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Research Article

DOES CLOPIDOGREL RESISTANCE INCREASE OVER TIME? A PROSPECTIVE STUDY in ACUTE CORONARY SYNDROME PATIENTS

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ABSTRACT

Objectives: Acute coronary syndromes (ACS) are life-threatening manifestations of cardiovascular disease caused by thrombus after endothelial injury. Clopidogrel, a P2Y12 inhibitor, is widely used in ACS, but its antiplatelet response may reduce by drug interactions, inadequate dosing, and CYP2C19 polymorphisms, causes clopidogrel resistance (CR). Mean platelet volume (MPV), an indicator of platelet size and activation, has also been associated with adverse cardiovascular outcomes. This study evaluated to show temporal changes in CR and MPV, the relationship between them in ACS patients.

Materials and Methods: This single-center prospective study included 90 ACS patients aged 18–80 years treated with clopidogrel (600 mg loading dose followed by 75 mg/day). Blood samples for MPV and CR were obtained within 24 hours of admission and after one month defined as first and second analyses. Platelet aggregation analysed by Multiplate aggregometry. Cut off values were ≥460 AU(aggregation unit) for CR and ≥9.3 fL for MPV.

Results: Most patients were male (83.3%), the mean age was 57.4±10.2 years and hypertension was the most common risk factor (49%). While MPV values didn't differ between both analyses (8.58±0.75 vs 8.59±0.71 fL, p=0.89), CR significantly increased over time (254.76±180.9 vs 348.2±175.2 AU, p=0.0001). CR observed in 27 patients (32.35%) and MPV values were similar in these patients at both analyses. Among patients prescribed lipid-lowering therapy firstly, AU values increased significantly (251.08±170.34 AU vs 344.3 ±167.8 AU p=0.0001).

Conclusions: Clopidogrel resistance increased over time without parallel changes in MPV, suggested different mechanisms underlying clopidogrel response. So routine CR test should be limited to selected high-risk patients.

Keywords: coronary artery disease, acute coronary syndrome, clopidogrel, clopidogrel resistance, mean platelet volume

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INTRODUCTION

Despite substantial advances in prevention and treatment strategies, cardiovascular diseases continue to impose the greatest burden of illness and death worldwide (1). Acute coronary syndromes (ACS) are life-threatening manifestations of cardiovascular disease that typically occur when a thrombus forms on a ruptured atherosclerotic plaque, leading to reduced coronary blood flow. Platelets are fundamental contributors to arterial thrombus formation and serve as critical drivers in the initiation and progression of acute coronary syndromes. Usually, circulating platelets are inactive. When platelets are activated by endothelial injury, their shape changes, their volume increases, they secrete ADP (adenosine diphosphate), a procoagulant agent, from their dense granules and expose purinergic P2Y12 receptors (2, 3). Released ADP further activates surrounding platelets, promoting thrombus formation (4). Inhibition of this aggregation process by antiaggregant agents is the cornerstone of ACS treatment. To date, the oral P2Y12 receptor antagonists prasugrel, ticagrelor, and clopidogrel have been extensively employed in the management of coronary syndromes. Data derived from the PLATO and TRITON-TIMI trials indicate that prasugrel and ticagrelor achieve stronger P2Y12 receptor inhibition compared with clopidogrel, although this enhanced antiplatelet efficacy is accompanied by an increased risk of bleeding (5). According to contemporary European guidelines, dual antiplatelet therapy consisting of aspirin combined with a potent P2Y12 inhibitor (prasugrel or ticagrelor) is recommended for a duration of twelve months (level of evidence IB). Clopidogrel is advised in specific clinical scenarios, including contraindication or unavailability of prasugrel or ticagrelor, advanced age (e.g. ≥70 years), elevated bleeding risk, or when concomitant anticoagulant therapy is required in the treatment of ACS patients (level of evidence IC) (6). In contrast, the most recent European guidelines addressing chronic coronary syndromes recommend clopidogrel as a safe and effective alternative to aspirin monotherapy in patients with a previous myocardial infarction or remote percutaneous coronary intervention (PCI) (level of evidence IA) (7).

Clopidogrel is administered as an inactive prodrug that requires hepatic bioactivation through the cytochrome P450 system, predominantly via CYP2C19 enzymes, to exert irreversible inhibition of the P2Y12 receptor. The antiplatelet efficacy of clopidogrel is influenced by multiple variables, including drug–drug interactions, coexisting medical conditions, as well as genetic and epigenetic determinants (8). Due to these factors, clopidogrel response may diminish over time and fail to achieve adequate platelet inhibition in 20–65% of patients (9). Insufficient response to antiplatelet therapy causes new-onset or recurrent ischemic cardiovascular events, which may be partly attributable to clopidogrel resistance (CR) (10). The concept of CRencompasses both clinical and laboratory components. Clinical resistance refers to the occurrence of ischemic events despite appropriate clopidogrel therapy, whereas laboratory resistance is characterized by inadequate platelet inhibition as demonstrated by in vitro platelet function testing (PFT) (11). Laboratory CR is variable because it depends on the sampling time, analytic technique, and thresholds. This variability leads to differences in predicting ischemic and bleeding risks (13). Therefore, routine laboratory PFT is not recommended in current guidelines because they are time-consuming, not standardized and not cost-effective. It should be considered only in patients undergoing high-risk PCI who are known carriers of CYP2C19 loss-of-function allele (7).

Even though baseline platelet parameters cannot replace PFT, they can be performed easily and quickly to provide information about platelet status. Several clinical studies have demonstrated that baseline platelet function assessments are associated with impaired responsiveness to antiplatelet therapy and an increased risk of adverse cardiovascular outcomes (14). Commonly evaluated platelet-related parameters include platelet count (PCT), mean platelet volume (MPV), platelet large cell ratio (P-LCR), and platelet distribution width (PDW) (15). When platelets are activated by intrinsic and extrinsic factors such as ADP, hormones, proteins, neurotransmitters, infectious agents and endothelial injury, they become larger and more prone to aggregation (16). Higher MPV may adversely affect clinical outcomes through these mechanisms. Both CR and MPV have been investigated as markers of platelet function in various cardiovascular diseases (17).

We aimed to determine whether laboratory-defined CR increases during the first month after ACS despite standard dual antiplatelet therapy, and to evaluate its association with mean platelet volume and short-term clinical outcomes.

MATERIALS AND METHODS

This was a single-center, prospective, comparative study designed to evaluate temporal changes in CR and MPV in ACS patients. Following local ethics committee approval (Protocol No: 24.04.2013/115), all patients diagnosed with

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ACS, admitted to the Cardiology Clinic of Akdeniz University in Antalya between June 2013–March 2014 were included in the study. After obtaining informed consent from the patients, the type of ACS and coronary artery disease (CAD) risk factors were recorded. All patients received a 300 mg loading dose of clopidogrel. Patients undergoing PCI received a total loading dose of 600 mg, and were then prescribed 75 mg/day of clopidogrel and statins at discharge. Patients aged <18 or >80 years, those prescribed prasugrel or ticagrelor, those who did not receive the loading dose, those who had previously used anticoagulant drugs, those with active malignancy or bleeding, and those in whom antiaggregant therapy was contraindicated were excluded. A total of 90 patients were included in the study. After loading therapy, CR was analyzed in a hirudin-containing tube using the Multiplate® impedance aggregometer (Roche Diagnostics, Switzerland). Following stimulation with ADP, platelet adhesion and aggregation on the electrodes were recorded as aggregation units (AU). According to the manufacturer's recommendations and prior validation studies, an ADP-induced aggregation value >460 AU was considered indicative of CR (18). Mean platelet volume was analyzed in a citrate-containing tube by ADVIA 120 (Bayer Diagnostics, Tarrytown, USA), an automated complete blood count device. Because no clinically established MPV threshold exists for this setting, the MPV cut-off value (9.33 fL) was defined as the mean plus one standard deviation of the study population and was considered an exploratory threshold rather than a clinically validated cut-off. After clopidogrel loading therapy, both CR and MPV were analyzed within 24 hours and one month later by the same methods. Clopidogrel resistance and MPV were also analyzed during adverse clinical events defined as ACS, heart failure, shock, stroke. In both analyses, patients were divided into four subgroups according to the MPV elevation and presence of CR: subgroup 1: CR (+), MPV normal; Subgroup 2: CR (−), MPV high; Subgroup 3: CR(+), MPV high; Subgroup 4: CR (−), MPV normal).

Statistical analysis

All statistical analyses were performed using PASW version 18.0 (SPSS/IBM, Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation , whereas categorical variables were presented as number and percentage. The normality of continuous variables was assessed using visual (histograms, probability plots) and analytical methods. For comparisons between two independent groups, the independent samples t-test was used for normally distributed variables and the Mann–Whitney U test for non-normally distributed variables. For within-group comparisons of repeated measurements (first vs second analysis), paired samples t-test or Wilcoxon signed-rank test was applied, as appropriate. Changes in mean platelet MPV and aggregation unit AU values between the first and second analyses were evaluated using paired comparisons. Differences in MPV between CR and non-CR patients at each time point were assessed using independent samples t-test or Mann–Whitney U test, as appropriate. Categorical variables, including the prevalence of CR between the first and second analyses and subgroup distributions based on CR and MPV status, were compared using the chi-square test or Fisher's exact test when expected cell counts were <5. The change in the number of CR patients between the two time points was specifically analyzed using chi-square testing. Agreement between repeated MPV and AU measurements was evaluated using Bland–Altman analysis. Mean differences and 95% limits of agreement were calculated to determine the consistency between the first and second measurements. Due to the small number of adverse clinical events observed during follow-up, no inferential statistical analysis was performed for clinical outcome comparisons; results were reported descriptively. A two-tailed p-value <0.05 was considered statistically significant.

RESULTS

All patients underwent coronary angiography; medical follow-up was planned for 5 patients, while PCI was performed in 85 (94.4%) patients. The mean age of the patients was 57.4 ± 10.2 and 83.3% of patients were male. Among the patients, the most prevalent CAD risk factor was arterial hypertension (49%). Forty-eight patients (53.3%) were diagnosed with ST-elevation myocardial infarction (STEMI), 27 (30%) were diagnosed with non–ST-elevation myocardial infarction (NSTEMI) and 15 patients (16.7%) were diagnosed with unstable angina pectoris (USAP). Clinical characteristics of the patients were shown in Table 1.

The first and second values were compared. The 0.1 fL increase in mean MPV was not statistically significant (8.58 ± 0.75 fL vs 8.59 ± 0.71 fL, p = 0.89). On the other hand, the increase in mean AU values, which reflects CR (254.76 ± 180.9 AU vs 348.2 ± 175.2 AU, p < 0.001) was found to be statistically significant. Minimum, maximum and mean values of the MPV and AU were shown in Figure 1 and 2.

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Table 1. Clinical characteristics of the patients

Variable	n (%)
Sex	
Male	75 (83.3%)
Female	15 (16.7%)
Comorbidities	
Diabetes mellitus	33 (36.7%)
Arterial hypertension	44 (49.0%)
Dyslipidemia	21 (23.3%)
History of smoking	38 (42.0%)
Family history of CAD	22 (24.4%)
History of CVD	2 (2.2%)
History of PAD	1 (1.1%)
History of CAD	21 (23.0%)
Type of ACS	
USAP	15 (16.7%)
NSTEMI	27 (30.0%)
STEMI	48 (53.3%)

Data are presented as n (%). ACS: Acute coronary syndrome; CAD: Coronary artery disease; CVD: Cerebrovascular disease; NSTEMI: Non–ST-segment elevation myocardial infarction; PAD: Peripheral arterial disease; STEMI: ST-segment elevation myocardial infarction; USAP: Unstable angina pectoris.

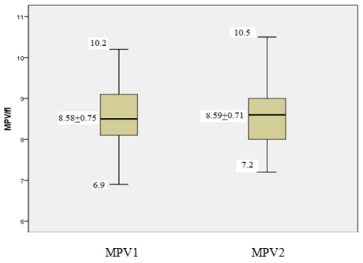

Figure 1. Distribution of MPV values in the first and second analyses. MPV: Mean platelet volume; MPV1: First MPV values; MPV2: Second MPV values.

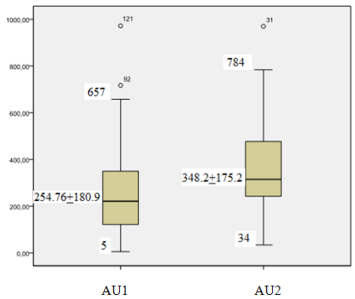

Figure 2. Distribution of AU values in the first and second analyses. AU: Aggregation units; AU1: First AU values; AU2: Second AU values

Both in the first and second analyses, the changes of mean MPV in clopidogrel resistant and non-resistant patients were within the normal range, and this difference was not statistically significant (First analysis: 8.62 fL vs 8.56 fL, p = 0.62; Second analysis: 8.52 fL vs 8.62 fL, p = 0.51). During the first analysis, 11 patients were diagnosed CR. During the second analysis, while 4 of these became drug responders, CR remained in 7 of them and a total of 23 patients were classified as CR with the addition of 16 new patients. At the second analysis, the number of patients with CR increased significantly (11 vs 23, p = 0.012). Seventeen of these 23 patients belonged to subgroup 1 (n=5) or subgroup 4 (n=12), both characterized by MPV values <9.3 fL. In both the first and second analyses, changes in subgroup numbers are shown in Table 2.

Table 2. Changes in subgroup distribution between the first and second analyses

		Second analysis				
		Subgroup 1	Subgroup 2	Subgroup 3	Subgroup 4	Total
First analysis	Subgroup 1	5	0	1	3	9
	Subgroup 2	3	1	0	7	11
	Subgroup 3	0	0	1	1	2
	Subgroup 4	12	8	1	47	68
	Total	20	9	3	58	90

In our study, CR was detected in 27 patients (32.35%). The most observed comorbidity in drug resistant patients was diabetes mellitus (DM) (52%) (p = 0.5). Other comorbidities included arterial hypertension (47%), smoking (33.3%), hyperlipidemia (29%), and chronic renal failure (3.7%). In the study cohort, 80 patients had not been prescribed statins previously; therefore, all were prescribed statins at discharge. At the second analysis time, the increase of AU values reflecting CR in these 80 patients (251.08 ± 170.34 AU vs 344.3 ± 167.8 AU) was found to be statistically significant (p < 0.001).

The consistency between MPV and AU values in both times was analyzed by Bland–Altman method. The mean difference between the first and second MPV values was found to be 0.014 fL, 95% CI: −0.18 to 0.15. Consequently, 96.7% consistency was observed between the first and second MPV values. The mean difference in AU values for CR was −91.56 AU, 95% CI: −129.64 to −53.47 AU. Only five patients' values were out of the confidence interval, resulting in 94.5% agreement between the first and second AU measurements. The results were shown in Figure 3 for MPV and Figure 4 for clopidogrel resistance.

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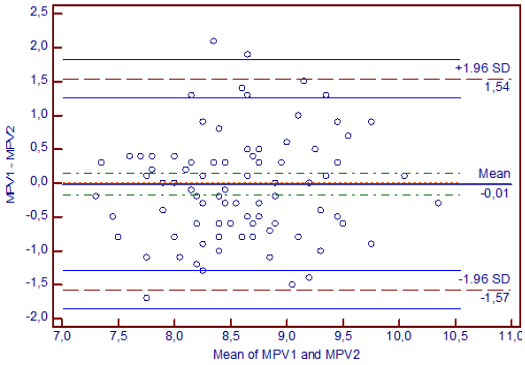

Figure 3. Bland–Altman plot of MPV1 and MPV2 demonstrating mean difference and 95% limits of agreement. MPV: Mean platelet volume; MPV1: First MPV values; MPV2: Second MPV values.

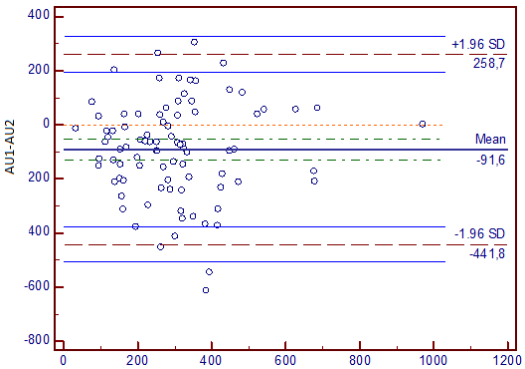

Figure 4. Bland–Altman plot of AU1 and AU2 demonstrating mean difference and 95% limits of agreement. AU: Aggregation units; AU1: First AU values; AU2: Second AU values.

No bleeding was observed in study patients. However, adverse clinical events were observed in four patients (one case of cerebrovascular disease, one case of congestive heart failure and two case of ACS events). Study parameters were performed in these patients, but due to the small number, statistical analysis wasn't performed.

DISCUSSION

In this study, we evaluated temporal changes in MPV and laboratory-defined CR and their impact on short-term prognosis in patients with ACS. We performed a double assessment of platelet reactivity assuming the changes in MPV and CR over time. The main findings of our study were the similarity in MPV values in both analysis times and the significant increase of CR and the number of the clopidogrel resistant patients in the second analysis time.

Although CR has been associated with adverse cardiovascular outcomes, the lack of standardized definitions and testing methodologies remains a major limitation. According to most trials, light transmission aggregometry (LTA) is the gold standard method to assess platelet functions but it is cumbersome and not well standardized (19-21). To find the best, CR was analyzed and compared by different methods in trials. Gegri et al. performed CR by VerifyNow Device (VND, threshold of 195 units), LTA (threshold of 40%) and whole blood impedance aggregometry (WBIA, threshold of 5 Ohms) in 96 patients who underwent interventional neuroradiological procedures for five years; consequently, all the three tests were 55% concordant (53/96) and 45% discordant (43/96). When the discordance was analyzed, 37 (28%) of these patients were responsive by VND and resistant by WBIA/LTA, 6 (7%) of these patients were resistant by VND but responsive by WBIA/LTA. The discordant groups differed in platelet counts and hematocrits. According to the Gegri's trial, impedance aggregometry and LTA were found to be concordant methods (22). Similarly, we analyzed CR by impedance aggregometry; however, our threshold to define CR was 460 AU and we compared CR and MPV as a baseline platelet parameters.

Depending on the laboratory methods and clinical factors, CR varies between 2%–30%. In our study, CR prevalence was 32.35% (10). While the mean AU value reflects CR and number of drug resistant patients increased significantly, mean MPV values were found to be similar. In addition, a significant proportion of these clopidogrel patients (17/23) had normal MPV values during the second analysis time. Both results showed that MPV did not have a significant effect on CR. Li et al. evaluated mean platelet volume (MPV) and laboratory-defined CR using the vasodilator-stimulated phosphoprotein (VASP) assay in 196 patients with non-cardioembolic stroke and reassessed the cohort after six months of follow-up (15). The incidence of clinical CR was significantly higher among patients with laboratory-confirmed resistance compared with those without laboratory resistance (χ^2 = 7.782, p = 0.005). Elevated MPV levels (⩾10.6 fL) were identified as an independent risk factor for clinical resistance (OR = 2.288; 95% CI: 1.088 – 4.814; p = 0.029). In contrast, mean MPV values did not differ significantly between the laboratory resistance and non-resistance groups (10.63 ± 0.98 vs 10.50 ± 0.89, p > 0.05). Similar to our results, Li et al. showed that MPV and laboratory CR weren't associated, but they detected that presence of DM (6.89 ± 2.31 vs 6.43 ± 1.66%, p = 0.01) and CYP2C19 polymorphisms were found to be significant risk factors for CR (CYP2C19 [636G>A], odds ratio [OR] = 2.894, 95% confidence interval [CI]: 1.427–5.552, p = 0.003; CYP2C19 (681G>A), OR = 2.654, 95% CI:

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1.401–5.027, p = 0.003). We didn't perform genetic analysis due to its high cost and clinical CR due to the small number of patients but we observed that more than half of our CR patients were diagnosed with diabetes mellitus. It is possible that this association might have reached statistical significance in a larger cohort (14/27, 52%, p = 0.5).

During the second analysis time, the number of clopidogrel-resistant patients increased significantly. Response to clopidogrel depends on analytic technique, inappropriate dosing, non-compliance, drug-drug interactions, comorbidities and polymorphism of P2Y12 receptor and CYP3A4 enzymes (10). Urban et al. performed prasugrel, clopidogrel, and ticagrelor response by VASP and platelet function assay (PFA) methods in 81 patients who underwent complex PCI on the first day and 30 days after PCI (23). They observed that both the number of ticagrelor and clopidogrel resistant patients decreased significantly by two different methods (Clopidogrel VASP: 59% vs 50%, PFA: 50% vs 34.1%; Ticagrelor VASP 12.1% vs 9.1%; PFA 15.2% vs 3%, p < 0.05). They analyzed CR by VASP, which requires flow cytometry, and by PFA, which is less sensitive than other methods; but we analyzed CR by impedance aggregometer which was more sensitive and more specific.

Clopidogrel is activated by CYP3A4. Atorvastatin is a lipid lowering drug, another CYP3A4 substrate that may competitively inhibit its activation. In our study, 88% of patients had not previously been prescribed statins and were initiated on statin therapy as part of ACS management according to current guidelines. In these 80 patients, drug–drug interactions via CYP450 pathways may have contributed to the observed increase in mean AU values. However, this association cannot establish causality in our dataset and should be interpreted as hypothesis-generating. Similar to our findings, Lau et al. reported that atorvastatin attenuated the antiplatelet effect of clopidogrel in patients with acute coronary syndrome in a dose-dependent manner; however, this interaction has not been consistently validated in large-scale clinical studies. Platelet inhibition values increased progressively in the presence of clopidogrel with atorvastatin doses of 0, 10, 20, and 40 mg (34 ± 23, 58 ± 15 [p = 0.027], 74 ± 10 [p = 0.002], and 89 ± 7 [p = 0.001], respectively) (24-26). In addition, 66.7% of the clopidogrel resistant patients were non-smokers in our study. A high proportion of CR among non-smokers was observed; however, nicotine-induced CYP450 enzyme induction may partly explain enhanced clopidogrel responsiveness in smokers. Similarly to our results, Bliden showed that current smokers treated with clopidogrel displayed significantly lower platelet aggregation and ADP-stimulated active GP IIb/IIIa expression compared with non-smokers (p < 0.001 for both) and in a multivariate Cox regression analysis, they found that current smoking was an independent predictor of platelet aggregation (p < 0.001) (27).

Treatment adherence may represent one of the potential contributors to variability in clopidogrel response. Agreement between repeated AU measurements was 94.5% according to Bland–Altman analysis, indicating overall consistency of measurements. However, the magnitude of change observed in some patients may raise the possibility of suboptimal adherence. Since treatment adherence was assessed only through patient self-report and was not objectively verified, this interpretation should be considered speculative. The observed increase in the number of patients classified as clopidogrel-resistant at one month may therefore reflect multifactorial influences rather than confirmed non-compliance alone.

Limitations

The absence of standard predictive values for MPV and CR resulted in variable findings depending on the method and the small sample size. A larger sample size might have yielded more robust statistical findings. The higher AU values observed at the second analysis suggested potential treatment adherence issues. Treatment adherence was assessed based on patients' verbal reports. MPV and CR measurements could not be performed at later follow-up intervals due to financial limitations. Furthermore, genetic analysis could have been performed to examine the relationship between CR and genetic variations, but we were unable to perform genetic analysis due to financial limitations.

CONCLUSION

In our study, the lack of parallelism between the increase in CR and MPV in vitro conditions, the significant decrease of clopidogrel response in patients who were prescribed statins, and high prevalence of CR in non-smokers suggested that there may be different mechanisms in the development of CR. Consequently, assessing the antiplatelet effect of P2Y12 inhibitors to predict adverse cardiovascular events is important. Current clinical guidelines do not support the routine use of platelet function testing. Instead, such testing may be considered in selected high-risk patients undergoing PCI, including those with complex left main disease, two-stent bifurcation techniques, suboptimal stent deployment, a history of stent thrombosis, or known CYP2C19*2/*3

polymorphisms, particularly when escalation from aspirin plus clopidogrel to aspirin combined with ticagrelor or prasugrel is contemplated. However, this recommendation is supported by weak evidence (Class IIb, Level C), largely due to the substantial variability among platelet function testing methodologies and the dynamic nature of CR over time (7).

Acknowledgments
None.

Data availibity statement
The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of competing interest
The authors declare no competing interests.

Ethics
Ethical approval for the study was obtained from the Local Ethics Committee of Akdeniz University (Protocol No: 24.04.2013/115).

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