Aspirin Resistance in Patients with Saphenous Vein Coronary Bypass Graft Occlusion

Safen Ven Koroner Baypas Greft Tıkanıklığında Aspirin Direnci

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ABSTRACT Objective: Autologous saphenous veins are widely used for coronary artery bypass surgery (CABG) despite a higher incidence of graft closure. Early initiation of antiplatelet drugs reduces the incidence of graft occlusions. In this study, we assessed the aspirin resistance by PFA-100® (Platelet Function Analyzer) system in the patients with saphenous vein graft (SVG) occlusion. **Material and Methods:** Fourty-four patients who underwent cardiac catheterization were evaluated. Patients were divided into two groups according to SVG patency. Patients with occluded SVG were compared with patients with patent SVG in terms of clinical, angiographical and laboratory parameters. **Results:** Thirteen of 44 (29.5%) patients were aspirin non-responder. The number of non-responders in patients with and without occlusion in SVG were similar (35% vs 24%, p= 0.4). Basal characteristics and mean aperture closure time/ADP (CT/ADP), aperture closure time/epinephrine (CT/EPI) values were similar in patients with occluded and patent SVGs. Hyperlipidemia was only significantly increased the risk of SVG occlusion in multivariate analysis. There was no significant difference between aspirin responders and nonresponders in terms of clinical parameters, major cardiovascular risk factors, occlusion in SVGs in any time period. However, mean platelet volume, CT/EPI and CT/ADP values were higher in the non-responder group. CT/EPI was negatively correlated with mean platelet volume and hematocrit levels. **Conclusion:** Aspirin resistance does not seem to play an important role in SVG occlusion.

Key Words: Aspirin; coronary artery disease; saphenous vein

ÖZET Amaç: Otolog safen venler koroner arter baypas cerrahisinde, yüksek greft tıkanıklığı insidansına rağmen sıkça kullanılmaktadır. Antiplatelet ilaçların baypas sonrası erken dönemde başlanması greft tıkanıklığı insidansını azaltmaktadır. Biz bu çalışmada, safen ven greft (SVG) tıkanıklığı olan hastalarda PFA-100® (Platelet Fonksiyon Analizatörü) yöntemini kullanarak aspirin direncini araştırdık. **Gereç ve Yöntemler:** Koroner angiografi yapılan 44 hasta incelendi. Hastalar SVG açıklığına göre 2 gruba ayrıldı. SVG tıkanıklığı olan hastalar, SVG'i açık olan hastalarla klinik, angiografik ve laboratuar parametreleri açısından karşılaştırıldı. **Bulgular:** Onüç (%29.5) hastada aspirin direnci vardı. SVG tıkanıklığı olan ve olmayan hastalardaki aspirin direnci benzerdi (%35 ve %24, p= 0.4). İki grup arasında başlangıç özelikleri ve ortalama Kollagen/ADP, Kollagen/Epinefrin değerleri açısından fark yoktu. Çoklu değişken analizlerinde, SVG tıkanıklığı riskini arttıran tek değişken hiperlipidemi idi. Aspirin direnci olan ve olmayan iki grup klinik özellikler ve majör kardiyovasküler risk faktörleri açısından karşılaştırıldığında, iki grup arasında fark yoktu. Fakat, ortalama trombosit hacmi, Kollagen/ADP ve Kollagen/Epinefrin değerleri aspirin direnci olan grupta daha yüksek idi. Kollagen/Epinefrin ile ortalama trombosit hacmi ve hemotokrit arasında negatif korelasyon vardı. **Sonuç:** Aspirin direnci SVG tıkanıklığında önemli bir rol oynamamaktadır.

Anahtar Kelimeler: Aspirin; koroner arter hastalığı; safen ven

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Coronary saphenous vein-graft disease is an important factor contributing to the morbidity after coronary bypass surgery (CABG).[1] Early and late occlusion of saphenous vein graft is a serious clini-

cal condition that limits the use of saphenous vein as a coronary bypass conduit. Saphenous vein grafts (SVGs) are closed with rate of 15% in the first year. Between one and six years, annual graft attrition rate is 1 to 25% and becomes 4 to 6% per year after that, so about half of SVGs have significant stenosis or are occluded after 10 years.[2,3] Aspirin is the cornerstone of antiplatelet therapy in cardiovascular medicine today. Early initiation of antiplatelet or anticoagulant drugs reduces the incidence of graft occlusion after coronary artery bypass surgery.[4,5] Despite the demonstrated benefits of aspirin in coronary heart disease, a large segment of the population underwent CABG does not benefit from aspirin.[6] Aspirin resistance defined by failure to effectively inhibit thromboxane synthesis is associated with a higher risk of recurrent myocardial ischemia and cardiovascular death.[7] In this study, we assessed the aspirin resistance in patients with SVG occlusion after CABG.

MATERIAL AND METHODS

STUDY POPULATION

Fourty-four patients who underwent cardiac catheterization because of angina and/or dyspnea were evaluated. All patients had a history of CABG with implantation of aortocoronary saphenous vein grafts and had been used aspirin at dose of 150-300 mg/day. Patients with acute or chronic inflammatory disease, myeloproliferative disorders, malignancy, renal, hepatic or thyroid disease and patients treated with immunsupressive or cytotoxic drugs, acute coronary syndromes, a hematocrit < 0.30 or > 0.52 and a platelet count < 100 G/L were excluded. A written consent was obtained from all patients, and our local ethical committee approved the study.

CORONARY ANGIOGRAPHY

All cineangoigrams were reviewed by two experienced cardiologists, who were blinded to the patients' clinical status and laboratory findings. The reviewers were informed about the number and localization of SVG's, and rewieved the cineangiogram only the determine the status of grafts. The bypass grafts were examined in multiple projections and the degree of stenosis was determined in the projection that showed the most severe narrowing. Patients were divided into two groups according to SVG patency. The occluded SVG was defined 100% stenosis and patent SVG was defined as < 20% narrowing in the graft. In patients with occluded grafts (100% stenosis), stumps of grafts were selectively injected or visualized on aortography in the appropriate projection. Patients with occluded SVGs were compared with the patients with patent SVG.

BLOOD SAMPLING AND LABORATORY DETERMINATIONS

Blood samples were drawn from each subject, 2-4 h after aspirin intake in the morning between 8 and 10 a.m. in the fasting state. Blood was withdrawn by antecubital venipuncture and the initial first mililiters of blood were discarded to avoid spontaneous platelet activation. Citrated blood (0.129 M trisodium citrate in dilution 1:10) were analyzed for aspirin resistance by PFA-100® (Platelet Function Analyzer, Dade Behring, Germany) using collogen and/or epinephrine (CT/EPI) and collogen and/or ADP (CT/ADP) cartridges to measure aperture closure time (CT). Aspirin resistance was defined as CT/EPI <186 s. Total cholesterol, HDL cholesterol and trigliseride levels were measured enzymatically by the autoanalyzer (Hitachi 911, Japon). LDL cholesterol levels determined with Friedewald formula.

STATISTICAL ANALYSES

Results are reported as mean ± standard deviation (SD) and percentiles. Student's t-test was used to compare normally distributed continuous variables and the Mann–Whitney U test for variables without normal distribution. Categorical variables were compared by using χ^2 test. In order to determine independent predictors of late saphenous vein graft occlusion, multiple logistic regression analysis was performed by including major risk factors atributable to atherosclerosis. Spearman correlation analysis was used to evaluate the relationship between different variables. A value of $p< 0.05$ was considered as statistically significant. SPSS-10.0 for Windows statistical software package program was used for statistical analyses.

RESULTS

This study included 44 patients (34 males, 10 females, ages ranged between 41 and 77 years). Of 44 patients, 13 (29.5%) were aspirin non-responder. The rate of non-responder patients in two groups were similar (35% vs 24%, p= 0.465). The time between surgery and control coronary angiography ranged between 5-192 months. There was no difference between both groups concerning age, gender, body masss index, time interval after surgery, major cardiovascular risk factors such as hyperlipidemia (HL), hypertension (HT), diabetes mellitus (DM), smoking, medical treatment including daily aspirin dosage, myocardial infarction (MI) history or left ventricle ejection fraction (Table 1). Furthermore, among laboratory parameters, white blood cell and platelet counts, hematocrit (Htc), mean platelet volume (MPV), fibrinogen and cholesterol levels, graft numbers, mean CT/ADP, CT/EPI values and rate of response to aspirine were similar in two groups (Table 2). However, on multivariate logistic regression analysis, among major risk factors atributable to atherosclerosis, only hyperlipidemia was found as an independent variable that significantly increased the risk of aortocoronary saphenous vein graft occlusion.

When aspirin responders were compared with nonresponders (aspirin resistant), there was no significant difference between both groups in terms of clinical parameters, major cardiovascular risk factors, medical treatments, aspirin dosages or occlusion rate in saphenous vein coronary grafts in any time period. However, mean platelet volume, CT/EPI and CT/ADP values were higher in non-responder group when compared to responder group (Table 3).

Mean CT/ADP and CT/EPI values were similar in patients with stenosis in saphenous vein grafts <12 months after surgery and those with patent saphenous grafts > 12 months after surgery. There was no difference in mean CT/ADP and CT/EPI values when the patients with stenosis in saphenous grafts < 12 months and > 36 months were compared with each other or with those without stenosis in saphenous vein grafts (Table 4).

On correlation analysis, CT/ADP was found to be negatively correlated (r= -0.4, p= 0.003) with age. In addition, CT/EPI was negatively correlated (r= -0.5, p= 0.024) with mean platelet volume and with hematocrit levels (r= -0.2, p= 0.042).

TABLE 1: Baseline characteristics of patients with saphenous vein graft stenosis and non-stenosis.

	Non-stenosis group (n = 21)	Stenosis group (n = 23)	p value
Age (years)	63.1 ± 9.6	65.1 ± 8.7	0.515
Male/female	16/5	18/5	0.534
BMI (kg/m^2)	26.3 ± 5.4	25.7 ± 4.9	0.618
Time interval after surgery (months)	52.8 ± 37.2	68.2 ± 57.6	0.327
Hypertension	10 (48%)	12 (52%)	0.739
Diabetes mellitus	7 (33%)	6 (26%)	0.502
Smoking	5 (24%)	6 (26%)	0.712
Hyperlipidemia	16 (76%)	14 (61%)	0.111
History of myocardial infarction	7 (33%)	7 (31%)	0.546
Ejection fraction (%)	51.1 ± 13.1	49.3 ± 11.7	0.429
Aspirin dose (mg/day)	209.5 ± 109.1	247.4 ± 90.5	0.214
Beta-blockers	18 (86%)	17(74%)	0.502
ACE inhibitors	13 (62%)	13 (57%)	0.610
Statins	11 (52%)	10 (44%)	0.508
Nitrates	10 (48%)	9 (39%)	0.228

BMI: body mass index, ACE: angiotensin converting enzyme.

Values are mean ± SD and percentiles.

P values are based on the student t test and Mann-Whitney U test for continuous variables and on the χ^2 test for categorical variables.

TABLE 2: Compared laboratory findings of patients with saphenous vein graft stenosis and without stenosis.

	No-stenosis group (n = 21)	Stenosis group (n = 23)	p value
Hematocrit (%)	43.1 ± 2.8	43.3 ± 2.5	0.617
White blood cells (nl^{-1})	8.1 ± 2.3	8.0 ± 2.7	0.762
Platelets	233.8 ± 53.6	247.4 ± 90.5	0.214
Mean Platelet Volume (fl)	11.0 ± 0.9	10.8 ± 1.0	0.446
Fibrinogen (mg/dl)	3.5 ± 1.3	4.3 ± 2.4	0.234
Total cholesterol (mg/dl)	234.7 ± 58.3	238.8 ± 42.2	0.406
LDL cholesterol (mg/dl)	147.9 ± 52.6	156.7 ± 31.3	0.117
HDL cholesterol (mg/dl)	39.2 ± 7.2	35.5 ± 6.6	0.230
Trigliserid (mg/dl)	166.5 ± 62.2	183.7 ± 123.3	0.306
Graft number	1.5 ± 0.5	1.9 ± 0.8	0.062
Patients with one or multipl saphenous vein grafts			
One	15 (47%)	17 (49%)	0.368
Two	16 (50%)	16 (46%)	0.478
Three or more	1 (3%)	2 (5%)	0.583
Internal mammary artery graft	17 (%)	18 (%)	0.818
CT/ADP	98.1 ± 47.8	94.6 ± 54.9	0.880
CT/EPI	219.9 ± 77.9	240.1 ± 72.8	0.272
Aspirin non-responders	5 (%24)	8 (%35)	0.465

LDL: low density lipoprotein, HDL: high density lipoprotein, CT/EPI: closure time for collagen/epinephrine, CT/ADP: closure time for collagen/adenosine diphosphate

Values are mean ± SD and percentiles.

P values are based on the student t test and Mann-Whitney U test for continuous variables and on the χ^2 test for categorical variables.

DISCUSSION

Autologous saphenous veins are widely used for CABG despite a higher incidence of early and late graft closure.[1] Four consecutive phases of aortocoronary bypass saphenous vein-graft disease were defined:[8] 1) an early postoperative phase of platelet thrombotic occlusion which is significantly prevented by platelet inhibitor therapy when started in the perioperative period and accompanied with a good surgical and technical experience; 2) an intermediate phase of platelet-related intimal hyperplasia within the first postoperative year which is not prevented with anti-platelet therapy; 3) a late phase of occlusion toward the end of the first year in which intimal hyperplasia and complicated platelet thrombi superimposed and platelet inhibitor therapy is of significant benefit in prevention, 4) a phase of atherosclerotic disease after the first year in which aspirin treatment is beneficial although there are come controversies about the duration.[9]

Several factors affect the fate of SVGs such as smoking,[10] hyperlipidemia,[11] recipient artery diameter,[12,13] and hypertension.[13] Some hemostatic factors such as factors VII and VIII, fibrinogen and tissue plasminogen activator are related to graft occlusion and the assessement of these factors may contribute to the identification of individuals at risk for an early vein graft closure.[14] Recently, Zimmermann et al.[15] demonstrated that platelet activation by aspirin is compromised within several days after CABG probably due to an impaired interaction between aspirin and platelet cyclooxygenase.

Aspirin exerts its antithrombotic effect primarily by interfering with the biosynthesis of thromboxane A_2[16,17] and several studies have demonstrated beneficial role of aspirin in primary or secondary prevention heart disease.[18,19] However, aspirin's antiplatelet effect is not uniform in all patients.[20]

Aspirin resistance, as defined by failure to effectively inhibit thromboxane synthesis, is associated with a higher risk of recurrent myocardial ischemia and cardiovascular death,[7] as well as recurrent cerebral ischemic attacks.[21] Gum et al.[22] reported that aspirin resistance was associated with

TABLE 3: Characteristics of the aspirin responder and non-responder groups.

	Non-responders (n= 13)	Responders (n= 31)	p value
Age (years)	65.1 ± 8.8	63.7 ± 9.3	0.145
Male/female	9/4	25/6	0.565
BMI (kg/m^2)	25.8 ± 6.4	24.9 ± 5.9	0.584
Time interval after surgery (months)	65.0 ± 58.7	58.2 ± 44.3	0.734
Hypertension	7 (54%)	14 (45%)	0.523
Diabetes mellitus	5 (39%)	8 (26%)	0.543
Smoking	4 (31%)	7 (23%)	0.767
Hyperlipidemia	8 (62%)	22 (71%)	0.754
History of myocardial infarction	4 (30%)	6 (19%)	0.224
Ejection fraction (%)	47.3 ± 18.1	52.4 ± 14.7	0.118
Aspirin dose (mg/day)	245.5 ± 93.4	220.7 ± 104.8	0.424
Beta-blockers	9 (69%)	26 (79%)	0.442
ACE inhibitors	9 (69%)	17 (55%)	0.368
Statins	6 (46%)	15 (48%)	0.585
Nitrates	5 (39%)	14 (45%)	0.794
Hematocrit (%)	44.1 ± 2.2	42.8 ± 2.6	0.116
White blood cells (nl-1)	8.0 ± 3.2	8.1 ± 2.9	0.654
Platelets	238.6 ± 59.6	242.4 ± 82.5	0.442
Mean Platelet Volume (fl)	11.1 ± 0.810	.2 ± 1.2	0.032*
Fibrinogen (mg/dl)	3.9 ± 1.4	3.8 ± 2.1	0.852
Total cholesterol (mg/dl)	240.2 ± 48.3	231.8 ± 54.1	0.424
LDL cholesterol (mg/dl)	149.9 ± 62.6	151.9 ± 41.3	0.516
HDL cholesterol (mg/dl)	37.4 ± 9.2	36.5 ± 7.1	0.584
Trigliseride (mg/dl)	170.8 ± 70.2	177.9 ± 100.3	0.422
Graft number	1.8 ± 0.8	1.6 ± 0.7	0.511
Occlusion in saphenous grafts (%)	8 (62%)	15 (48%)	0.316
Occlusion <12 months (%)	4 (31%)	6 (19%)	0.556
Occlusion >36 months (%)	3 (23%)	7 (22.5%)	0.824
CT/EPI	122.9 ± 26.3	273.3 ± 40.9	0.001*
CT/ADP	76.5 ± 10.7	103.1 ± 56.9	0.022*

BMI: body mass index, ACE: angiotensin converting enzyme, LDL: low density lipoprotein, HDL: high density lipoprotein, CT/EPI: closure time for collagen/epinephrine, CT/ADP: closure time for collagen/adenosine diphosphate.

Values are mean ± SD and percentiles.

P values are based on the student t test and Mann Whitney-U test for continuous variables and on the χ^2 test for categorical variables.

* statistically significant.

4.1-fold excess adjusted hazard of serious vascular events, independent of age, gender and conventional vascular risk factors. Additionally, the incidence of aspirin resistance ranges between 5-61% depending on timing and technique of examination, time of the last aspirin intake, dose of aspirin as well as heterogenecity of patient population.[23-28]

Aspirin resistance may be a consequence of following mechanisms:[29-32] 1) nonadherence to aspirin; 2) requirement for higher doses of aspirin; 3) alternative upstream pathways of platelet activation that are not blocked by aspirin; 4) aspirin-insensitive thromboxane synthesis; 5) drugs that interfere with the antithrombotic effects of aspirin; 6) platelet glycoprotein polymorphism.

Grotemeyer et al.[25] found that patients with elevated platelet reactivity despite aspirin were more likely to experience vascular death, MI or cerebrovascular accident. Andersen et al.[24] demonstrated that P-selectin but not β-thromboglobulin

TABLE 4: Comparison of CT/ADP and CT/EPI values of the patients with occlusion in SVG <12 months after surgery with occlusion>12 months and comparison of the patients with occlusion<12 months and >36 months with those without stenosis in saphenous vein grafts.

	Occlusion < 12 months (n= 10)	Occlusion > 12 months (n= 13)	p value
CT/ADP	97.2 ± 37.4	93.7 ± 61.2	0.813
CT/EPI	234.6 ± 72.1	238.2 ± 82.4	0.834
	Occlusion < 12 months (n= 10)	No-stenosis group (n= 21)	
CT/ADP	97.2 ± 37.4	98.1 ± 47.8	0.724
CT/EPI	234.6 ± 72.1	219.9 ± 77.9	0.546
	Occlusion > 36 months (n= 10)	No-stenosis group (n= 21)	
CT/ADP	95.9 ± 66.1	98.1 ± 47.8	0.818
CT/EPI	230.5 ± 79.5	219.9 ± 77.9	0.525

CT/EPI: closure time for collagen/epinephrine, CT/ADP: closure time for collagen/adenosine diphosphate.

Values are mean ± SD.

P values are based on the Mann Whitney-U test for continuous variables.

was significantly higher in the non-responders suggesting increased activation of platelets in this group. Similarly, we found higher mean platelet volumes reflecting more reactive platelets[33] in non-responders. Moreover, CT/EPI was negatively correlated with MPV contributing to the hypothesis that there is an increased activation of platelets in patients with aspirin resistance. In the same way, Gavaghan et al.[34] found increased plasma beta-thromboglobulin in patients with coronary vein graft occlusion and suggested that patients at highest risk for saphenous bypass graft occlusion might be identified preoperatively by the evidence of platelet activation. Therefore, it may be suggested that aspirin resistance may play a role in occlusion of SVGs. However we found that there was no significant difference in occlusion of SVGs between aspirin responders and non-responders. It may be due to the fact that pathogenesis of saphenous aorto-coronary vein graft disease is multifactorial and hemostatic factors are only one of them.

In conclusion, aspirin resistance does not play an important role in aortocoronary saphenous vein graft occlusion. However, further and larger studies are required.

STUDY LIMITATIONS

The most important limitation of our study is the small number of patients in both groups. Some may argue about the cut-off level for CT/EPI in our laboratory since it was lower than reported previously by Christiaens et al.[23] and Andersen et al.,[24] however it was higher than defined by Grundmann et al.[21] and Watala et al.[35]

REFERENCES

1. Angelini GD, Newby AC. The future of saphenous vein as a coronary artery bypass conduit. Eur Heart J 1989;10(3):273-80.
2. Bourassa MG. Fate of venous grafts: the past, the present and the future. J Am Coll Cardiol 1991;17(5):1081-3.
3. Fitzgibbon GM, Kafka HP, Leach AJ, Keon WJ, Hooper GD, Burton JR. Coronary bypass graft fate and patient outcome: angiographic follow-up of 5,065 grafts related to survival and reoperation in 1,388 patients during 25 years. J Am Coll Cardiol 1996;28(3):616-26.
4. Goldman S, Copeland J, Moritz T, Henderson W, Zadina K, Ovitt T, et al. Improvement in early saphenous vein graft patency after coronary artery bypass surgery with antiplatelet therapy: results of a Veterans Administration Cooperative Study. Circulation 1988;77(6): 1324-32.
5. Henderson WG, Goldman S, Copeland JG, Moritz TE, Harker LA. Antiplatelet or anticoagulant therapy after coronary artery bypass surgery. A meta-analysis of clinical trials. Ann Intern Med 1989;111(9):743-50.
6. 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(7329):71-86.
7. Eikelboom JW, Hirsh J, Weitz JI, Johnston M, Yi Q, Yusuf S. Aspirin-resistant thromboxane biosynthesis and the risk of myocardial infarction, stroke, or cardiovascular death in patients at high risk for cardiovascular events. Circulation 2002;105(14): 1650-5.

8. Fuster V, Chesebro JH. Role of platelets and platelet inhibitors in aortocoronary artery vein-graft disease. Circulation 1986;73(2):227-32.
9. Stein PD, Dalen JE, Goldman S, Théroux P. Antithrombotic therapy in patients with saphenous vein and internal mammary artery bypass grafts. Chest 1998;114(5 Suppl):658S-665S.
10. Michos ED, Ardehali R, Blumenthal RS, Lange RA, Ardehali H. Aspirin and clopidogrel resistance. Mayo Clin Proc 2006;81(4):518-26.
11. Macchi L, Sorel N, Christiaens L. Aspirin resistance: definitions, mechanisms, prevalence, and clinical significance. Curr Pharm Des 2006;12(2):251-8.
12. Cameron AA, Davis KB, Rogers WJ. Recurrence of angina after coronary artery bypass surgery: predictors and prognosis (CASS Registry). Coronary Artery Surgery Study. J Am Coll Cardiol 1995;26(4):895-9.
13. Domanski MJ, Borkowf CB, Campeau L, Knatterud GL, White C, Hoogwerf B, et al. Prognostic factors for atherosclerosis progression in saphenous vein grafts: the postcoronary artery bypass graft (Post-CABG) trial. Post-CABG Trial Investigators. J Am Coll Cardiol 2000;36(6):1877-83.
14. Moor E, Hamsten A, Blombäck M, Herzfeld I, Wiman B, Rydén L. Haemostatic factors and inhibitors and coronary artery bypass grafting: preoperative alterations and relations to graft occlusion. Thromb Haemost 1994;72(3):335-42.
15. Zimmermann N, Wenk A, Kim U, Kienzle P, Weber AA, Gams E, et al. Functional and biochemical evaluation of platelet aspirin resistance after coronary artery bypass surgery. Circulation 2003;108(5):542-7.
16. Awtry EH, Loscalzo J. Aspirin. Circulation 2000;101(10):1206-18.
17. Tulunay FC. [Aspirine in Cardiovascular Disease]. Turkiye Klinikleri J Med Sci 1990;10(3): 178-82.
18. Cairns JA, Théroux P, Lewis HD Jr, Ezekowitz M, Meade TW. Antithrombotic agents in coronary artery disease. Chest 2001;119(1 Suppl):228S-252S.
19. Sanmuganathan PS, Ghahramani P, Jackson PR, Wallis EJ, Ramsay LE. Aspirin for primary prevention of coronary heart disease: safety and absolute benefit related to coronary risk derived from meta-analysis of randomised trials. Heart 2001;85(3):265-71.
20. Patrono C, Coller B, Dalen JE, FitzGerald GA, Fuster V, Gent M, et al. Platelet-active drugs: the relationships among dose, effectiveness, and side effects. Chest 2001;119(1 Suppl): 39S-63S.
21. Grundmann K, Jaschonek K, Kleine B, Dichgans J, Topka H. Aspirin non-responder status in patients with recurrent cerebral ischemic attacks. J Neurol 2003;250(1):63-6.
22. Gum PA, Kottke-Marchant K, Welsh PA, White J, Topol EJ. A prospective, blinded determination of the natural history of aspirin resistance among stable patients with cardiovascular disease. J Am Coll Cardiol 2003; 41(6):961-5.
23. Christiaens L, Macchi L, Herpin D, Coisne D, Duplantier C, Allal J, et al. Resistance to aspirin in vitro at rest and during exercise in patients with angiographically proven coronary artery disease. Thromb Res 2002;108(2-3):115-9.
24. Andersen K, Hurlen M, Arnesen H, Seljeflot I. Aspirin non-responsiveness as measured by PFA-100 in patients with coronary artery disease. Thromb Res 2002;108(1):37-42.
25. Grotemeyer KH, Scharafinski HW, Husstedt IW. Two-year follow-up of aspirin responder and aspirin non responder. A pilot-study including 180 post-stroke patients. Thromb Res 1993;71(5):397-403.
26. Cattaneo M. Aspirin and clopidogrel: efficacy, safety, and the issue of drug resistance. Arterioscler Thromb Vasc Biol 2004;24(11):1980-7.
27. Bhatt DL. Aspirin resistance: more than just a laboratory curiosity.J Am Coll Cardiol. 2004;43(6):1127-9
28. Hankey GJ, Eikelboom JW. Aspirin resistance. BMJ 2004;328(7438):477-9.
29. Weber AA, Przytulski B, Schanz A, Hohlfeld T, Schrör K. Towards a definition of aspirin resistance: a typological approach. Platelets 2002;13(1):37-40.
30. Eikelboom JW, Hankey GJ. Aspirin resistance: a new independent predictor of vascular events? J Am Coll Cardiol 2003;41(6):966-8.
31. MacDonald TM, Wei L. Effect of ibuprofen on cardioprotective effect of aspirin. Lancet 2003;361(9357):573-4.
32. Macchi L, Christiaens L, Brabant S, Sorel N, Ragot S, Allal J, et al. Resistance in vitro to low-dose aspirin is associated with platelet PIA1 (GP IIIa) polymorphism but not with C807T(GP Ia/IIa) and C-5T Kozak (GP Ibalpha) polymorphisms. J Am Coll Cardiol 2003;42(6):1115-9.
33. Threatte GA. Usefulness of the mean platelet volume. Clin Lab Med 1993;13(4):937-50.
34. Gavaghan TP, Hickie JB, Krilis SA, Baron DW, Gebski V, Low J, et al. Increased plasma beta-thromboglobulin in patients with coronary artery vein graft occlusion: response to low dose aspirin. J Am Coll Cardiol 1990;15(6):1250-8.
35. Watala C, Golanski J, Rozalski M, Boncler MA, Luzak B, Baraniak J, et al. Is platelet aggregation a more important contributor than platelet adhesion to the overall platelet-related primary haemostasis measured by PFA-100? Thromb Res 2003;109(5-6):299-306.