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The Effect of Anti-platelet Resistance on Development of Left Ventricular Thrombus Formation After Myocardial Infarction: Prospective, Observational Case-control Research

Antiplatelet Direncinin Miyokard İnfarktüsü Sonrası Sol Ventrikül Trombüsü Gelişimine Etkisi: Prospektif, Gözlemsel, Vaka-kontrol Çalışması

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This study is a thesis from the Cardiology Clinic of Turkey Yüksek İhtisas Hospital and is registered in the National Thesis Center with the number 10370472. Thesis author Dr. Mehmet Vedat Çaldır and it was accepted in January/2007. It has the same title as this study.

ABSTRACT Objective: Left ventricular (LV) thrombus is a serious complication of acute myocardial infarction (MI). In this study, the effect of biochemical resistance to antiplatelet agents used after ST elevation MI on LV thrombus development was investigated. **Material and Methods:** Patients who were diagnosed with anterior MI and undergone primary percutaneous coronary intervention were included in this study. The patients were divided into two groups: Patients with thrombus (Group 1) and the patients without thrombus (Group 2). PFA-100 platelet analyzer was used to measure platelet reactivity. Clopidogrel resistance was defined as collagen adenosine 5-diphosphate closure time (COLL/ADP CT) <120 seconds and acetylsalicylic acid (ASA) resistance was defined as collagen epinephrine closure time (COLL/EPI CT) <180 seconds. Group 1 and Group 2 were compared with ASA and clopidogrel resistance. **Results:** The mean CT for COLL/EPI was similar in two groups (Group 1: 221.4±64.8 sec, Group 2: 217.7±70.2 sec; p=0.81). ASA resistance was detected in 24 (26.7%) patients in the whole patient group. There was no difference between the two groups in terms of ASA resistance [8 patients (26.7%) in Group 1, 16 patients (26.7%) in Group 2; p=1.0]. The mean closure times for COLL/ADP were similar in two groups (Group 1: 145.9±63.9 sec, Group 2: 155.9±63.9 sec; p=0.48). Clopidogrel resistance was detected in 27 (30%) patients in the whole patient group. There was no difference between two groups in terms of clopidogrel resistance [9 (30%) patients in Group 1, 18 (30%) patients in Group 2; p=1.0]. There was no difference between two groups in patients with both clopidogrel and aspirin resistance. **Conclusion:** In vivo resistance to dual antiplatelet therapy does not appear to be an effective mechanism in the development of LV thrombus after MI.

Keywords: Clopidogrel; thrombosis; aspirin; platelet resistance

ÖZET Amaç: Sol ventrikül [left ventricular (LV)] trombüsü, akut miyokard infarktüsünün ciddi bir komplikasyonudur. Bu çalışmada, ST elevasyonlu miyokard infarktüsü sonrası kullanılan antitrombosit ajanlara karşı biyokimyasal direnç varlığının LV mural trombüs gelişimi üzerine etkisi incelenmiştir. **Gereç ve Yöntemler:** Bu çalışmaya, anteriyor miyokard infarktüsü tanısı konulan ve primer perkütan koroner girişim yapılmış hastalar dâhil edildi. Hastalar 2 gruba ayrıldı. LV'de trombüs saptanan hastalar (Grup 1) ve trombüs saptanmayan hastalar (Grup 2). Trombosit reaktivitesini ölçmek için PFA-100 platelet analizörü kullanıldı. Klopidogrel direnci, kollajen adenozin 5-difosfat kapanma süresi [collagen adenosine 5-diphosphate closure time (COLL/ADP CT)] <120 sn olarak tanımlandı ve asetilsalisilik asit (ASA) direnci, kollajen epinefrin kapanma süresi [collagen epinephrine closure time (COLL/EPI CT)] <180 sn olarak tanımlandı. Grup 1 ve Grup 2 ASA ve klopidogrel direnci açısından karşılaştırıldı. **Bulgular:** COLL/EPI için ortalama kapanma süresi 2 grupta benzerdi (Grup 1: 221,4±64,8 sn, Grup 2: 217,7±70,2 sn; p=0,81). Tüm hasta grubunda 24 (%26,7) hastada ASA direnci saptandı. ASA direnci açısından 2 grup arasında fark yoktu [Grup 1'de 8 hasta (%26,7), Grup 2'de 16 hasta (%26,7); p=1,0]. COLL/ADP için ortalama kapanma süreleri 2 grupta benzerdi (Grup 1: 145,9±63,9 sn, Grup 2: 155,9±63,9 sn; p=0,48). Tüm hasta grubunda 27 (%30) hastada, klopidogrel direnci saptandı. Klopidogrel direnci varlığı açısından 2 grup arasında fark yoktu [Grup 1'de 9 (%30) hasta, Grup 2'de 18 (%30) hasta; p=1,0]. Ayrıca 2 grup arasında klopidogrel ve aspirin direncinin birlikte olduğu hastalar arasında da fark saptanmadı. **Sonuç:** İkili antitrombosit tedaviye in vivo direnç, miyokard infarktüsü sonrası LV trombüsü gelişiminde etkili bir mekanizma gibi görünmemektedir.

Anahtar Kelimeler: Klopidogrel; tromboz; aspirin; trombosit direnci

Left ventricular (LV) thrombus formation is a well recognized complication of acute myocardial infarction (MI). It has been reported that the LV thrombus incidence is between 20% and 40% in subjects who are diagnosed with large anterior wall MI.[1] LV thrombus develops because of the stasis, endocardial

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tissue inflammation, and hypercoagulability few days after the acute MI.[2] Recently, LV thrombus has ceased to be a common complication of acute MI due to early intervention with dual antiplatelet and anticoagulant therapy.[3] Embolisation and thus post MI mortality and morbidity risk increases with the effect of post-MI LV thrombus.[4] Strategies that are developed to prevent this complication represent an important therapeutic goal.

Platelets are effectively involved in the atherothrombotic pathogenesis of acute coronary syndromes, and ischemic cerebrovascular and peripheral obstructive arterial diseases.[5] Platelet accumulation is highly associated with the cardiovascular disease development and thus the platelet accumulation inhibition can be an effective way to prevent the development of these diseases. It is required to use platelet antiaggregants in the primary and secondary prevention of cardiovascular diseases.[6] However, the risk of MI, cerebrovascular diseases and death due to these events may be increased because of the resistance to these platelet antiaggregants.[7]

In the current study, the effects of antiplatelet agents, and resistance to these agents in mural thrombus formation after ST elevation MI were examined.

MATERIAL AND METHODS

DESIGN OF THE STUDY

This study is designed on a thesis of profession in cardiology (Registration number: 10370472). It is a prospective, observational case-control study. Written consent forms were obtained from the participants and the study was approved by the institutional ethics committee in May/2006. However, the ethics committee approval number could not be reached because the hospital where the study was conducted was closed and the archive data of the ethics committee was destroyed.This study has been prepared in accordance with the Declaration of Helsinki Principles.

STUDY GROUP

Patients who were diagnosed with acute anterior MI and admitted to coronary intensive care were included in the study. Patients were divided into two groups (62 male, 28 female; mean age 59.8±11.6). Group 1 was composed of 30 patients with LV thrombus detected by echocardiography and Group 2 was composed of 60 patients without thrombus. The demographic characteristics of the patients were similar. Acute MI was diagnosed according to criteria such as the presence of typical chest pain**,** continuing for 20 minutes or longer, the presence of >2 mm ST segment elevation in two consecutive chest derivation detected in electrocardiography (ECG), the rise or fall of serum troponin level which is minimum one value more than 99th percentile of the upper reference limit.[8] In ninety patients, all physical examinations were performed five days later. Patients' systolic and diastolic blood pressures were measured. Venous blood samples were collected for hematological parameters, fibrinogen, C reactive protein, lipid panel, blood sugar and creatinine measurements. All patients underwent coronary angiography and primary percutaneous intervention was performed. They also underwent transthoracic echocardiography 5 days following the admission to the hospital.

The exclusion criteria were failure in use of acetylsalicylic acid (ASA) or clopidogrel for any reason, use of glycoprotein IIb/IIIa antagonist after hospitalization, low hematocrit level (<28%), thrombocytopenia (<150000/mm^3) or thrombocytosis (>400000/mm^3), use of non-steroidal anti-inflammatory agent, severe kidney (creatinine clearance <30 mL/min) and/or liver failure, known coagulation disorders or use of anticoagulants, previous MI or dilated cardiomyopathy.

ECHOCARDIOGRAPHIC EVALUATION

In this study, a high resolution cardiac ultrasound system which was composed of 3.5 and 3.75 MHz short focus transducers was used. Results were recorded in order to use them again in the frame by frame analysis. Optimal cardiac apex images were taken from the long and short axis projections by using all depths of field settings and minimizing the potential near the field artifact.[9] Meanwhile, optimal LV wall resolution**,** particularly the endocardial boundaries were maintained. We excluded subjects whose endocardial borders diagnosis was not well determined and whose cardiac apex was not clearly

observed.

An experienced and blinded echocardiographer visualized the echo images of the participants. It was defined that LV thrombus was an echodense mass with definite margins and it was found adjacent to an area of hypo-or akinetic myocardium. Furthermore, it was contiguous but distinct from the endocardium.[10]

ANTIPLATELET RESISTANCE MEASUREMENT

The Platelet Function Assay or Platelet Function Analyser-100 (PFA-100) (DADE Behring, Germany) is a platelet function analyser that aspirates blood which anticoagulated by using sodium citrate solution, in vitro from a blood specimen into disposable test cartridges through a microscopic aperture cut into a biologically active membrane at the end of a capillary. The membrane of the cartridges are coated with collagen and adenosine diphosphate (ADP) or collagen and epinephrine inducing a platelet plug to form which closes the aperture. Anticoagulated whole blood passes through the membranes at a high shear rate to simulate the in vivo hemodynamics in the small capillaries. Platelets adhere to the membranes and gradually occlude a small aperture in the center of each membrane. The time, in seconds, for blood to completely occlude the aperture is referred to as the closure time (CT). Collagen and epinephrine closure time (COLL/EPI CT) <180 sec was determined as ASA resistance and collagen adenosine 5-diphosphate closure time (COLL/ADP CT) <120 sec was determined as clopidogrel resistance.[11-13] All ninety patients were using ASA and clopidogrel CT measurements of all patients were performed on the fifth day after MI. Group 1 and Group 2 were compared according to whether ASA and clopidogrel resistance were present. In addition, the association of ASA and clopidogrel resistance with coronary artery disease, classical risk factors, age, ejection fraction (EF), and laboratory values was compared in all patients.

STATISTICAL ANALYSIS

All statistical analyses were done by using SPSS 15.0 (SPSS for Windows 15.0, Chicago, IL) program. In order to compare the groups, "Student t-test" was used for continuous variables and "chi-square" test was used for categorical variables. Frequency (%) was used to represent the categorical variables and mean±standard deviation was used to represent the continuous variables. P values less than 0.05 were considered to be significant (p<0.05).

RESULTS

The mean CT for COLL/EPI was similar between the groups (Group 1: 221.4±64.8 sec, Group 2: 217.7±70.2 sec; p=0.81). ASA resistance (COLL/EPI CT <180 sec) was detected in 24 (26.7%) patients in the entire patient group. There was no difference between groups in terms of the ASA resistance [8 (26.7%) patients in Group 1, 16 (26.7%) patients in Group 2; p=1.0] (Table 1, Figure 1). Mean closure times for COLL/ADP were

TABLE 1: Demographic characteristics and laboratory results.

	Group 1	Group 2	p value
Age (year)	58.3±13.6	60.7±10.5	0.30
Gender (M/F)	23/7	39/21	0.26
EF (%)	32.8±6.9	35.4±7.4	0.11
ASA dosage (mg)	201.7±100.4	226.7±94.5	0.25
Hb (g/dL)	13.13±1.70	12.75±1.66	0.32
Hct (%)	39.35±5.13	38.19±4.78	0.29
Leukocyte (1000/µL)	9.88±3.11	10.37±2.14	0.38
Platelet (1000/µL)	257.27±61.80	262.00±47.12	0.67
Fibrinogen (g/dL)	4.33±1.89	4.68±2.11	0.44
Glucose (mg/dL)	112.33±35.59	107.67±33.72	0.54
Creatinin (mg/dL)	1.15±0.66	1.13±0.67	0.92
Uric Acid (mg/dL)	6.41±1.91	6.74±1.64	0.89
T. Chol (mg/dL)	170.07±50.98	152.33±48.20	0.11
LDL Chol (mg/dL)	99.80±44.20	74.78±38.10	0.007
HDL Chol (mg/dL)	37.83±10.17	41.12±13.71	0.25
Trigliserit (mg/dL)	160.60±79.05	169.92±81.15	0.60
Diabetes mellitus (n) (%)	9 (30%)	21 (35%)	0.64
Hypertension (n) (%)	12 (32.4%)	25 (41.7%)	0.58
Smoking (n) (%)	13 (34.2%)	25 (41.7%)	0.58
Coll/Epi CT (sec)	221.37±64.82	217.68±70.17	0.81
Coll/ADP CT (sec)	145.93±63.88	155.88±63.98	0.48
ASA resistance (+)	8 (26.7%)	16 (26.7%)	1.0
(Coll/Epi CT <180 sec) (n) (%)			
Clopidogrel resistance (+)	9 (30%)	18 (30%)	1.0
(Coll/ADP CT<120 sec) (n) (%)			

ASA: Acetyl salicylic acid; Coll/Epi CT: Collagen epinefrin closure time; Coll/ADP CT: Collagen adenosine diphosphate closure time; EF: Ejection fraction; Hb: Hemoglobin; Hct: Hematocrit; HDL Chol: High density lipoprotein cholesterol; LDL Chol: Low density lipoprotein cholesterol; T.Chol: Total cholesterol.

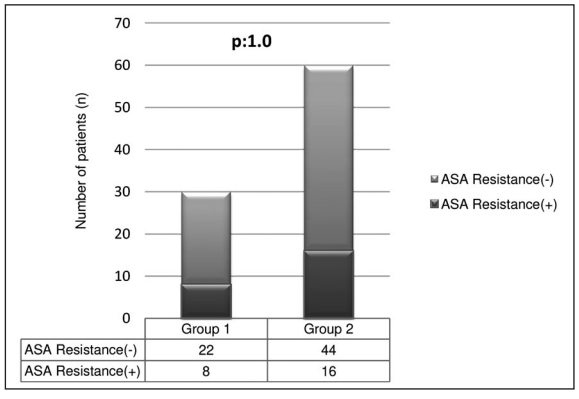

FIGURE 1: ASA resistance frequency between group 1 and group 2. Group 1: Patients with trombus; Group 2: Patients without thrombus; ASA: Acetyl salicylic acid.

similar between two groups (Group 1: 145.9±63.9 sec, Group 2: 155.9±63.9 sec; p=0.48). Clopidogrel resistance (COLL/ADP CT <120 sec) was detected in 27 (30%) patients in the entire patient group.

There was no difference between two groups in terms of the presence of clopidogrel resistance [9 (30%) patients in Group 1, 18 (30%) patients in Group 2; p=1.0] (Table 1, Figure 2). ASA and clopidogrel resistance together was detected in 19 (21.1%) patients in the entire patient group. There was no difference between the two groups in patients with both clopidogrel and aspirin resistance.

When the association of ASA and clopidogrel resistance with clinical and laboratory variables is examined; no significant difference was found between the groups in terms of biochemical parameters and risk factors except for the low density lipoprotein cholesterol levels (Group 1: 99.8±44.2 mg/dL, Group 2: 74.8±38.1; p=0.007) (Table 1). No significant difference was found between the patients with ASA resistance and those without ASA resistance in terms of gender (ASA resistance was detected in 19 of 62 male patients [30.6%], and 5 in 28 female patients [17.9%]; p=0.21). Similarly, no significant difference was found between those with and without clopidogrel resistance in terms of gender (ASA resistance was detected in 19 of 62 male patients [30.6%], and 8 in 28 female patients [28.2%]; p=0.84).

There was also no statistically significant difference between the ages of the subjects with and without resistance to both antiplatelet agents (There is ASA resistance: 63.3±11.2 years, there is no ASA resistance: 58.6±11.6 year; p=0.34; there is clopidogrel resistance: 61.8±8.2 year, there is no clopidogrel resistance: 59.0±12.8 year; p=0.30). There was no statistically significant difference in the EF levels of both antiplatelet resistance (There is ASA resistance: 35.7±7.7%, there is no ASA resistance: 34.1±7.2%; p=0.35; there is clopidogrel resistance: 34.3±7.7%, there is no clopidogrel resistance: 34.6±7.2%; p=0.88).

When the presence of resistance is compared with the risk factors of classical coronary artery disease, it has been shown that there was an ASA and clopidogrel resistance respectively in 12 (32.4%) and 13 (35.1%) of 37 patients with hypertension. Furthermore, it was also indicated that there was ASA and clopidogrel resistance respectively in 12 (22.6%) and 14 (26.4%) of 53 patients without hypertension (p=0.31 for the ASA resistance and p=0.37 for the clopidogrel resistance; respectively). There was ASA and clopidogrel resistance respectively in 8 (21.1%) and 8 (21.1%) of 38 patients who were smokers. However, there was ASA and clopidogrel resistance respectively in 16 (30.8%) and 19 (36.5%) of 52 patients who were not smokers (p=0.30 for ASA resistance and p=0.11 for clopidogrel resistance). There was ASA and clopidogrel resistance respectively in 12 (40%) and 9 (30%) of 30 patients with diabetes mellitus disease. However, there was ASA and clopidogrel resistance respectively in 12 (20%) and 18 (30%) of 60 patients without diabetes mellitus disease (p=0.043 for ASA resistance and p=1.0 for clopidogrel resistance). According to these findings, only ASA resistance was found statistically more in

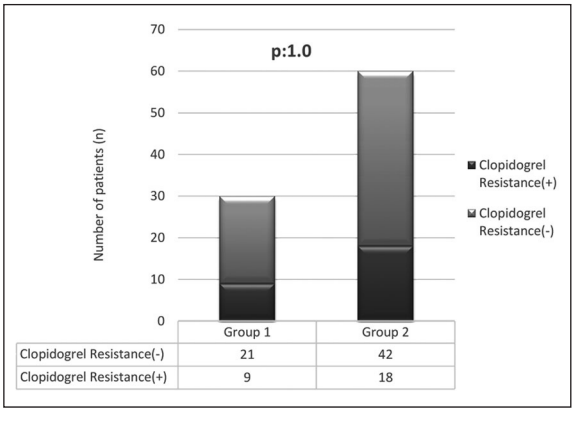

FIGURE 2: Clopidogrel resistance frequency between Group 1 and Group 2. Group 1: Patients with trombus; Group 2: Patients without thrombus.

TABLE 2: Relationship between ASA resistance and coronary artery disease risk factors.

	ASA resistance (+) (Coll/Epi CT <180 sec)	ASA resistance (-) (Coll/Epi CT >180 sec)	p value
Gender (M/F)	19 (30.6%)/5 (17.9%)	43 (69.4%)/23 (82.1%)	0.21
Age	63.3±11.2	58.6±11.6	0.34
EF (%)	35.7±7.7	34.1±7.2	0.35
HT	12 (32.4%)	25 (67.6%)	0.31
Smoking	8 (21.1%)	30 (78.9%)	0.30
DM	12 (40%)	18 (60%)	0.43

ASA: Acetyl salicylic acid; Coll/Epi CT: Collagen epinefrin closure time; Coll/ADP CT: Collagen adenosine diphosphate closure time; EF: Ejection fraction; HT: Hypertension; DM: Diabetes mellitus.

TABLE 3: Relationship between clopidogrel resistance and coronary artery disease risk factors.

	Clopidogrel resistance (+) (Coll/ADP CT <120 sec)	Clopidogrel resistance (-) (Coll/ADP CT >120 sec)	p value
Gender (M/F)	19 (30.6%)/8 (28.2%)	43 (69.4%)/20 (71.8%)	0.84
Age	61.8±8.2	59.0±12.8	0.30
EF (%)	34.3±7.7	34.6±7.2	0.88
HT	13 (35.1%)	34 (64.9%)	0.37
Smoking	8 (21.1%)	30 (78.9%)	0.11
DM	9 (30%)	21 (70%)	1.0

ASA: Acetyl salicylic acid; Coll/Epi CT: Collagen epinefrin closure time; Coll/ADP CT: Collagen adenosine diphosphate closure time; EF: Ejection fraction; HT: Hypertension; DM: Diabetes mellitus.

those with diabetes. Furthermore, neither ASA nor clopidogrel resistance was associated with other risk factors (Table 2, Table 3).

DISCUSSION

It has been shown that LV thrombus incidence is high among patients who have experienced acute MI. Even though large anterior infarcts with depressed LV systolic function is observed in the majority of the patients with LV thrombi, there can also be thrombi in small apical infarcts with good global systolic function.[14] Thrombus development following an acute MI has complex underlying mechanisms. These include blood stasis due to the LV regional wall akinesia or dyskinesia, subendocardial damage due to the prolonged ischemia, and hypercoagulability. LV thrombus is a severe complication of acute MI and which can lead to thromboembolism (such as an ischemic stroke). Thus, systemic embolism prevention should be the main focus of the LV thrombus treatment.[15]

Cardiovascular diseases are commonly treated with clopidogrel and ASA.[16,17] In order to prevent the secondary MI and stroke, low dose ASA is commonly used in clinics. Furthermore, low dose ASA is also used for the primary prevention of the cardiovascular diseases.[18] Vascular death, ischemic stroke and MI risks are reduced with the use of clopidogrel in patients with a cardiovascular disease background.[19]

Antiplatelet resistance is clinically defined as the occurrence of thrombotic and embolic vascular events despite the use of oral antiplatelets at therapeutic doses.[20,21] In the literature, ASA and clopidogrel resistances were detected respectively in the range of 4-30% and 5.5-45% in different groups of patients with different cardiovascular diseases by using different methods.[22] Antiplatelet resistance is determined either via the measurement of thromboxane products in blood or via the demonstration of thromboxane dependent aggregation in laboratory conditions. Thromboxane dependent aggregation is evaluated by using Optic agregometry, PFA-100, Ultegra

Rapid Platelet Function Assay (Ultegra RPFA), impedance agregometry, thrombelastography, multiple electrode aggregometry and VerifyNow system.[23] The measurement of blood thromboxane products is performed by detecting the serum thromboxane B2 level, urinary 11-dehydrotromboxane B2 level, soluble P-selectin level.[24]

In a large number of studies investigating the association of ASA resistance with clinical events, an increase from 1.8 to 4.1 fold in major cardiovascular events was detected.[25] Similarly, an increase in the frequency of stent thrombosis and major cardiovascular events was found in the presence of clopiogrel resistance.[26,27] The use of new P2Y12 inhibitors, such as prasugrel and ticagrelor, which adequately inhibit P2Y12-dependent platelet function in the vast majority of treated subjects, appears the best solution to the problem of clopidogrel resistance.[28] According to a recently published study, ticagrelor-based dual antiplatelet therapy reduces LV thrombus formation by nearly 50 percent in patients with ST-elevation MI compared to clopidogrel-based dual antiplatelet therapy.[29]

It has been shown that anticoagulant therapy is an effective way to prevent the thrombus formation even though there are contradictory findings about the effects of antiplatelet therapy on the thrombus formation prevention.[30] According to the WATCH trial in which 1,600 subjects with heart failure were examined, cerebrovascular events were similarly affected by warfarin, clopidogrel, and acetylsaliycilic acid. No difference between these three agents was found in terms of the LV thrombus formation.[31]

The effects of antiplatelet agents and resistance to these agents on the mural thrombus development after ST elevation MI were examined in this study. Two groups of patients were formed according to the LV thrombus formation at the echocardiographic examination. ASA and clopidogrel treatments were administered to all patients. In our study, ASA and clopidogrel resistances were respectively detected in 26.7% (n=24) and 30% (n=27) of patients. These findings are similar to those in the literature. Furthermore, no difference was detected between subjects with/without LV thrombus in terms of ASA or clopidogrel resistance. Consequently, we demonstrated that LV thrombus formation after MI cannot be prevented by antiplatelet agents.

There were some limitations to our study. For instance, the study population was not sufficiently large. Furthermore, the pharmacokinetics of clopidogrel may be affected by the concomitant use of lipophilic statins, nitrates, diuretics, other antihylipidemic or antihypertensive agents. However, in our study, we evaluated our patients only in terms of atorvastatin. In addition, the clopidogrel dose given to patients could be doubled to overcome clopidogrel resistance. However, this dose was not given to patients. The two-dimensional ECG is an effective and non-invasive method that is used to detect the LV thrombi; although the thrombus can possibly be masked by variable echo densities from the structures adjacent to the transducer, when visualized from the apical window. It is possible that transducer-related fixed artifacts may lead to an inappropriate impression of rounded apical mass or anatomic structures (false tendons or trabeculae), which would change the diagnosis. Furthermore, inadequate detection of <5-6 mm small thrombi is also possible.[12]

CONCLUSION

Although the number of patients in our study is low, and there is no detailed analysis in terms of applied treatments, both risk factors and biochemical variables were shown to have no effect on antiplatelet resistance for both groups. The lack of difference between the two groups in terms of antiplatelet resistance suggests that antithrombotics are ineffective against thrombus formation in the LV after MI.

In conclusion, there is a need for wider and controlled studies in order to determine whether antiplatelets reduce the frequency of mural thrombosis and related complications after MI.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct con-

nection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Mehmet Vedat Çaldır, Yeşim Akın;* ***Design:*** *Mehmet Vedat Çaldır;* ***Control/Supervision:*** *Yeşim Akın;* ***Data Collection and/or Processing:*** *Mehmet Vedat Çaldır;* ***Analysis and/or Interpretation:*** *Mehmet Vedat Çaldır, Yeşim Akın;* ***Literature Review:*** *Mehmet Vedat Çaldır;* ***Writing the Article:*** *Mehmet Vedat Çaldır;* ***Critical Review:*** *Yeşim Akın;* ***References and Fundings:*** *Mehmet Vedat Çaldır;* ***Materials:*** *Mehmet Vedat Çaldır.*

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