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The effect of ticagrelor based dual antiplatelet therapy on development of late left ventricular thrombus after acute anterior ST elevation myocardial infarction

Bernas Altıntaş [a,*], Rojhat Altındağ [b], Önder Bilge [c], Erkan Baysal [c], Önder Öztürk [c], Barış Yaylak [d], Hüseyin Ede [e], Mehmet Zülkif Karahan [c], Cengiz Burak [f], İbrahim Halil Tanboğa [g,h]

[a] Department of Cardiology, Gazi Yaşargil Training and Research Hospital, Diyarbakır, Turkey
[b] Department of Cardiology, Diyabakır Gazi Yaşargil Training and Research Hospital, Diyarbakır, Turkey
[c] Department of Cardiology, Diyabakır Gazi Yaşargil Training and Research and Education Hospital, Diyarbakır, Turkey
[d] Department Cardiology, Dr.Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, İstanbul, Turkey
[e] Department of Cardiology, Bozok University School of Medicine, Yozgat, Turkey
[f] Department of Cardiology, Mardin State Hospital, Mardin, Turkey
[g] Department of Cardiology, Hisar Intercontinental Hospital, Istanbul, Turkey
[h] Department of Biostatistics, Ataturk University Medical School, Erzurum, Turkey

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ABSTRACT

Aim: The aim of this study is to investigate the impact of ticagrelor as compared to clopidogrel based dual antiplatelet therapy (DAPT) during post-discharge management on the incidence of left ventricular (LV) thrombus in patients with first acute anterior ST elevation myocardial infarction (STEMI).
Method: 641 patients who met the inclusion criteria were divided into two groups based on the receipt of either ticagrelor or clopidogrel based DAPT.
Result: Left ventricular thrombus was detected in 73 (11.4%) patients at the first month echocardiographic examination. Ticagrelor based DAPT was associated with significantly less incidence of LV thrombus when compared to clopidogrel [20 (7.4%) vs 53 (14.0%) OR: 0.50 (0.29–0.86)]. Penalized maximum likelihood estimation (PMLE) logistic regression analyses were performed to fourteen candidate variables for identifying the independent predictors of LV thrombus, ticagrelor (compared with clopidogrel) [OR: 0.53 (0.28–0.96), $p = 0.039$], body mass index (BMI) [OR: 0.58 (0.44–0.77), $p < 0.001$], KILLIP class (I vs II–IV) [OR: 0.35 (0.14–0.83), $p = 0.017$], age [OR: 1.22 (1.08–1.40), $p < 0.001$], poor postprocedural myocardial blush grade (MBG) [OR: 3.35 (1.32–8.15), $p = 0.012$] and LVEF predischarge [OR: 0.79 (0.72–0.86), $p < 0.001$] were found to be associated with LV thrombus.
Conclusion: Our study demonstrated that the incidence of LV trombus was significantly lower with ticagrelor than clopidogrel-based DAPT during postdischarge treatment for anterior STEMI patients.

1. Introduction

Left ventricular (LV) thrombus is a serious complication of acute myocardial infarction (MI) and associated with increased risk of arterial thromboembolism, particularly in patients with an anterior ST elevation myocardial infarction (STEMI) [1,2]. In addition to anterior STEMI, other risk factors for the development of LV thrombus include severe apical asynergy, LV aneurysm and reduced LV ejection fraction (LVEF). Contemporary treatment in the primary percutaneous coronary intervention (p-PCI) era has led to a dramatic decrease in the incidence of LV thrombus after STEMI, especially in hospital period, but LV thrombus still occurs in the range of 2.9% to 15% [3]. On the basis of the inconsistent results of several studies that investigated clopidogrel based dual antiplatelet therapy (DAPT) with vitamin K antagonist (VKA), the current guidelines do not recommend prophylactic VKA treatment in patients with potential risk factors for LV thrombus formation, due to risk of serious bleeding [4,5]. Therefore, during the post-discharge management, P2Y12 inhibitors may become more important for the prevention of LV thrombus and systemic embolism.

Ticagrelor, a novel reversible and direct-acting oral antagonist of the adenosine diphosphate receptor P2Y12, has a faster onset and achieves more consistent P2Y12 inhibition than clopidogrel [6,7]. Ticagrelor was used in patients with STEMI and non-STEMI in the PLATelet inhibition and patient Outcomes (PLATO) trial, in which a reduction in thrombotic

* Corresponding author at: Peyas Mahallesi, Selahaddin Eyubbi Bulvarı, 229. Sokak Hamzaoğulları Sitesi B/20 Kayapınar, Diyarbakır 21070, Turkey.
E-mail address: bernasaltintas@gmail.com (B. Altıntaş).

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events, including death from vascular causes, non-fatal myocardial infarction, or stroke, but a higher risk of non-procedure-related bleeding as compared to clopidogrel was observed [8]. The real-world data reveal that since recommendations for ticagrelor as a first line medication began to appear in guidelines, its usage has rapidly increased especially in cases with STEMI managed by primary PCI (p-PCI) [9,10]. Despite this rapidly increasing in the use of ticagrelor, the relationship between ticagrelor and LV thrombus formation after STEMI has not been investigated.

The aim of this study is to investigate the impact of ticagrelor-based DAPT as compared to clopidogrel-based DAPT during post-discharge management on the incidence of LV thrombus formation in patients with the first acute anterior STEMI.

2. Methods

2.1. Study population

This is a retrospective study including patients with anterior STEMI who have undergone p-PCI between January 2014 and January 2018. Only subjects that underwent p-PCI and received acetyl salicylic acid and an additional P2Y12 inhibitor (clopidogrel or ticagrelor) were included. All subjects enrolled in the study were followed up for 4 weeks after discharge. The primary endpoint of the study was the development of LV thrombus at first month. The exclusion criteria were as follows: patients who died during the follow-up period; patients with concurrent pericardial disease, atrial fibrillation, previously diagnosed left ventricular systolic dysfunction (defined as LVEF < 50%), chronic pulmonary disease, pulmonary hypertension, moderate to severe valvular heart disease, or acute pulmonary embolism on admission; patients with identified thrombus on predischarge echocardiogram; patients who required anticoagulation for other indications (atrial fibrillation, valvular disease, reinfarction, due to severe LV dysfunction or occurrence of thromboembolic complications of other diseases) during the discharge and follow-up period; patients who were not followed up within 4 weeks after discharge. DAPT was discontinued or interrupted for any reason, or underwent a change in P2Y12 inhibitor during the follow-up period. The informed consent of each subject and the approval of the local ethics committee were obtained. The study protocol conforms to the Declaration of Helsinki [11].

2.2. Coronary angiography

Coronary angiography was performed within 90 min of hospital admission. All patients received dual antiplatelet therapy with a loading dose of aspirin (300 mg) and clopidogrel (600 mg) or ticagrelor (180 mg) before procedure. Preprocedural anticoagulation consisted of intravenous unfractionated heparin (70 IU/kg) in all cases. Then, p-PCI with stent implantation was performed according to the current guidelines [12]. An optimal angiographic result was defined as the presence of thrombolysis in myocardial infarction (TIMI) grade 2–3 flow in the left anterior descending artery following p-PCI. An unsuccessful procedure was defined as a procedure resulting in TIMI grade 0–1 flow [13].

2.3. Echocardiography

Following prompt p-PCI, which was performed according to the current guidelines, all patients underwent an echocardiogram before the discharge from the hospital (defined as predischarge) and a month later (defined as post-discharge). Standard two-dimensional echocardiography with a digital ultrasonic device system (iE33; Philips, Netherlands) was performed for each patient in a left lateral decubitus position. LV thrombus was defined as an echodense mass adjacent to an abnormally contracting myocardial segment. It had to be distinguishable from the underlying myocardium, have a clear thrombus-blood interface, and be visible in at least two different transducer positions. The 16-segment model was used for scoring the severity of segmental wall motion abnormalities according to the American Society of Echocardiography guideline [14]. The echocardiographic evaluation of LV function was completed with the assessment of systolic and diastolic diameters and volumes. A modified Simpson's method was used to assess the LVEF.

2.4. Statistical analyses

All statistical analyzes were performed using “rms”, “logistf”, “glmnet” and “pROC” packages with R-software v. 3.5.1 (R statistical software, Institute for statistics and mathematics, Vienna, Austria). Continuous variables were presented as median and interquartile range, whereas categorical variables were presented as counts and percentages.

2.4.1. Primary outcome

The primary outcome was the presence of thrombus in the LV at first month echocardiographic examination of the patients who were consecutively enrolled the study.

2.4.2. Candidate predictors

It is important that candidate predictors to be included in the model are clinically and biologically plausible and that their association with LV thrombus has been demonstrated in previous studies. Variables with very low or very high frequency were not included in the model. The candidate predictors were chosen according to these principles. As a result, we included 14 candidate predictors in our final model. The candidate predictors were antiplatelet therapy (clopidogrel vs ticagrelor), age, sex, body mass index (BMI), hypertension, diabetes mellitus, smoking, KILLIP class, time from symptoms onset to PCI, number of diseased coronary artery (single vs multivessel), preprocedural coronary collateral flow (TIMI 0–1 vs TIMI 2–3, postprocedural TIMI flow(TIMI 0–2/slow flow vs TIMI 3), postprocedural myocardial blush grade (MBG) (no/minimal vs moderate/good), LVEF predischarge.

2.4.3. Sample size calculation

To build clinical model, sample size should be sufficiently large and number of predictors should be sufficiently conservative. Specifically there should be at least 10 patients with outcome in relation to the degrees of freedom of the predictors included in the model (outcome/df > 10). In our clinical model, 14 candidate predictors were identified while outcomes were present in 73 patients (73/14 = 5.2). Therefore the penalized maximum likelihood estimation (PMLE) logistic regression method was used to reduce the overfitting risk.

2.4.4. Statistical modelling

PMLE logistic regression method was used to evaluate the relationship between outcome and candidate predictors with the reason of overfitting risk. Age, BMI, LVEF predischarge, time from symptoms onset to PCI were included in the model as flexible smooth parameters using with restricted cubic spline. In PMLE logistic regression, unlike maximizing the log likelihood in traditional multivariable logistic regression, maximizing the penalized log likelihood is used. Therefore the maximizing log likelihood of the model is adjusted with penalty factor. The relative importance of each predictor in the models was estimated with partial χ^2 value for each predictor divided by the model's total χ^2, which estimates the independent contribution of the predictor to the variance of the outcome.

2.4.5. Performance of the model and intervalidation

Loess algorithm was used for relationship between observed and predicted outcome. The calibration was evaluated by plotting the observed outcome on the y-axis and predicted outcome on the x-axis. Deviation from the 45° line indicates bias for the predicted outcome. The discrimination of the model was evulated by calculating c-index. Internal validation was performed by bootstrap resampling that used 200 random samples drawn with replacement. Predictive models were developed in each bootstrap sample and evaluated in the entire cohort to quantify the optimism in the estimated apparent performance.

3. Results

The study included 796 consecutive patients who were enrolled after the discharge from the hospital. During the follow-up period, the number of excluded patients and the reasons for exclusion were as follows: 25 patients (3.1%) were excluded due to anticoagulant usage for any reason, 60 patients (7.5%) were excluded due to the interruption or discontinuation of DAPT or a change in P2Y12 inhibitor usage, and 70 patients (8.7%) (28 patients who died during follow up) were excluded due to a lack of echocardiographic examination at the end of the follow-up period. The remaining 641 patients, median age 60 (52–68) years were included in the study in accordance with the inclusion criteria. The study consisted of 186 female (29.0%) and 455 male (71.0%) patients. Left ventricular thrombus was detected in 73 (11.4%) patients. The patients were classified into two groups based on their clopidogrel or ticagrelor usage. There were 378 patients in the clopidogrel group and 263 patients in the ticagrelor group. The demographic, clinical, angiographic, echocardiographic characteristics and medical therapy of the groups are shown in Table 1. LV thrombus was identified in 53 patients (14.0%) of clopidogrel group and in 20 patients (7.6%) of ticagrelor group at first month echocardiographic examination. Ticagrelor was associated with less incidence of LV thrombus when compared to clopidogrel [OR: 0.50 (0.29–0.86) $p = 0.012$]. Whereas in-hospital course LV thrombus had been identified in 49 patients (5.1%) (in 30 (5.4%) patients used clopidogrel and in 19 (4.9%) patients used ticagrelor. LV EF was found to be lower than 35% in 262 patients (157 patients of clopidogrel group and 105 patients of ticagrelor group). LV thrombus was identified in 38 patients (24.2%) of clopidogrel group and in 16 patients (15.2%) of ticagrelor group

Table 1
Baseline demographic, clinical, angiographic and echocardiographic characteristics and medical therapy of the study patients according to P2Y12 inhibitors.

Variable	All patients (n = 641)	Clopidogrel group (n = 378)	Ticagrelor group (n = 263)	*p* value
Age (year)	60 (52–68)	62 (54–68)	59 (50–68)	0.06
Male [n (%)]	455 (71)	274 (72.5)	181 (68.8)	0.31
Hypertension [n (%)]	168 (26.2)	100 (26.5)	68 (25.9)	0.86
Diabetes mellitus [n (%)]	118 (18.4)	66(17.5)	52 (19.8)	0.45
Current smoking [n (%)]	266 (41.5)	159 (42.1)	107 (40.7)	0.72
Family history of CAD [n (%)]	121 (18.9)	119 (22.5)	74 (20.1)	0.37
History of hyperlipidemia [n (%)]	164 (25.6)	95 (25.1)	69 (26.2)	0.75
BMI	24.3 (22.8–26.0)	25 (22–26)	24 (22–26)	0.55
Previous PCI [n (%)]	73 (11.4)	42 (11.1)	31 (11.8)	0.79
Time from symptoms onset to PCI (hour)	4 (3.75–5)	4.5 (4–5)	4 (3.5–5)	0.50
KILLIP class	1 (1–2)	1(1–2)	1(1–2)	0.23
Multivessel CAD [n (%)]	237 (37.0)	147 (38.9)	90 (34.2)	0.22
No-reflow/slow flow (TIMI 0–1–2)	56 (8.7)	31 (8.2)	25 (9.5)	0.56
Poor MBG (postprocedural) [n (%)]	51 (8)	30 (11.4)	21 (5.7)	0.11
Good Coronary collateral flow [n (%)]	205 (32.0)	123 (32.5)	82 (31.2)	0.59
LV EF predischarge (%)	35 (32–39)	35 (32–39)	35 (33–39)	0.38
LV EF at first month (%)	40 (37.5–44)	40 (38–44)	40 (36–44)	0.12
LV thrombus at first month	73 (11.4)	53 (14.0)	20 (7.6)	0.012
Medical therapy				
ASA [n (%)]	641 (100)	378(100)	263(100)	1.00
ACEI-ARA [n (%)]	597 (93.1)	348 (91.8)	249 (94.7)	0.19
β-Blocker [n (%)]	540 (84.2)	321 (84.9)	219 (83.3)	0.57
Statin [n (%)]	590 (92.0)	347 (91.8)	243 (92.4)	0.78

Data are expressed as median interquartile range and count (percentage); ASA, acetyl salicylic acid; ACEI-ARA, angiotensin-converting enzyme inhibitor-angiotensin II receptor antagonist; BMI, body mass index; CAD, coronary artery disease; EF, ejection fraction; LV, Left ventricle; MBG, myocardial blush grade; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.

($p < 0.001$). The relationship between 13 candidate predictors as well as ticagrelor vs clopidogrel and LV thrombus were examined in a model using both traditional univariable (Table 2) and PMLE logistic regression analyses with partial chi-square values (Table 3). In PMLE logistic regression, ticagrelor (compared with clopidogrel) [OR: 0.53 (0.28–0.96), $p = 0.039$], BMI [OR: 0.58 (0.44–0.77), $p < 0.001$], KILLIP class (I vs II–IV) [OR: 0.35 (0.14–0.83), $p = 0.017$], age [OR: 1.22 (1.08–1.40), $p < 0.001$], Poor MBG [OR: 3.35 (1.32–8.15), $p = 0.012$] and LVEF predischarge [OR: 0.79 (0.72–0.86), $p < 0.001$] were found to be associated with LV thrombus. The demographic,

Table 2
Traditional univariable logistic regression analyses in prediction of LV thrombus at 1-month.

Variable	Univariable LR, unadjusted OR and 95% CI	*p* value
Age (year)	1.27(1.15–1.41)	<0.001
Sex (=male)	0.62(0.37–1.02)	0.064
Diabetes mellitus (=yes)	1.96(1.13–3.41)	0.017
Hypertension	1.16(0.67–1.99)	0.598
Smoking	0.86(0.52–1.42)	0.563
BMI (kg/m^2)	0.59(0.46–0.76)	<0.001
KILLIP class (I vs II–IV)	1.29(0.78–2.13)	0.317
Antiplatelet treatment (=ticagrelor)	0.50(0.29–0.86)	0.012
Multivessel disease (=yes)	1.47(0.90–2.41)	0.123
LVEF predischarge (%)	0.80(0.75–0.85)	<0.001
Time from symptom onset to PCI (h)	1.37(1.19–1.59)	<0.001
Poor MBG (0, I) (=yes)	1.64(0.79–3.40)	0.180
No-reflow/slow flow (TIMI 0–2) (=yes)	0.76(0.29–1.98)	0.576
Good collateral flow (Rentrop 2–3) (=yes)	0.76(0.44–1.31)	0.329

CI = confidence interval; OR = odds ratio; BMI, body mass index; CAD, coronary artery disease; EF, ejection fraction; LV, left ventricle; MBG, myocardial blush grade; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial.

Table 3
Penalized logistic regression analyses with partial χ^2 values in prediction of LV thrombus at 1-month ($R^2 = 0.337$ and Brier score = 0.08).

Variable	Penalized LR adjusted OR and 95% CI	*p* value	Proportion of overall χ^2
LVEF predischarge (%)	0.79(0.72–0.86)	<0.001	0.39
BMI (kg/m^2)	0.58(0.44–0.77)	<0.001	0.35
Age (year)	1.22(1.08–1.40)	0.164	0.16
Poor MBG (0, I) (=yes)	3.35(1.32–8.15)	0.012	0.09
KILLIP class (I vs II–IV)	0.35(0.14–0.83)	0.017	0.08
Antiplatelet treatment (=ticagrelor)	0.53(0.28–0.96)	0.039	0.06
Diabetes mellitus	1.82(0.89–3.64)	0.101	0.04
Sex (male)	1.60(0.79–3.35)	0.194	0.03
Hypertension	0.66(0.33–1.29)	0.222	0.03
Multivessel disease	1.27(0.71–2.27)	0.419	0.02
Time from symptom onset to PCI (h)	1.08(0.87–1.34)	0.478	0.02
Smoking	1.24(0.63–2.46)	0.528	0.02
Good collateral flow (Rentrop 2–3) (=yes	0.91(0.46–1.74)	0.775	0.01
No-reflow/slow flow (TIMI 0–2) (=yes)	1.12(0.36–3.02)	0.836	0.01

CI = confidence interval; OR = odds ratio; BMI, body mass index; CAD, coronary artery disease; EF, ejection fraction; LV, left ventricle; MBG, myocardial blush grade; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.

clinical, angiographic and echocardiographic characteristics of the study patients with and without LV thrombus are shown in Table 4. In Fig. 1, the probability of LV thrombus and age, BMI and LVEF were plotted by both P2Y12 inhibitors. As it is shown in Fig. 2 the model's calibration function estimate was slightly nonlinear, with the corrected calibration showing good agreement with the apparent calibration. There a was good discrimination with a c-index of 0.856 in our apparent model and optimism-corrected c-index was slightly reduced to 0.820 (Table 5 and Fig. 3). We also developed a nomogram using variable coefficient in estimating the risk of LV apical thrombus (Fig. 4).

4. Discussion

To the best of our knowledge, this was the first study evaluating the potential role of ticagrelor on the development of LV thrombus during

Table 4
Demographic, clinical, angiographic and echocardiographic characteristics of study patients with and without LV thrombus.

Variable	Absence of LV thrombus (n = 568)	Presence of LV thrombus (n = 73)	*p* value
Age (year)	59(50–69)	64(58–70)	0.004
Male [n (%)]	410(72.2)	45(61.6)	0.06
Hypertension [n (%)]	147(25.9)	21(28.8)	0.59
Diabetes mellitus [n (%)]	97(17.1)	21 (28.8)	0.15
Current smoking [n (%)]	238(41.9)	28(38.4)	0.56
Family history of CAD [n (%)]	108(19.0)	13(17.8)	0.80
History of hyperlipidemia [n (%)]	146(25.7)	18(24.7)	0.84
BMI	24(22.8–26)	24.3(21.8–29)	0.25
Previous PCI [n (%)]	66(11.6)	7(9.6)	0.60
Time from symptoms onset to PCI (hour)	4(3.5–5)	5(4–6.5)	<0.001
KILLIP class	1(1–2)	1(1–2)	0.09
Multivessel CAD [n (%)]	204(35.9)	33(45.2)	0.12
No-reflow/slow flow (TIMI 0–1–2)	49(8.6)	7(9.6)	0.78
Poor MBG (postprocedural) [n (%)]	42(7.3)	9(12.3)	0.51
Good coronary collateral flow [n (%)]	187(32.9)	18(24.7)	0.33
P2Y12 inhibitors			0.012
Clopidogrel [n (%)]	325(57.2)	53(72.6)	
Ticagrelor [n (%)]	243(42.8)	20(27.4)	
LV EF predischarge (%)	36(33–39)	31(30–35)	<0.001
LV EF at first month (%)	41(38–45)	36 (34.5–41)	<0.001

Data are expressed as median interquartile range and count (percentage); BMI, body mass index; CAD, coronary artery disease; EF, ejection fraction; LV, left ventricle; MBG, myocardial blush grade; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.

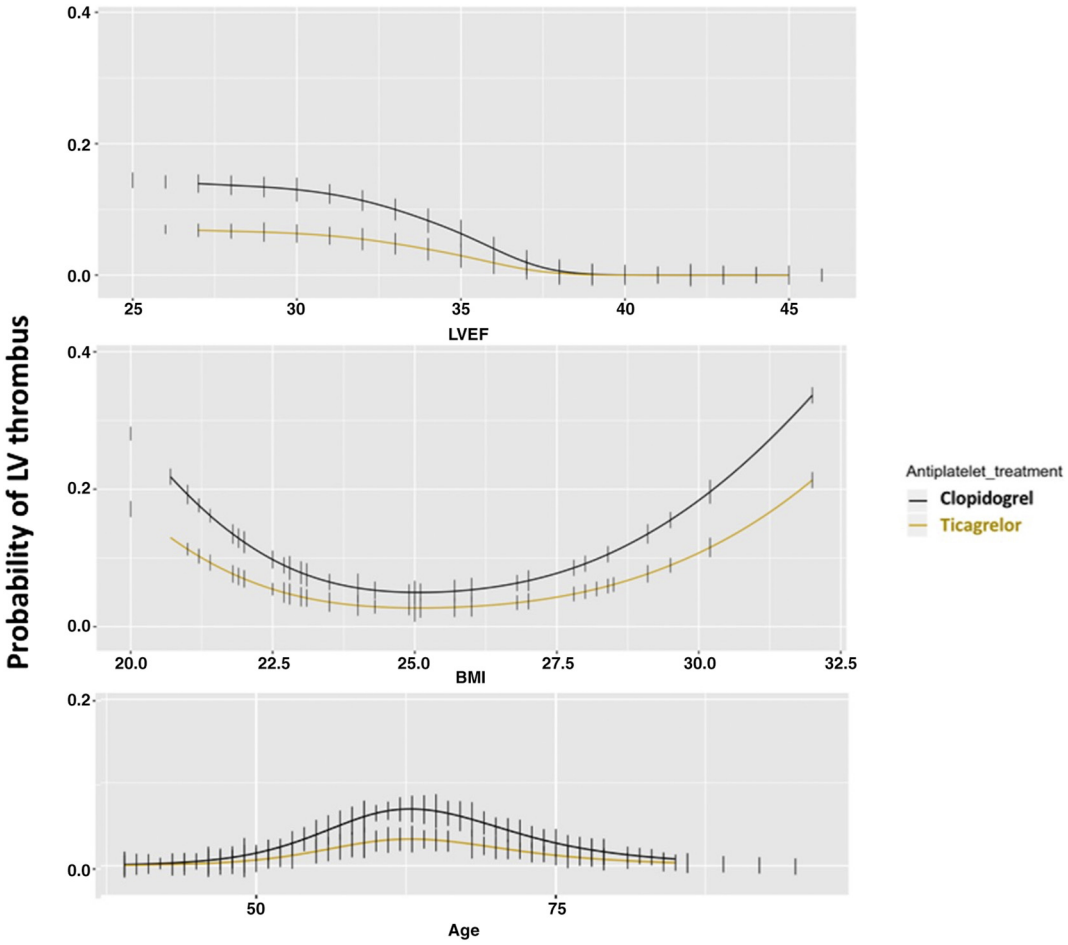

Fig. 1. The probability of LV thrombus and age, BMI and LVEF were plotted by both P2Y12 inhibitors.

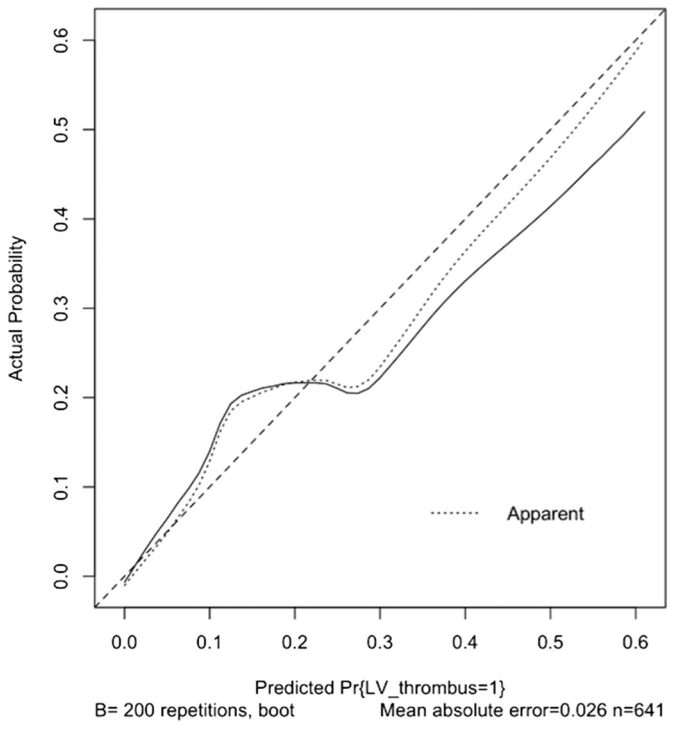

Fig. 2. Bootstrap overfitting-corrected calibration curve estimate for development of LV thrombus model.

the post-discharge period among the patients with first acute anterior STEMI who underwent p-PCI. We found that LV thrombus was detected in 11.4% of all study patients and that it was less commonly observed in patients using ticagrelor than in patients using clopidogrel (7.6% vs 14.0%). This study demonstrated that ticagrelor versus clopidogrel-based DAPT, age, BMI, KILLIP class, poor MBG and LVEF predischarge associated with the development of LV thrombus during follow-up among the patients with their first acute anterior STEMI who underwent p-PCI.

LV thrombus is a frequently seen complication of STEMI and has been investigated in many studies for its relevance to the risk of systemic embolization. Similar to the findings of our study, there were some studies showed some sort of relation between age, KILLIP class > 1, BMI and the development of LV thrombus after myocardial infarction [15–17]. However, an anterior location of STEMI and reduced LVEF were found to be the most powerful predictors of LV thrombus in most of these studies [18–21]. The relation between LV thrombus and poor postprocedural MBG, another finding of our study, may be explained by low LVEF and regional wall akinesia/dyskinesia.

A meta-analysis of 19 studies conducted between 2000 and 2015 (10,076 patients who undergone pPCI for STEMI) showed that the

Table 5
Performance measures before (apparent) and after bootstrap-corrected optimism.

Validation	Calibration intercept (95% CI)	Calibration slope (95% CI)	AUC (95% CI)
Apparent	0.000	1.000	0.856
Internal	0.276	0.202	0.820

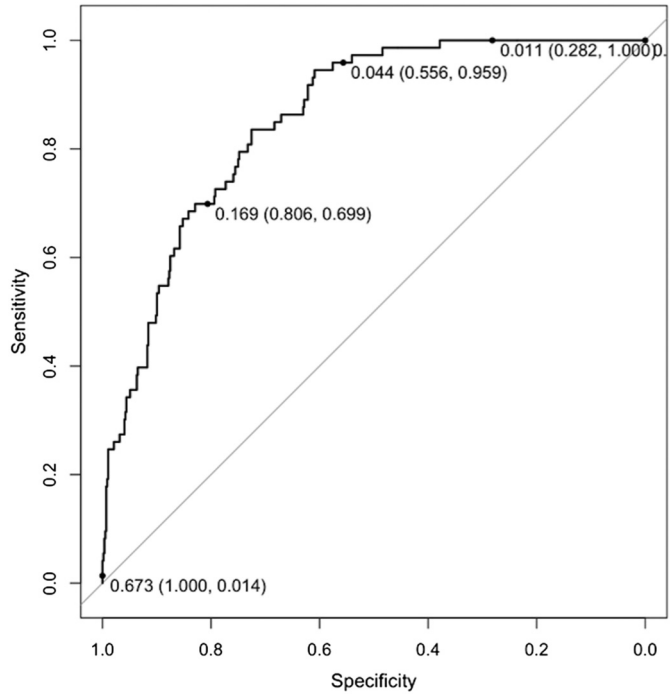

Fig. 3. Receiver operating characteristic (ROC) curves to discriminate LV thrombus from non-LV thrombus for the penalized logistic regression model.

incidence of LV thrombus was 2.7% after all forms of STEMI. Among patients with anterior STEMI, the incidence of LV thrombus was 9.1% which decreased to 7.5% in a sensitivity analysis of the studies that included >100 patients [22]. Khoury et al. evaluated the data of patients underwent p-PCI following all STEMI and they found that the incidence of LV thrombus in hospital course was 1.5% [23]. They suggested that the improved PCI practice and prolonged anticoagulation in patients with EF ≤ 35% or apical akinesia/dyskinesia might be the possible reason for the low incidence of LV thrombus. They also reported that 90% of patients with LV thrombus had acute anterior wall MI. These findings were inconsistent with our study, but there were significant differences in respect to the design of these studies including the types of reperfusion therapies, follow-up periods, durations of anticoagulant therapy, durations of DAPT and diagnostic modalities. Despite these differences, the studies showed that the incidence of LV thrombus following acute anterior STEMI was decreased in the PCI era as compared to the pre-PCI era. The current literature is insufficient to state a similar reduction in post-discharge LV thrombus formation in the PCI era as compared to the pre-PCI era. Solheim et al. and Osherov et al. reported that the incidence of LV thrombus in patients with anterior STEMI who were treated with fibrinolytic therapy and/or PCI was 15% in the first 3 months after the index event, including the in-hospital and discharge periods [24,25]. In 2012, Delewi et al. reported that the late LV thrombus was detected in 6.2% of patients with anterior STEMI under clopidogrel-based DAPT [26]. In 2015, Meurin et al. also reported that the incidence of late LV thrombus was found to be 19% with the same imaging modality in a similar patient population after first 3 months of the post-discharge period [27]. In addition 5% of patients were treated with ticagrelor-based DAPT.

Systemic thromboembolic events due to LV trombus in patients with reduced LVEF remain as a great risk for patients with anterior STEMI [28]. Prophylactic warfarin treatment was suggested for such patients based on the data derived from pooled results of studies on patients with STEMI during the pre-PCI era [29,30]. The balance between the prevention of thromboembolism and the risk of bleeding is the most important factor when choosing the best antithrombotic strategy. In two recently published studies, the use of prophylactic warfarin treatment in patients receiving clopidogrel-based DAPT was associated with a higher bleeding rate than DAPT alone [31,32]. Furthermore, another recently published study that included 460 patients with anterior STEMI treated with p-PCI showed that the addition of warfarin to DAPT for the prevention of thromboembolic complications was associated with more adverse clinical events as compared to managing patients without warfarin therapy. The researchers suggested that in the absence of LV thrombus, the addition of warfarin should not be considered for the management of patients with apical akinesis or dyskinesis detected with TTE [33].

It is necessary to evaluate different antithrombotic therapies in high-risk patients because prophylactic warfarin treatment with DAPT for the prevention of LV apical thrombus poses a significant bleeding risk. It seems that there are no widely accepted, useful, alternative treatments for the prevention of LV thrombus after hospital discharge among patients receiving DAPT. Moreover, studies comparing different P2Y12 inhibitors containing DAPT with respect to the development of LV apical thrombus and systemic embolization are lacking.

Platelet ADP receptors play a major role in platelet aggregation, which is one of the important steps in thrombus formation. In healthy volunteers, ticagrelor was associated a rapid onset of action and the dose-dependent and near-complete inhibition of ADP-induced platelet aggregation (IPA) [34]. Pharmacodynamic studies showed that patients with stable CAD and ACS achieved significantly greater IPA within 1 h when treated ticagrelor as compared to those treated with clopidogrel [7,35,36]. In the PLATO trial, which was a phase III clinical trial evaluating the efficacy and safety of ticagrelor in patients with ACS, a subgroup analysis of the patients with STEMI revealed that ticagrelor reduced the primary composite endpoint of death from vascular cause, MI, or stroke, which was consistent with the overall PLATO results [37]. The SWEDEHEART study showed that patients discharged with ticagrelor had a lower incidence of stroke, as well as death due to MI or stroke. It was also reported that this difference in outcomes was consistent at the 12th month and 24th month of follow-up [38]. Another long-term clinical trial of ticagrelor – the PEGASUS trial – also showed that low-dose ticagrelor could prevent stroke well beyond 1 year after MI [39]. The incidence of LV thrombus, which is known to be one of the primary causes of embolization during stroke, was not reported in these studies.

In the subgroup analysis of PLATO trial, patients with coronary stents, ticagrelor use, as compared to clopidogrel, reduced the incidence of stent thrombosis [40]. The reduction in stent thrombosis was consistent regardless of acute coronary syndrome type, the presence of diabetes mellitus, stent type (drug-eluting or bare metal), CYP2C19 genetic status, the loading dose of aspirin, the dose of clopidogrel before randomization, and the use of glycoprotein IIb/IIIa inhibitors at randomization. Despite the rapidly increasing use of ticagrelor, the relationship between ticagrelor and other types of thrombus formation was not investigated. A clinical report published in 2015 concerning four patients with confirmed or suspected LVAD thrombosis showed that the use of ticagrelor, rather than clopidogrel, prevented the development of thrombus [41]. The mechanism via which ticagrelor acts remains unknown, but abundant white clots in LVAD thrombus may represent a potential explanation. Our study is the first study to reveal that the incidence of LV thrombus during the post-discharge period among the patients with their first anterior STEMI who underwent p-PCI was lower in ticagrelor-based DAPT. It is reasonable to speculate that the efficacy of ticagrelor could be based on the stronger antithrombotic effects based on its above mentioned pharmacokinetic and pharmacodynamic characteristics. In addition these effects continue as long as the DAPT duration.

Our study is the first study to reveal that the incidence of LV thrombus after the discharge period among the patients with their first anterior STEMI who underwent p-PCI was lower in ticagrelor-based DAPT. However, because our study has a retrospective design,

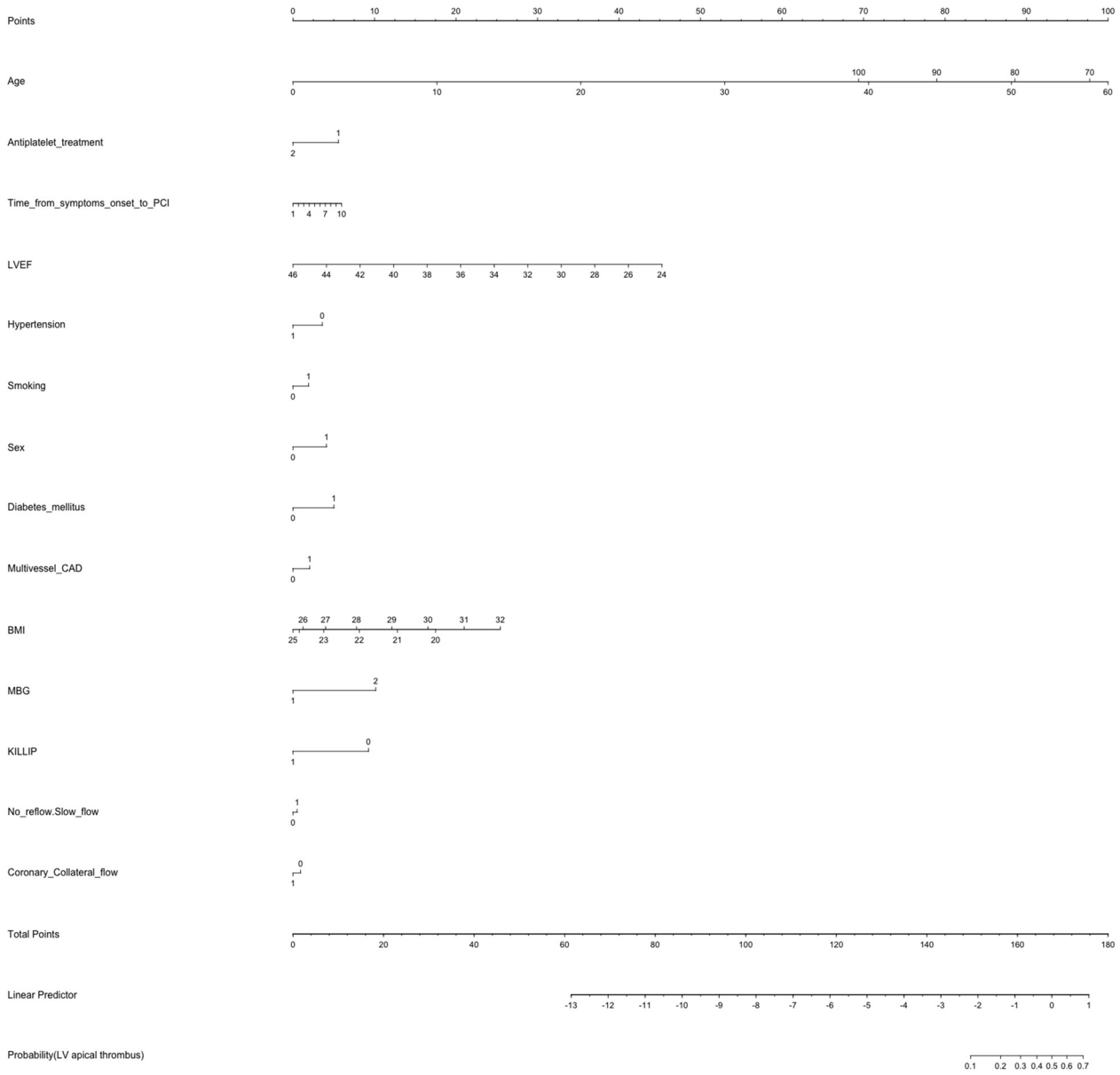

Fig. 4. Nomogram for predicting the probability of LV thrombus.

we could not evaluate its protective effect in terms of clinical endpoints, such as embolic complications. Thus, warfarin use seems to be only option in case of LV thrombus along with DAPT since it cannot be combined with ticagrelor according to the current guidelines. Still, the need for anticoagulates is obvious. However bleeding risk should be considered while determining the duration of the triple-drug treatment in patients with LV thrombus. Non-VKA OAC studies, such as the PIONEER-AF PCI and REDUAL-PCI trials, which evaluated different combinations of OAC and P2Y12 inhibitors after PCI, can be pioneering in this respect, although they were designed for different indications [42,43].

5. Conclusion

Our study was the first study comparing ticagrelor versus clopidogrel based DAPT for LV thrombus formation among patients with their first acute anterior STEMI who underwent p-PCI. We found that the incidence of LV thrombus was lower with ticagrelor during the post-ischarge period as compared to clopidogrel, and the prognostic effect of ticagrelor-based DAPT was demonstrated for LV thrombus. Large-scale prospective studies or subgroup analyses of RCTs including ticagrelor are needed to confirm this difference and its clinical importance.

6. Study limitations

Our study has several limitations. This was a retrospective study from a single large tertiary referral center, which may have introduced detection and treatment bias, and the power to detect significant changes may be limited by the sample size. Echo contrast and CMR were not used, which may have led to the underestimation of the incidence of LV thrombus. Due to the nature of the regression analysis, unmeasured variables may exist that could be significant predictors of LV thrombus.

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Conflict of interest

None.

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