Original Paper

Aspirin Resistance in Hypertensive Patients

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*Aspirin resistance is associated with poor clinical prognosis. The authors investigated aspirin resistance in 200 hypertensive patients (111 men, age: 68.3±11.4 years) by the Ultegra Rapid Platelet Function Assay-ASA (Accumetrics Inc., San Diego, CA). Aspirin resistance was defined as an aspirin reaction unit ≥550. Aspirin resistance was detected in 42 patients. Aspirin resistance was present in 25.6% of the patients with poor blood pressure control, while in 17.8% of the patients with controlled blood pressure (*P=*.182). Female gender and creatinine levels were significantly higher (*P=*.028 and P=.030, respectively), while platelet count was significantly lower (*P=*.007) in aspirin-resistant patients. Multivariate analysis revealed that female gender (odds ratio [OR], 2.445;* P=*.045), creatinine levels (OR, 1.297;* P=*.015) and platelet count (OR, 0.993;* P=*.005) were independent predictors of aspirin resistance. The frequency of aspirin resistance is not low in hypertensive patients. Female hypertensive patients, especially, with higher creatinine levels and lower platelet count are at higher risk for aspirin resistance.* J Clin Hypertens (Greenwich). *2010;12:714–720.* ©*2010 Wiley Periodicals, Inc.*

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Aspirin is an effective antiplatelet agent, exhibiting its action by irreversibly inhibiting platelet cyclooxygenase-1 enzyme, thus preventing the production of thromboxane A2 (TXA2). It has been used in the primary and secondary prevention of thromboembolic vascular events.[1,2] The Antithrombotic Trialists' Collaboration (a large metaanalysis of 287 randomized trials of antiplatelet therapy) reported that aspirin was protective in most of the patients at increased risk of occlusive vascular events, including those with an acute or previous myocardial infarction, unstable or stable angina, stroke or cerebral ischemia, peripheral arterial disease, or atrial fibrillation.[3] The metaanalysis demonstrated a 32% reduction of nonfatal myocardial infarction, nonfatal stroke, and vascular death in patients treated with 75–150 mg aspirin daily.[3]

Despite strong evidence in favor of aspirin use, aspirin therapy fails to prevent clinical (thrombotic) events in certain patients. These patients do not respond adequately to aspirin therapy. This condition is named "aspirin resistance," but there are various synonyms, including "aspirin nonresponsiveness," "aspirin treatment failure," "inadequate aspirin efficacy," and "biochemical or laboratory aspirin resistance."[4] Clinically, aspirin resistance is assessed in the occurrence of further thrombotic events despite aspirin administered in "usual" prophylactic dosages. It is defined in the laboratory setting as the failure of aspirin to suppress the platelet production of TXA2, to reduce platelet activation, and to fully inhibit platelet aggregation.

Estimates of aspirin resistance prevalence vary widely (5.5%–60%), reflecting the diversity of laboratory assays employed and confounding factors deriving from the broad range of disease states investigated.[5–8] Possible causes of aspirin resistance include poor compliance or inadequate dose,[9,10] reduced bioavailability,[11] increased platelet turnover, upregulation of nonplatelet pathways of thromboxane production,[12,13] drug interactions,[14,15] and genetic variability.[16–20] Despite ongoing research, there is currently no standardized approach to the diagnosis and no proven effective treatment for aspirin resistance.

Although aspirin resistance has been well demonstrated in cardiovascular disorders such as coronary artery disease,[12,21] heart failure,[22] cerebrovascular disease,[23,24] diabetes,[25–27] obesity,[28] metabolic syndrome,[29] and hyperlipidemia,[30] little is known about aspirin response and its prognostic value in patients with hypertension. The aim of this study was to explore the prevalence of aspirin resistance in patients with hypertension and to clarify the predictors of aspirin resistance in these patients.

METHODS

The investigation conforms with the principles outlined in the Declaration of Helsinki. The study was approved by the local ethics committee and all participants gave written informed consent before participating. Patients were selected among the cases admitted to the outpatient clinics of Marmara University Medical Faculty Department of Cardiology between May 2007 and September 2008.

Two hundred consecutive hypertensive patients (111 men and 89 women, mean age: 68.3 $\pm$ 11.4 years) who had been taking aspirin regularly for primary or secondary cardiovascular protection were included in the study. Hypertension was defined according to guidelines from the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7).[31] All the hypertensive patients were taking 100–300 mg/d aspirin for at least 1 week. Exclusion criteria included ingestion of ticlopidine, clopidogrel, cilostazol, dipyridamole, and antiinflammatory drugs for at least 10 days.

Compliance with aspirin treatment was ascertained by a personal interview at the time of inclusion. None of the patients missed any aspirin dose in the 7 days prior to platelet aggregation testing. A questionnaire on smoking habits, clinical history of coronary artery disease, diabetes, hyperlipidemia, and renal failure was carried out. Weight and height were measured to determine body mass index. Blood pressure of the subjects was measured by a blinded, trained physician with a mercury sphygmomanometer using appropriate cuff sizes. All patients were comfortably seated in a chair, with the legs uncrossed, feet flat on the floor, and the back and arm supported. The middle of the cuff on the upper arm was at the level of the right atrium. Recorded systolic and diastolic blood pressures were the means of 3 measurements separated by 60 seconds after a 5-minute rest period. By the general definition, blood pressure was considered uncontrolled if systolic blood pressure was $\geq$140 mm Hg or diastolic blood pressure was $\geq$90 mm Hg. By the disease-specific definition, blood pressure was considered uncontrolled in patients with diabetes, coronary artery disease, or chronic kidney disease if systolic blood pressure was $\geq$130 mm Hg or diastolic blood pressure was $\geq$80 mm Hg.

Fasting blood samples were obtained to determine blood glucose, creatinine, triglyceride, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, C-reactive protein, hemoglobin, hematocrit, and platelet and leukocyte count.

Assessment of Aspirin Resistance With Ultegra Rapid Platelet Function Assay

From every patient, 2 mL blood samples were drawn into tubes containing 3.2% citrate 1 to 4 hours after aspirin intake. Aspirin-induced platelet inhibition was measured using a commercially available point-of-care assay, the Ultegra Rapid Platelet Function Assay-ASA (the VerifyNow System) (Accumetrics, San Diego, CA). This is a whole blood optical detection system that measures agonist-induced platelet aggregation using cationic propyl gallate to activate platelets. Platelet function measurement is based on the ability of activated platelets to bind fibrinogen. The instrument measures the change in optical signal caused by aggregation. If aspirin has produced the expected antiplatelet effect, fibrinogen-coated beads will not agglutinate, and light transmission will not increase. The results are reported as aspirin reaction units (ARU). The cutoff point is set as 550 ARU according to the manufacturer's clinical studies using optical aggregometry as the comparison standard. An ARU $\geq$550 indicates absence of aspirin-induced platelet dysfunction and is defined as aspirin-resistant. An ARU $<$550 indicates platelet dysfunction consistent with aspirin has been detected and is defined as aspirin-sensitive.[32]

Since clopidogrel, ticlopidine, cilostazol, dipyridamole, and antiinflammatory drugs may interfere

Table I. The Patient Characteristics With Comparison of Aspirin-Resistant and Aspirin Sensitive Hypertensive Patients

	Hypertensive Patients (n=200)	Aspirin-Resistant (n=42)	Aspirin-Sensitive (n=158)	*P* Value[a]
Age, y	68.3±11.4	68.4±10.1	68.2±11.8	.912
Sex (female/male), n	89/111	25/17	64/94	**.028**
Coronary artery disease, %	43.7	46.3	43.0	.704
Hyperlipidemia, %	58.0	52.4	59.5	.406
Diabetes, %	39.0	50.0	36.1	.100
Renal failure, %	20.0	28.6	17.7	.118
Smoking, %	34.5	35.7	34.2	.898
Body mass index, kg/m^2	28.08±5.40	28.01±4.06	28.10±5.71	.928
Subjects with controlled blood pressure, %	59.0	50.0	61.4	.182
Systolic blood pressure, mm Hg	134.3±21.9	136.7±23.3	133.7±21.5	.433
Diastolic blood pressure, mm Hg	77.2±14.4	76.9±13.0	77.3±14.8	.865
Heart rate, per min	80±16	76±14	81±16	.090

P values set in boldface indicate statistical significance. [a]*P* value comparing aspirin-resistant and aspirin-sensitive hypertensive patients.

with normal platelet function and lead to low ARU values, patients using these drugs were excluded from the study.

Statistical Analysis

All statistical tests were performed with a commercially available statistical analysis program (SPSS 11.0 for Windows [SPSS Inc, Chicago, IL]). Continuous variables were expressed as mean ± standard deviation while categorical variables were expressed as ratio. To evaluate the differences between mean values of quantitative variables, Student *t*-test was used for parametric variables and the Mann-Whitney U test for nonparametric variables. Categorical variables were compared using chi-square test. Pearson's correlation was used for univariate analysis. A logistic regression analysis was employed to determine significant predictors of aspirin resistance in hypertensive patients. In all cases, a *P* value of .05 or less was considered statistically significant.

RESULTS

Two hundred consecutive hypertensive patients were included in the study. Aspirin resistance was detected in 42 patients (21%). The general characteristics and laboratory parameters of the hypertensive patients, together with comparing aspirin-sensitive and aspirin-resistant patients are presented in Table I and Table II.

There was not any significant difference in age distribution between aspirin-resistant and aspirin-sensitive hypertensive patients (*P*=.912). The female frequency was significantly higher in aspirin-resistant hypertensive patients (59.5% vs 40.5%, *P*=.028). The frequencies of coronary artery disease, diabetes, and renal failure were insignificantly higher in aspirin-resistant hypertensive patients (*P*=.704, *P*=.100, and *P*=.118, respectively).

Daily aspirin dose and duration of aspirin therapy were similar between the aspirin-resistant and aspirin-sensitive hypertensive patients (*P*=.722 and *P*=.899, respectively). The median aspirin dose was 100 mg/d in both aspirin-resistant and aspirin-sensitive patients.

Among the hypertensive patients, 82 of them (41%) had poor blood pressure control. Aspirin resistance was detected in 17.8% of the patients who had blood pressure within normal limits, while aspirin resistance was present in 25.6% of the patients with poor blood pressure control, but the difference was not statistically significant (*P*=.182). There were not any significant differences in heart rate, systolic, or diastolic blood pressure measures between the aspirin-resistant and aspirin-sensitive hypertensive patients (*P*=.090, *P*=.433, and *P*=.865, respectively).

Among the laboratory parameters, creatinine level was significantly higher and platelet count was significantly lower in aspirin-resistant patients compared to aspirin-sensitive patients (*P*=.030 and *P*=.007, respectively).

There were significant, but relatively weak relations between ARUs and serum creatinine levels (*P*=.006, *r*=0.196) and platelet count (*P*=.023, *r*=−0.163). Univariate analysis revealed no significant association between ARUs and age (*P*=.820), body mass index (*P*=.387), systolic or diastolic blood pressure (*P*=.292 and *P*=.560, respectively), glucose (*P*=.322), C-reactive protein (*P*=.777), total cholesterol (*P*=.630), triglyceride (*P*=.196), high-density lipoprotein cholesterol (*P*=.302), low-density lipoprotein cholesterol (*P*=.415), hemoglobin

Table II. Laboratory Parameters of the Patients With Comparison of Aspirin-Resistant and Aspirin-Sensitive Hypertensive Patients

	Hypertensive Patients (n=200)	Aspirin-Resistant (n=42)	Aspirin-Sensitive (n=158)	*P* Value[a]
Aspirin reaction unit	476.84±74.95	588.98±33.13	447.04±50.76	**<.001**
Aspirin dose, mg/d				
Mean ± standard deviation	168±94	173±96	167±94	.722
Median	100	100	100	
Duration of aspirin therapy, months	39±63	40±66	39±63	.899
Glucose, mg/dL	126±54	126±65	126±51	.989
Creatinine, mg/dL	1.65±1.68	2.42±2.74	1.45±1.19	**.030**
C-reactive protein, mg/dL	23.66±50.16	26.74±44.28	22.75±51.95	.723
Triglyceride, mg/dL	144±94	121±67	150±99	.092
Total cholesterol, mg/dL	184±51	173±57	186±49	.172
HDL cholesterol, mg/dL	44±12	41±12	45±12	.151
LDL cholesterol, mg/dL	109±42	107±51	110±40	.740
Hemoglobin, g/dL	13.0±1.9	12.5±2.5	13.1±1.7	.114
Hematocrit, %	39.3±9.1	37.6±7.7	39.8±9.5	.159
Leukocytes, per mm^3	9454±3579	9356±2541	9504±4043	.901
Platelet, $\times 10^3/mm^3$	259.8±101.6	222.1±62.4	269.7±107.6	**.007**

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein. *P* values set in boldface indicate statistical significance. [a]*P* value comparing aspirin-resistant and aspirin-sensitive hypertensive patients.

Table III. Multivariate Analysis for Predictors of Aspirin Resistance

Variable	Odds Ratio	95% Confidence Interval	*P* Value
Age	1.010	0.975–1.047	.577
Female gender	2.445	1.019–5.866	**.045**
Coronary artery disease	1.145	0.478–2.743	.762
Diabetes	2.200	0.958–5.052	.063
Hyperlipidemia	0.604	0.239–1.524	.285
Renal failure	1.799	0.831–3.899	.136
Smoking	2.140	0.520–8.798	.423
Systolic blood pressure	1.010	0.993–1.027	.265
Creatinine	1.297	1.052–1.599	**.015**
Hematocrit	0.996	0.957–1.038	.863
Platelet	0.993	0.987–0.998	**.005**

P values set in boldface indicate statistical significance.

(*P*=.058), hematocrit (*P*=.401), or leukocyte count (*P*=.394).

We modeled a logistic regression analysis to determine the independent predictors of aspirin resistance. Multivariate analysis for predictors of aspirin resistance is presented in Table III. Multivariate analysis revealed that female gender (OR, 2.445; 95% CI, 1.019–5.866; *P*=.045), serum creatinine levels (OR, 1.297; 95% CI, 1.052–1.599; *P*=.015) and platelet count (OR, 0.993; 95% CI, 0.987–0.998; *P*=.005) were independent predictors of aspirin resistance in this cohort of hypertensive patients.

DISCUSSION

Aspirin resistance has been associated with coronary artery disease, cerebrovascular disease, diabetes, heart failure, and hyperlipidemia.[21–30] In parallel with data from recent studies, it is now known that the mechanisms underlying aspirin resistance are multifactorial. The benefit of antiplatelet therapy with aspirin in subjects with hypertension is well established and supported by strong trial data.[33,34] However, little is known about aspirin response in patients with arterial hypertension and results are conflicting.

The novel finding of this study was the demonstration of high aspirin resistance prevalence in hypertensive patients. We detected aspirin resistance in 21% of the hypertensive patients using the Ultegra Rapid Platelet Function Assay-ASA system (Accumetrics Inc., San Diego, CA). Various studies reporting relationships between hypertension and aspirin resistance were conducted in different patient populations such as stable coronary artery disease, and association of hypertension with aspirin resistance were shown by either univariate or multivariate analysis. Wang and coworkers[35] investigated aspirin resistance in 328 patients with stable cardiac and cerebral vascular diseases, diabetes mellitus, hypertension, and hyperlipidemia and

reported that hypertension and diabetes were relative risk factors of aspirin resistance. Similarly, Abaci and coworkers[36] studied aspirin resistance in 184 patients with a diagnosis of stable coronary artery disease or diabetes mellitus and reported that univariate analysis of aspirin nonresponsiveness was closely associated with hypertension. However, they could not show any association between hypertension and aspirin nonresponsiveness in multivariate analysis.

Our study suggests that aspirin might not have provided its desirable effects in 1 out of every 5 patients with hypertension. Such a high prevalence of aspirin resistance may be anticipated in hypertensive patients, since a number of factors including increased arterial stiffness, shear stress, and endothelial dysfunction might contribute to altered platelet reactivity and lead to relatively high frequency of aspirin resistance among subjects with hypertension.[29] However, the mechanisms underlying aspirin resistance are multifactorial and, as in our study, most patients have other cardiovascular diseases such as diabetes, hyperlipidemia, and coronary artery disease. Multivariate analyses performed to define the independent predictors of aspirin resistance are not always sufficient since some confounding factors may be missed or may not be included in the analysis. We believe that a sample with only hypertensive patients might be better in identifying the effect of hypertension on aspirin resistance. Yet, our sample and data are important as they reflect the actual hypertensive patient profile in community practice.

We also explored the effect of blood pressure control on aspirin resistance. Aspirin resistance was detected in 17.8% of the patients who had blood pressure within normal limits while aspirin resistance was present in 25.6% of the patients with poor blood pressure control; however, the difference was not statistically significant (P=.182). We believe that the reason for the lack of statistical significance was likely due to low power since there were only 42 subjects with aspirin resistance. There were not any significant differences in mean systolic and diastolic blood pressure measures between the aspirin-resistant and aspirin-sensitive hypertensive patients. Multivariate analysis also did not reveal any significant association between blood pressure measures and aspirin resistance. Feher and coworkers[37] investigated the presence of hypertension and aspirin resistance among patients with cardiovascular and cerebrovascular disease who were taking aspirin 100 to 325 mg daily. Interestingly, they found a significantly higher prevalence of hypertension among aspirin-sensitive patients compared with that seen in aspirin-resistant patients. However, they also noted that there was a significantly higher rate of β-blocker and angiotensin converting enzyme inhibitor usage among aspirin-sensitive patients and additive effect of these drugs might contribute to effective antiplatelet therapy. In our study, as the medications of the patients were diverse, they could not be incorporated into the statistical analysis. Therefore, we could not draw definite conclusions about the blood pressure control and aspirin resistance.

In most of the studies,[38,39] a higher female frequency in aspirin-resistant hypertensive patients is reported. Similarly, in our study, multivariate analysis revealed female gender as an independent predictor of aspirin resistance in hypertensive patients. Additionally, the frequencies of coronary artery disease, diabetes, and renal failure were insignificantly higher in aspirin-resistant hypertensive patients. We believe that larger numbers are needed to make definitive statements about the demographics that may be associated with aspirin resistance.

Previous studies on the effects of different doses of aspirin on different populations showed that by increasing aspirin dose, the frequency of aspirin resistance decreased both in healthy subjects[40] and in patients with stable coronary artery disease.[38] However, in our study, we did not find any difference in daily aspirin intake dose and duration of aspirin therapy between the aspirin-resistant and aspirin-sensitive hypertensive patients.

We found that creatinine level was significantly higher in aspirin-resistant patients and multivariate analysis also revealed serum creatinine levels as an independent predictor of aspirin resistance. Similarly, Lee and coworkers[38] studied 468 consecutive stable coronary artery disease patients and found that renal insufficiency was a univariate predictor of aspirin resistance. In addition to creatinine levels, we also found platelet count as the other independent predictor of aspirin resistance. Platelet count was significantly lower in aspirin-resistant patients compared to aspirin-sensitive patients. Similar to our data, Wang and coworkers[41] found that platelet count was a statistically significant univariate and multivariate predictor of aspirin nonresponsiveness when treated as continuous variables, with OR of 0.993. However, Lee and coworkers[42] and Navaez and coworkers[43] found that high platelet count was related with aspirin resistance. We believe that these conflicting results might be due to the multifactorial nature of aspirin resistance.

Study Limitations

There are some limitations to our study. It has been suggested that aspirin resistance may not be consistent over time, and measurement of aspirin resistance should be done more than once. In our study, measurement of aspirin resistance was done only once. As our study was not a clinical follow-up study, aspirin resistance was defined only biochemically and not clinically. Patients' use of aspirin was based on response to a questionnaire and was not confirmed by pill count or serum salicylate levels. Moreover, we could not include the medications of the patients into statistical analysis due to diversity of drugs. Lastly, although our sample size was not so small, factors affecting aspirin response might not be controlled in every patient and not included in the analysis (such as genetic variability or exercise status). Examination of various well characterized populations is necessary to fully elucidate the epidemiology of aspirin resistance in hypertensive patients. Yet, our study is important as it was conducted to explore aspirin resistance in hypertensive patients and the patients reflected the actual hypertensive patient profile in community practice.

CONCLUSIONS

We found that a significant number of hypertensive patients was resistant to aspirin therapy. Multivariate analysis revealed female gender, serum creatinine levels, and platelet count were independent predictors of aspirin resistance in this cohort of hypertensive patients. Further research exploring the epidemiology and mechanisms of aspirin resistance in hypertensive patients will provide additional information for preventing future cardiovascular events.

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REFERENCES

1 Ridker PM, Manson JE, Buring JE, et al. The effect of chronic platelet inhibition with low-dose aspirin on atherosclerotic progression and acute thrombosis: clinical evidence from the Physicians' Health Study. *Am Heart J*. 1991;122:1588–1592.

2 Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *Lancet*. 1988;2:349–360.

3 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.

4 Hennekens CH, Schror K, Weisman S, et al. Terms and conditions: semantic complexity and aspirin resistance. *Circulation*. 2004;110:1706–1708.

5 Macchi L, Sorel N, Christiaens L. Aspirin resistance: definitions, mechanisms, prevalence, and clinical significance. *Curr Pharm Des*. 2006;12:251–258.

6 Shantsila E, Watson T, Lip GY. Aspirin resistance: what, why and when? *Thromb Res*. 2007;119:551–554.

7 Hankey GJ, Eikelboom JW. Aspirin resistance. *Lancet*. 2006;367:606–617.

8 Gasparyan AY, Watson T, Lip GY. The role of aspirin in cardiovascular prevention: implications of aspirin resistance. *J Am Coll Cardiol*. 2008;51:1829–1843.

9 Cotter G, Shemesh E, Zehavi M, et al. Lack of aspirin effect: aspirin resistance or resistance to taking aspirin? *Am Heart J*. 2004;147:293–300.

10 Schwartz KA, Schwartz DE, Ghosheh K, et al. Compliance as a critical consideration in patients who appear to be resistant to aspirin after healing of myocardial infarction. *Am J Cardiol*. 2005;95:973–975.

11 Maree AO, Curtin RJ, Dooley M, et al. Platelet response to low-dose enteric-coated aspirin in patients with stable cardiovascular disease. *J Am Coll Cardiol*. 2005;46:1258–1263.

12 Zimmermann N, Wenk A, Kim U, et al. Functional and biochemical evaluation of platelet aspirin resistance after coronary artery bypass surgery. *Circulation*. 2003;108:542–547.

13 Zimmermann N, Weber AA, Hohlfeld T. Aspirin "resistance". *Herz*. 2008;33:270–278.

14 Catella-Lawson F, Reilly MP, Kapoor SC, et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N Engl J Med*. 2001;345:1809–1817.

15 Capone ML, Sciulli MG, Tacconelli S, et al. Pharmacodynamic interaction of naproxen with low-dose aspirin in healthy subjects. *J Am Coll Cardiol*. 2005;45:1295–1301.

16 Maree AO, Curtin RJ, Chubb A, et al. Cyclooxygenase-1 haplotype modulates platelet response to aspirin. *J Thromb Haemost*. 2005;3:2340–2345.

17 Andrioli G, Minuz P, Solero P, et al. Defective platelet response to arachidonic acid and thromboxane A(2) in subjects with Pl(A2) polymorphism of beta(3) subunit (glycoprotein IIIa). *Br J Haematol*. 2000;110:911–918.

18 Macchi L, Christiaens L, Brabant S, et al. Resistance in vitro to low-dose aspirin is associated with platelet PlA1 (GP IIIa) polymorphism but not with C807T(GP Ia/IIa) and C-5T Kozak (GP Ibalpha) polymorphisms. *J Am Coll Cardiol*. 2003;42:1115–1119.

19 Papp E, Havasi V, Bene J, et al. Glycoprotein IIIA gene (PlA) polymorphism and aspirin resistance: is there any correlation? *Ann Pharmacother*. 2005;39:1013–1018.

20 Pamukcu B, Oflaz H, Nisanci Y. The role of platelet glycoprotein IIIa polymorphism in the high prevalence of in vitro aspirin resistance in patients with intracoronary stent restenosis. *Am Heart J*. 2005;149:675–680.

21 Borna C, Lazarowski E, van Heusden C, et al. Resistance to aspirin is increased by ST-elevation myocardial infarction and correlates with adenosine diphosphate levels. *Thromb J*. 2005;3:10.

22 Sane DC, McKee SA, Malinin AI, et al. Frequency of aspirin resistance in patients with congestive heart failure treated with antecedent aspirin. *Am J Cardiol*. 2002;90:893–895.

23 Hohlfeld T, Weber AA, Junghans U, et al. Variable platelet response to aspirin in patients with ischemic stroke. *Cerebrovasc Dis*. 2007;24:43–50.

24 Berrouschot J, Schwetlick B, von Twickel G, et al. Aspirin resistance in secondary stroke prevention. *Acta Neurol Scand*. 2006;113:31–35.

25 Watala C, Pluta J, Golanski J, et al. Increased protein glycation in diabetes mellitus is associated with decreased aspirin-mediated protein acetylation and reduced sensitivity of blood platelets to aspirin. *J Mol Med*. 2005;83:148–158.

26 Anfossi G, Russo I, Trovati M. Resistance to aspirin and thienopyridines in diabetes mellitus and metabolic syndrome. *Curr Vasc Pharmacol*. 2008;6:313–328.

27 Fateh-Moghadam S, Plöckinger U, Cabeza N, et al. Prevalence of aspirin resistance in patients with type 2 diabetes. *Acta Diabetol*. 2005;42:99–103.

28 Tamminen M, Lassila R, Westerbacka J, et al. Obesity is associated with impaired platelet-inhibitory effect of acetylsalicylic acid in nondiabetic subjects. *Int J Obes Relat Metab Disord*. 2003;27:907–911.

29 Kahraman G, Sahin T, Kilic T, et al. The frequency of aspirin resistance and its risk factors in patients with metabolic syndrome. *Int J Cardiol*. 2007;115:391–396.

30 Friend M, Vucenik I, Miller M. Research pointers: platelet responsiveness to aspirin in patients with hyperlipidaemia. *BMJ*. 2003;326:82–83.

31 Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289:2560–2572.

32 Chen WH, Lee PY, Ng W, et al. Aspirin resistance is associated with a high incidence of myonecrosis after non-urgent percutaneous coronary intervention despite clopidogrel pretreatment. *J Am Coll Cardiol*. 2004;43:1122–1126.

33 Lip GY, Felmeden DC. Antiplatelet agents and anticoagulants for hypertension. *Cochrane Database Syst Rev*. 2004;3:CD003186.

34 Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet*. 1998;351:1755–1762.

35 Wang CB, Hu DY, Shi XB, et al. Aspirin resistance in patients taking small dose of aspirin. *Zhongguo Wei Zhong Bing Ji Jiu Yi Xue*. 2006;18:219–223.

36 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.

37 Feher G, Koltai K, Papp E, et al. Aspirin resistance: possible roles of cardiovascular risk factors, previous disease history, concomitant medications and haemorrheological variables. *Drugs Aging*. 2006;23:559–567.

38 Lee PY, Chen WH, Ng W, et al. Low-dose aspirin increases aspirin resistance in patients with coronary artery disease. *Am J Med*. 2005;118:723–727.

39 Gum PA, Kottke-Marchant K, Poggio ED, et al. Profile and prevalence of aspirin resistance in patients with cardiovascular disease. *Am J Cardiol*. 2001;88:230–235.

40 Gonzalez-Conejero R, Rivera J, Corral J, et al. Biological assessment of aspirin efficacy on healthy individuals: heterogeneous response or aspirin failure? *Stroke*. 2005; 36:276–280.

41 Wang JC, Aucoin-Barry D, Manuelian D, et al. Incidence of aspirin nonresponsiveness using the Ultegra Rapid Platelet Function Assay-ASA. *Am J Cardiol*. 2003;92: 1492–1494.

42 Lee YK, Kim HS, Park JY, et al. Incidence of aspirin resistance in the patient group of a university hospital in Korea [in Korean]. *Korean J Lab Med*. 2008;28:251–257.

43 Narvaez I, Sagastagoitia JD, Vacas M, et al. Prevalence and biologic profile of aspirin resistance in patients with angiographically proven coronary artery disease. *Thromb Res*. 2007;120:671–677.