Acta Cardiol Sin 2016;32:321–327
Original Article
doi: 10.6515/ACS20150727A

Cardiac Pharmacology

Antiplatelet Effect of Sequential Administration of Cilostazol in Patients with Acetylsalycilic Acid Resistance

Muzaffer Cakmak,[1] Bora Demircelik,[2] Mustafa Cetin,[3] Zehra Cetin,[3] Serhat Isık,[4] Hulya Cıcekcıoglu,[3] Feridun Vasfi Ulusoy[3] and Beyhan Eryonucu[2]

Background: Acetylsalicylic acid (ASA) resistance in patients with coronary artery disease is an important medical problem that can affect treatment decision-making and outcomes. Cilostazol has been investigated to determine its effectiveness in patients with acetylsalicylic acid resistance. The aim of this study was to evaluate the antiplatelet efficacy of sequential administration of CLZ in patients with ASA resistance.

Methods: A total of 180 patients were enrolled in our study. Patients with stable coronary artery disease were first given orally ASA 100 for 10 days, followed by collagen/epinephrine induced closure time (CTCEPI) measurements. Those who were found to be resistant to orally 100 mg of ASA were given orally 300 mg of ASA for an additional 10 days after which we repeated CTCEPI measurements. Those patients with resistance to orally 300 mg ASA were then given CLZ at a daily dose of orally 200 mg for 10 days followed by a final CTCEPI measurement.

Results: The rate of resistance to 100 mg ASA was 81/180 (45%) compared to a rate of 35/81 (43.2%) with 300 mg ASA. Of the 35 patients found to be resistant to 300 mg ASA, 22 (62.9%) also failed to respond to CLZ treatment. Overall, sequential administration of 300 mg ASA and 200 mg CLZ resulted in a reduction in the number of non-responders from 45% to 12.2%.

***Conclusions*:** Initiation of CLZ could be of benefit in some patients with ASA-resistance for whom an effective anti-aggregant effect is of clinical importance.

Key Words: Angina pectoris • Cardiovascular outcome • Pharmacodynamics

INTRODUCTION

Acetylsalicylic acid (ASA), which inhibits the aggregation of platelets by irreversible inhibition of cyclooxygenase-1, has been shown to reduce the risk of cardiovascular events by approximately 25%.[1] However, about 10-20% of patients treated with ASA experience recurrent ischemic events within 5 years, otherwise known as clinical ASA resistance.[2,3]

High-dose ASA or combination therapies are treatment strategies that have been suggested to overcome this problem, although neither approach is routinely recommended in stroke patients. A meta-analysis showed that high-dose ASA (500-1500 mg/day) was no more effective than low-dose ASA (75-325 mg) for preventing cardiovascular events, and was instead associated with an increased risk of bleeding complications.[2-4] A similar increased risk of bleeding in stroke patients has been reported when ASA is used in combination with other drugs, which undermines the potential benefits of the added antiplatelet effect provided by such drug combinations.[5,6]

Received: February 26, 2015 Accepted: July 27, 2015
[1]Department of Internal Medicine; [2]Department of Cardiology, Turgut Ozal Unıversity; [3]Department of Cardiology; [4]Department of Endocrinology, Ankara Numune Education and Research Hospital.
Address correspondence and reprint requests to: Dr. Bora Demırcelık, Department of Cardıology, Turgut Ozal Unıversıty, Ankara, Turkey. Tel: 0905052663748; Fax: 0903123462388; E-mail: drdemircelik@yahoo.com

Cilostazol (CLZ) is a phosphodiesterase inhibitor that has gained approval by the US Food and Drug Administration for the treatment of intermittent claudication.[7] Recent studies have shown that the addition of CLZ to ASA treatment prevented the development of restenosis after coronary stenting or progression of symptomatic intracranial stenosis, prompting the use of this drug combination after percutaneous coronary intervention and for the treatment of a select group of stroke patients.[8-10] Some studies have shown that addition of CLZ to other antiplatelet agents does not prolong bleeding time.[11-13]

The aim of this study was to evaluate the antiplatelet efficacy of sequential administration of CLZ in patients with ASA resistance.

MATERIALS AND METHODS

Patient selection

Patients presenting to the outpatient clinics with stable coronary artery disease (CAD) were approached for enrollment into the study and consenting patients were screened for eligibility. Patients with abnormal blood counts, hepatic or renal disease, or those taking drugs known to affect platelet function were excluded. The study protocol was approved by the local ethics committee and written informed consent was obtained from all patients.

Measurements of ASA resistance

ASA resistance was evaluated by measuring collagen/epinephrine induced closure time (CTCEPI) using a PFA-100 automated test system which simulates platelet-based hemostasis *in vitro*. The test cartridge simulates an injured blood vessel and measures the time required to form a platelet plug, defined as closure time (CT), that occludes a microscopic aperture cut into a collagen/epinephrine- or collagen/ADP-coated membrane under a high shear flow condition.[14,15] The collagen/epinephrine cartridge is the primary cartridge for detecting aspirin effect on platelet aggregation. All blood samples were tested according to manufacturer instructions not earlier than 30 min after and within 2 hours of blood sampling. The maximal CT for collagen/epinephrine cartridges is 300 s and values greater than 300 s are reported as non-closure. ASA resistance is defined as the presence of a normal CTCEPI (82-165s) despite at least 7 days of ASA treatment.

Study design

All patients were first given ASA at a daily dose of 100 mg (ASA100) for a period of 10 days after which CTCEPI was measured. Patients found to be resistant to 100 mg ASA were subsequently given 300 mg ASA (ASA300) for an additional 10 days after which CTCEPI measurements were repeated. Finally, patients with resistance to 300 mg ASA were prescribed CLZ at a daily dose of 200 mg for 10 days, followed by a final measurement of CTCEPI (Figure 1).

Statistical analysis

Data analyses were performed using the Statistical Package for Social Sciences (SPSS) version 13.0 software (SPSS Inc., Chicago, IL, USA). Values for discrete variables are provided as mean ± standard deviation, whereas percentages are used for categorical variables. Comparisons of categorical variables were performed using Pearson's Chi-square test or, in the event of an expected cell size of 5, Fisher's exact test. Numerical variables were compared using the Mann-Whitney U test, and Spearman's correlation analysis was used to evaluate correlations between variables. Multiple logistic regression analysis was performed searching for factors associated with

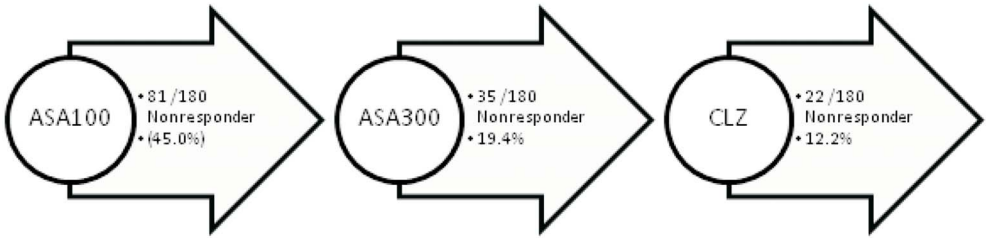

Figure 1. *Response rates of the antiplatelet treatments given to participants in the study. ASA, acetylsalicylic acid; CLZ, cilostazol.*

non-responders in the ASA 100 and 300 mg groups. In all analyses, p-values of < 0.05 were considered statistically significant.

RESULTS

A total of 180 (91 male, 88 female) patients with stable CAD were included in the study, with an overall mean age of 60.6 ± 8.9 (41-83) years. Eighty-one (45%) of the patients were resistant to 100 mg of ASA, of which 35 patients (43.2%) also failed to respond to 300 mg ASA. Finally, out of the 35 non-responders to 300 mg ASA, 22 (62.9%) did not respond to CLZ. Overall, the non-response rate to any of the medications was 12.2% (22/180). A comparison of responders and non-responders in each of the three groups (ASA100, ASA300 and CLZ) revealed a higher frequency of male patients among responders in the ASA100 group compared to non-responders in the same group (69.1% vs. 36.0%; p = 0.003). Moreover, significantly more responders in the ASA300 were taking beta blockers compared to non-responders in the same group (89.1% vs. 71.4%, p = 0.04). A summary of intergroup comparison is provided in Table 1.

Mean CTCEPI values of non-responders after administration of 100 mg and 300 mg of ASA were significantly lower than those in responders to CLZ (ASA100 100.8 ± 27.3 vs. 131.1 ± 21.5; p = 0.04; ASA300 104.5 ± 23.0 vs. 131.2 ± 22.3; p = 0.001). There was no significant difference between responders and non-responders to CLZ with regard to mean age, body mass index, waist circumference, systolic and diastolic blood pressure, values of complete blood counts and serum levels of high sensitive C-reactive protein, homocysteine, fibrinogen, insulin, fasting blood glucose and HbA1c (Table 2).

CTCEPI values of patients in the ASA100 group showed a negative correlation with Hb (r = -0.29, p =0.01) and hematocrit (r = -0.35, p = 0.002), while having apositive correlation with CTCEPI values in the CLZ group (r = 0.63, p = 0.007) and total cholesterol levels (r = 0.28, p = 0.01). On the other hand, CTCEPI values of the

Table 1. Comparison of baseline characteristics of responders and non-responders to treatment with 100 mg ASA, 300 mg ASA100, and 200 mg CLZ

Variables	ASA100			ASA300			CLZ		
	Non-responders (n = 81)	Responders (n = 99)	p-value	Non-responders (n = 35)	Responders (n = 46)	p-value	Non-responders (n = 22)	Responders (n = 13)	p-value
Male gender, n (%)	56 (69.1)	35 (36)	0.003	26 (74.3)	30 (65.2)	0.38	17 (77.3)	9 (69.2)	0.60
Smoking, n (%)	24 (29.6)	20 (20)	0.35	13 (37.1)	11 (23.9)	0.20	6 (27.3)	7 (53.8)	0.12
HT, n (%)	55 (67.9)	75 (76)	0.44	24 (68.6)	31 (67.4)	0.91	16 (72.7)	8 (61.5)	0.49
HPL, n (%)	61 (75.3)	79 (80)	0.63	27 (77.1)	34 (73.9)	0.74	17 (77.3)	10 (76.9)	0.98
Family history of CAD, n (%)	27 (33.3)	51 (52)	0.09	14 (40.0)	13 (28.3)	0.27	8 (36.4)	6 (46.2)	0.57
MI, n (%)	46 (56.8)	59 (60)	0.78	21 (60.0)	25 (54.3)	0.61	14 (63.6)	7 (53.8)	0.57
SVD, n (%)	36 (44.4)	51 (52)	0.51	15 (42.9)	21 (45.7)	0.80	8 (36.4)	7 (53.8)	0.31
MVD (%)	45 (55.6)	47 (48)	0.65	20 (57.1)	25 (54.3)	0.83	14 (63.6)	6 (46.2)	0.31
DM, n (%)	52 (64.2)	47 (48)	0.17	23 (65.7)	29 (63.0)	0.82	17 (76.9)	8 (59.1)	0.24
Beta blocker, n (%)	66 (81.5)	87 (88)	0.55	25 (71.4)	41 (89.1)	0.04	16 (72.7)	9 (69.2)	0.56
ACEI, n (%)	31 (38.3)	51 (52)	0.22	10 (28.6)	21 (45.7)	0.12	7 (31.8)	3 (23.1)	0.58
ARB, n (%)	29 (35.8)	35 (36)	0.99	14 (40)	15 (32.6)	0.49	9 (40.9)	5 (38.5)	0.89
CCB, n (%)	16 (19.8)	20 (20)	0.98	7 (20)	7 (19.6)	0.96	4 (18.2)	3 (23.1)	0.73
Statin, n (%)	46 (56.3)	59 (60)	0.82	16 (47.1)	29 (63)	0.15	12 (52.4)	43 (38.5)	0.50

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; CAD, coronary artery disease; CCB, calcium channel blocker; CLZ, cilostazol; DM, diabetes mellitus; HPL, hyperlipidemia; HT, hypertension; MI, myocardial infarction; MVD, multi vessel disease; SVD, single vessel disease.

Table 2. Comparison of responders and non-responders to cilostazol

Variables	Responder (n = 13)	Non-responders (n = 22)	p-value
Age, years	59.2 ± 11.9	62.9 ± 7.3	0.16
BMI, kg/m^2	29.0 ± 5.8	27.5 ± 4.4	0.53
Waist circumference	102.5 ± 12.6	100.1 ± 6.2	0.50
SBP, mmHg	137.7 ± 24.9	124.7 ± 21.6	0.10
DBP, mmHg	83.1 ± 17.0	75.4 ± 11.5	0.16
Insulin	13.0 ± 13.4	6.5 ± 2.4	0.16
FBG, mg/dl	96.3 ± 21.5	105.2 ± 50.9	0.73
HbA1c, %	7.5 ± 2.0	8.7 ± 2.2	0.70
TC	187.8 ± 59.5	174.5 ± 43.8	0.68
TG	167.0 ± 73.4	150.5 ± 82.0	0.50
HDL-C	33.5 ± 5.9	35.2 ± 8.3	0.78
LDL-C	123.0 ± 53.4	109.4 ± 31.5	0.59
Hb, g/dl	14.5 ± 1.8	14.4 ± 1.2	0.71
Platelet	233.0 ± 96.2	253.6 ± 66.3	0.45
Htc, %	42.5 ± 5.5	42.5 ± 3.3	0.97
MPV, fL	8.9 ± 0.7	8.8 ± 1.0	0.97
Uric acid	6.2 ± 1.8	5.8 ± 0.9	0.82
hsCRP	3.7 ± 4.3	2.8 ± 4.0	0.94
Hcy	17.5 ± 10.3	17.4 ± 12.0	0.94
Fibrinogen	373.5 ± 74.3	357.5 ± 68.5	0.57
ASA100 CTCEPI	131.1 ± 21.5	100.8 ± 27.3	0.04
ASA300 CTCEPI	131.2 ± 22.3	104.5 ± 23.0	0.001
CLZ CTCEPI	275.0 ± 43.2	119.2 ± 19.1	< 0.001

ASA, acetyl salicylic acid; BMI, body mass index; CLZ, cilostazol; CTCEPI, collagen/epinephrine induced closure time; DBP, diastolic blood pressure; FBG, fasting blood glucose; Hb, hemoglobin; Hcy, homocysteine; HDL, high dansity lipoprotein; hsCRP, high sensitive c reactive protein; Htc, hematocrit; LDL, low dansity lipoprotein; MPV, mean platelet volüme; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

ASA300 only showed a positive correlation with CTCEPI values in the CLZ group ($r = 0.56$, $p < 0.001$). The results of correlation analysis are summarized in Table 3.

We performed multivariate logistic regression including variables to assess the independent predictors of non-responders in the ASA100 and 300 mg groups. Multiple logistic regression analysis revealed the factors associated with ASA resistance: a history of current smoking (odds ratio 1.34, 95% confidence interval 0.75-2.36) (Table 4).

DISCUSSION

In our study, the antiplatelet effect of ASA was observed in 55% of patients at a dose of 100 mg, compared to a response rate of 80.6% when the dose was increased to 300 mg. Sequential administration of CLZ increased the rate of an effective antiplatelet response to 87.8%. The effect of CLZ on "anti-platelet naïve" patients was not evaluated.

Platelets are the first line of defense against the loss of endothelium integrity due to their ability to adhere to injured vessels and to accumulate at sites of vascular injury. Not only do they play an important role in physiologic hemostatic balance, they have also been shown to release several bioactive mediators involved in inflammation, atherogenesis and atherothrombosis.[16]

The beneficial effects of ASA in decreasing the risk for cardiovascular disease in diabetic or non-diabetic patients with CAD are undisputable.[2,17] However, the presence of ASA resistance robs some patients of the protective effects of the drug against atherothrombotic cardiovascular diseases.[18-21] Cilostazol is an oral phosphodiesterase III inhibitor with several identified pleiotropic effects such as vasodilation as well as the inhibition of platelet function and of vascular smooth muscle cell growth.[22] It gained FDA approval for the treatment of patients with symptomatic peripheral artery disease, an indication for which clinical safety has been proven.[23]

To date, several studies have evaluated the efficacy of CLZ in combination with other antiplatelet medications. In one such study where triple antiplatelet therapy (aspirin plus cilostazol plus clopidogrel or ticlopidine) was given to patients following placement of a coronary artery stent, CLZ was reported to be associated with a more effective antithrombotic effect.[24] In another study on patients with diabetes mellitus, a triple combination of antiplatelet medications, one of which was CLZ, was found to be superior to dual therapy (without CLZ) in terms of rate of restenosis following implantation of drug-eluting stents.[24] In a study where two different dual combinations were compared, angiographic restenosis occurred significantly less frequently in patients receiving ASA plus CLZ compared to patients who were given ASA and clopidogrel.[25] A recent meta-analysis showed CLZ to be a safe and effective treatment option for the reduction of risk of restenosis and repeat revascularization following PCI.[26]

We did not observe the association between platelet reactivity and cardiovascular risk factors except for

Table 3. Results of correlation analysis between CTCEPI values and several parameters for the three treatment groups

Variables	CLZ CTCEPI		ASA 100 CTCEPI		ASA 300 CTCEPI	
	r	p-value	r	p-value	r	p-value
CLZ CTCEPI	1.00	-	0.63	0.007	0.56	< 0.001
ASA 100 CTCEPI	0.63	0.007	1.00	-	0.04	0.82
ASA 300 CTCEPI	0.56	< 0.001	0.04	0.82	1.00	-
Age	-0.19	0.27	-0.10	0.40	-0.01	0.97
WC	0.07	0.68	-0.18	0.13	-0.24	0.06
Insulin	0.22	0.32	-0.10	0.51	0.04	0.82
FBG, mg/dl	0.08	0.64	0.22	0.06	-0.20	0.11
HbA1c, %	-0.08	0.83	0.14	0.48	-0.18	0.49
TC	0.06	0.75	0.28	0.01	-0.19	0.14
TG	0.02	0.89	0.14	0.21	-0.19	0.13
HDL-C	0.13	0.44	0.19	0.10	0.11	0.38
LDL-C	0.09	0.63	0.17	0.15	-0.16	0.19
Hb, g/dl	0.04	0.84	-0.29	0.01	0.08	0.55
Platelet	0.11	0.52	0.12	0.29	-0.09	0.46
Htc, %	-0.01	0.94	-0.35	0.002	0.17	0.18
MPV, fL	-0.09	0.59	0.001	1.00	-0.18	0.16
Uric acid	0.02	0.92	-0.18	0.13	-0.21	0.10
hsCRP	0.06	0.74	-0.03	0.82	-0.15	0.25
Hcy	0.10	0.60	-0.17	0.17	0.08	0.54
Fibrinogen	0.04	0.82	0.004	0.97	-0.06	0.63
BMI	0.14	0.41	0.03	0.79	0.03	0.83

Abbreviation as Table 2.

Table 4. Multivariate logistic regression analysis for the predictors of non-responder ASA 100 and 300 mg groups

Variables	OR (95% CI)	p value
Age (per year)	1.11 (0.92-2.13)	0.49
Male	0.63 (0.31-1.54)	0.45
BMI (kg/m^2)	0.84 (0.72-1.91)	0.34
SBP (mm/Hg)	0.89 (0.93-1.11)	0.17
DBP (mmHg)	0.95 (0.13-1.00)	0.14
TC (mg/dl)	1.22 (0.97-1.74)	0.18
TG (mg/dl)	1.03 (0.87-1.47)	0.82
LDL-c (mg/dl)	1.22 (0.73-1.51)	0.26
HDL-c (mg/dl)	0.51 (0.08-1.16)	0.19
FBG (mg/dl)	0.62 (0.58-1.35)	0.35
CRP (mg/L)	1.33 (1.15-1.83)	0.30
Smoking habits	1.34 (0.75-2.36)	0.003
On ACEI/ARB	0.79 (0.35-1.78)	0.57

All values are presented as mean ± SD, median value (interquartile range) or n (%).
ACEI/ARB, (on the use of) angiotensin converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; DBP, diastolic blood pressure; FBG, fasting glucose; HDL-c, high density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; OR, odds ratio; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

current smoking. In the literature there are some reports about increased AR in people taking ASA and smoking.[26,27] The concentration of 8-izo-PGF2α, the prostaglandin synthesized from arachidonic acid in non-enzymatic process catalyzed by free radicals, is elevated in smokers. This substance increases the platelet response to agonists used in the laboratory tests.[28-30]

We were unable ascertain any parameter that could be used to predict the antiplatelet efficacy of CLZ prior to initiation of treatment. Resistance to 100 mg of ASA was observed more frequently in men. In a similar study, lower CT values were reported in men compared to women, although the difference was deemed statistically insignificant.[31] No significant differences between responders and non-responders to CLZ were observed in our patient population with regards to baseline characteristics, metabolic and lipid parameters, values on blood counts and levels of inflammatory markers. The lack of any significant difference could be attributed to the fact that all patients who received CLZ had confirmed ASA resistance, which is a distinguishing characteristic of this study.

CONCLUSIONS

Our study findings show that administration of 100-300 mg of ASA provides sufficient anti-platelet activity in the majority of patients. Initiation of CLZ could be of benefit in some patients with ASA-resistance for whom an effective anti-aggregant effect is of clinical importance. However, we do not recommend empirical initiation of combination anti-platelet therapy, but rather that patients are tested for resistance to 100 mg then 300 mg ASA before considering treatment with CLZ.

CONFLICT OF INTEREST

None.

REFERENCES

1. Paikin JS, Hirsh J, Ginsberg JS, et al. Multiple daily doses of acetyl-salicylic acid (ASA) overcome reduced platelet response to once daily ASA after coronary artery bypass graft surgery: a pilot randomized controlled trial. *J Thromb Haemost* 2015;13:448-56.
2. Antithrombotic Trialists Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71-86.
3. Howard PA. Aspirin resistance. *Ann Pharmacother* 2002;36: 1620-4.
4. Peters RJ, Mehta SR, Fox KA, et al. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: observations from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. *Circulation* 2003;108:1682-7.
5. Bhatt DL, Fox KA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006;354:1706-17.
6. Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet* 2004; 364:331-7.
7. Biscetti F, Ferraccioli G, Flex A. New therapeutic effects of cilostazol in patients with ischemic disorders. *Curr Vasc Pharmacol* 2015;13:399-404.
8. Lee SW, Park SW, Kim YH, et al. Drug-eluting stenting followed by cilostazol treatment reduces late restenosis in patients with diabetes mellitus the DECLARE-DIABETES Trial (A Randomized Comparison of Triple Antiplatelet Therapy with Dual Antiplatelet Therapy after Drug-Eluting Stent Implantation in Diabetic Patients). *J Am CollCardiol* 2008;51:1181-7.
9. Weintraub WS, Foster J, Culler SD, et al. Methods for the economic and quality of life supplement to the cilostazol for RESTenosis (CREST) trial. *J Invasive Cardiol* 2004;16:257-9.
10. Kwon SU, Cho YJ, Koo JS, et al. Cilostazol prevents the progression of the symptomatic intracranial arterial stenosis: the multicenter double-blind placebo-controlled trial of cilostazol in symptomatic intracranial arterial stenosis. *Stroke* 2005;36:782-6.
11. Kim JS, Lee KS, Kim YI, et al. A randomized crossover comparative study of aspirin, cilostazol and clopidogrel in normal controls: analysis with quantitative bleeding time and platelet aggregation test. *J Clin Neurosci* 2004;11:600-2.
12. Tamai Y, Takami H, Nakahata R, et al. Comparison of the effects of acetylsalicylic acid, ticlopidine and cilostazol on primary hemostasis using a quantitative bleeding time test apparatus. *Haemostasis* 1999;29:269-76.
13. Wilhite DB, Comerota AJ, Schmieder FA, et al. Managing PAD with multiple platelet inhibitors: the effect of combination therapy on bleeding time. *J Vasc Surg* 2003;38:710-3.
14. Kundu SK, Heilman EJ, Sio R, et al. Characterization of an in vitro platelet function analyzer, PFA-100TM. *Clin Appl Thromb Hemost* 1996;2:241-9.
15. Mammen EF, Comp PC, Gosselin R, et al. PFA-100 system: a new method for assessment of platelet dysfunction. *Semin Thromb Hemost* 1998;24:195-202.
16. Michelson AD. How platelets work: platelet function and dysfunction. *J Thromb Thrombolysis* 2003;16:7-12.
17. Chen CN, Chen HR, Chang HI, et al. Relationship between the antiplatelet effect of aspirin and serum VCAM-1 concentration in patients at high risk for cardiovascular events. *Acta Cardiol Sin* 2010;26:28-36.
18. Grotemeyer KH. Effects of acetylsalicylic acid in stroke patients. Evidence of non-responders in a subpopulation of treated patients. *Thromb Res* 1991;63:587-93.
19. Gum PA, Kottke-Marchant K, Poggio ED, et al. Profile and prevalence of aspirin resistance in patients with cardiovascular disease. *Am J Cardiol* 2001;88:230-5.
20. Helgason CM, Bolin KM, Hoff JA, et al. Development of aspirin resistance in persons with previous ischemic stroke. *Stroke* 1994;25:2331-6.
21. Gum PA, Kottke-Marchant K, Welsh PA, et al. A prospective, blinded determination of the natural history of aspirin resistance among stable patients with cardiovascular disease. *J Am Coll Cardiol* 2003;41:961-5.
22. Chang CC, Duann YF, Yen TL, et al. Andrographolide, a novel NF-B inhibitor, inhibits vascular smooth muscle cell proliferation and cerebral endothelial cell inflammation. *Acta Cardiol Sin* 2014; 30:308-15.
23. Thompson PD, Zimet R, Forbes WP, et al. Meta-analysis of results from eight randomized, placebo-controlled trials on the effect of cilostazol on patients with intermittent claudication. *Am J Cardiol* 2002;90:1314-9.

24. Lee SW, Park SW, Hong MK, et al. Triple versus dual antiplatelet therapy after coronary stenting: impact on stent thrombosis. *J Am Coll Cardiol* 2005;46:1833-7.
25. Ahn Y, Jeong MH, Jeong JW, et al. Randomized comparison of cilostazol vs clopidogrel after drug-eluting stenting in diabetic patients — clilostazol for diabetic patients in drug-eluting stent (CIDES) trial. *Circ J* 2008;72:35-9.
26. Biondi-Zoccai GG, Lotrionte M, Anselmino M, et al. Systematic review and meta-analysis of randomized clinical trials appraising the impact of cilostazol after percutaneous coronary intervention. *Am Heart J* 2008;155:1081-9.
27. Hung J, Lam JYT, Lacoste L, et al. Cigarette smoking acutely increases platelet thrombus formation in patients with coronary artery disease taking aspirin. *Circulation* 1995;92:2432-6.
28. Davis JW, Hartman CR, Lewis HD, et al. Cigarette smoking induced enhancement of platelet function: lack of prevention by aspirin in men with coronary artery disease. *J Lab Clin Med* 1985;105:479-83.
29. Cipollone F, Ciabattoni G, Patrono C, et al. Oxidant stress and aspirin-insensitive tromboxane synthesis in severe unstable angina. *Circulation* 2000;102:1007-13.
30. Porosińska A, Pierzchała K. Aspirin resistance theory. *Neurol Neurochirur Pol* 2006;40:313-9.
31. Abaci A, Caliskan M, Bayram F, et al. A new definition of aspirin non-responsiveness by platelet function analyzer-100 and its predictors. *Platelets* 2006;17:7-13.