2 only)**	**0.685**	
	+ ABI ≤ 0.9	0.777	0.35
	+ ABI <1.0	0.741	0.51
	+ ABI ≤ 0.9 or CAVI ≥ 9.0	0.830	0.047*
	+ ABI <1.0 or CAVI ≥ 9.0	0.774	0.13
	+ Carotid US pathological findings	0.725	0.61
	+ QTc prolongation	0.680	0.72
Base model 3 (Age, HT, DL, DM)	**(Model 3 only)**	**0.737**	
	+ ABI ≤ 0.9	0.771	0.47
	+ ABI <1.0	0.765	0.40
	+ ABI ≤ 0.9 or CAVI ≥ 9.0	0.818	0.044*
	+ ABI <1.0 or CAVI ≥ 9.0	0.779	0.11
	+ Carotid US pathological findings	0.767	0.37
	+ QTc prolongation	0.732	1.00

Supplemental Table. Comparisons of patient characteristics and cardiovascular examination parameters between patients who had CAE and those who did not from the start of tyrosine kinase inhibitor therapy to the evaluation

Cardiovascular examinations	CAE (+) n=8	CAE (-) n=66	*P*
Carotid US pathological findings, n (%)	2 (25.0%)	12 (18.5%)	0.645
IMT, n (%)	1 (12.5%)	10 (15.4%)	1.00
Presence of plaque, n (%)	5 (62.5%)	36 (55.4%)	1.00
ABI ≤ 0.9, n (%)	2 (25.0%)	6 (9.09%)	0.206
ABI < 1.0, n (%)	3 (37.5%)	14 (21.2%)	0.374
CAVI ≥ 9.0, n (%)	2 (33.3%)	16 (26.2%)	0.656
QTc prolongation, n (%)	7 (87.5%)	18 (28.6%)	0.002*

Abbreviations: CAE: cardiovascular adverse events; US: ultrasonography; IMT: intima media thickness; ABI: ankle-brachial index; CAVI: cardiac ankle vascular index; QTc: collected QT. Carotid US was not performed in one patient without CAE. Electrocardiography was not performed in three patients without CAE. *$p < 0.05$.