RESISTANCE TO ANTIPLATELET DRUGS IN PATIENTS WITH CEREBROVASCULAR DISEASE

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Abstract:

INTRODUCTION: Cardiovascular diseases and stroke are steadily the leading causes of death in Latvia. Therefore, the greatest efforts should be given to recognize associative factors which may be modifiable to decrease the burden of ischemic events.

OBJECTIVES: The aim of this study was to examine the frequency of aspirin and clopidogrel resistance and its associated risk factors in patients with acute cerebrovascular events.

METHODS: The prospective, descriptive study included 204 patients. Patients were considered biochemical resistant to aspirin if platelet aggregation was ≥550 ARU, whereas biochemical clopidogrel resistance was defined when platelet inhibition was >230 PRU.

RESULTS: Biochemical aspirin resistance was found in 27 (13%) patients, whereas clopidogrel resistance - in 44 (22%) patients. Five patients (2%) had resistance to both antiplatelet drugs. In the analysis of blood parameters, none were associated with aspirin resistance, except the level of triglycerides which were lower in the aspirin resistance group (p=0.001; r=0.26). In the analysis of clopidogrel sensitivity there was a difference in diabetes prevalence where it was more frequent in the clopidogrel resistance group (15.6% vs. 40.9%; p=0.001; r=0.255). Patients with clopidogrel resistance had higher levels of triglycerides 1.7 (1.3-2.6) than patients grouped as sensitive 1.4 ((1.1-2.0), p=0.033; r=0.16).

CONCLUSION: Biochemical aspirin and clopidogrel resistance are quite common in patients with cerebrovascular diseases in Latvia. Our study found that patients with diabetes and elevated glycosylated hemoglobin level were more prone to clopidogrel biochemical resistance. However, the association between aspirin resistance and clinical, laboratory data remains inconclusive.

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Keywords: aspirin, clopidogrel, resistance, stroke

Introduction

According to the World Health Organization, ischemic heart disease and stroke are the leading causes of global death rates around the world, accounting for 15.2 million deaths in 2016 (World Health Organization, 2018). Likewise, cardiovascular diseases and stroke are steadily the leading causes of death in Latvia (OECD, 2017). Therefore, the greatest efforts should be given to recognize the associative factors which may be modifiable to decrease the burden of ischemic events for the improvement of preventive measures of cerebrovascular diseases.

Atherosclerosis is a chronic systemic inflammatory disease affecting all arteries in the body, where platelet activation takes one of the main roles (Badimon et al., 2012). Therefore, antiplatelet therapy is recommended as standard therapy for the prevention of stroke (Kim et al., 2009). The most commonly used antiplatelet agents for the prevention of ischemic stroke are acetylsalicylic acid (aspirin) and clopidogrel. According to guidelines, aspirin is the first line therapy for atherothrombotic stroke prevention (Powers et al., 2018). However, clopidogrel has also shown equal effectiveness in preventing recurrent ischemic stroke compared to aspirin (CAPRIE Steering Committee, 1996). If there is a resistance to antiplatelets, the prevention of stroke is not sufficient and it may lead to recurrent atherothrombotic events.

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Resistance is defined as the ability to not be affected by something (English Oxford Dictionary, 2018). An exact definition of "resistance" to antiplatelet therapy on the basis of physiology does not exist. Therefore, patients should be categorized as sensitive versus resistant to antiplatelet drugs (Feher et al., 2010). The term clinical aspirin failure (clinical 'resistance') refers to those patients who have had recurrent ischemic events while on aspirin therapy. The term platelet non-responsiveness to aspirin (laboratory 'resistance', biochemical aspirin resistance) describes the inability of aspirin to inhibit arachidonic acid and/or collagen induced platelet aggregation (Mijajlovic et al., 2013). The mechanism of antiplatelet resistance is multifactorial. These mechanisms can be divided into clinical, cellular and genetic factors. Clinical factors are the poor compliance to prescribed medication, problems with drug absorption, drug interactions, hyperglycemia, hyperlipidemia. Cellular factors are the dysregulation of COX-1 (cyclooxygenase-1) and COX-2 mRNA, platelet activation by erythrocytes and fluctuations of hormone levels. Genetic factors are the polymorphism of enzymes, their receptors and clotting factors (Fong et al., 2011).

Although the exact prevalence of antiplatelet resistance in ischemic stroke is not known, the prevalence of clinical aspirin failure ranges from 5% to 60% (whereas clinical clopidogrel resistance has been reported from 4 to 30% (Kim et al., 2018; Zhang, Wang, & Zhou, 2017; Nguyen, Diodati, &Pharand, 2005). The causes of discrepancy in the prevalence of antiplatelet medications can be explained by different factors. Nevertheless, there is need to identify those patients, who may have resistance to antiplatelet medications because this could be one of the measures which may be managed to decrease the high incidence of cerebrovascular events in Latvia. Therefore, the aim of the study was to examine the frequency of aspirin and clopidogrel resistance and its associated risk factors in patients with acute cerebrovascular events.

Materials and methods

The prospective, descriptive study included patients hospitalized in the Neurology Department of PaulsStradins Clinical University Hospital between October 2016 and December 2017. Inclusion criteria for all consenting patients were as follows: age older than 18 years; hospitalization due to acute ischemic stroke or transient ischemic attack; intra- or extra cranial severe artery stenosis; use of dual antiplatelet therapy (aspirin (100mg) and clopidogrel (75mg)) at least for 5 days. Excluding criteria were: the period of dual antiplatelet therapy less than 5 days; technical errors as hemolysis of blood sample or long blood sample transportation period to the laboratory (more than 2 hours); patient disagreement to participate in the study.

A biochemical resistance test was performed using a peripheral blood sample taken from both arms of patients into 2 Greiner Vacuette tubes containing 3.2% sodium citrate. Samples were collected at the hospital with subsequent transportation to laboratory in an hour. Platelet function was determined through the VerifyNow System analyzer. The VerifyNow System analyzer measured aspirin induced platelet dysfunction with arachidonic acid as an activating agonist. The results were expressed in Aspirin Reaction Units (ARU). Clopidogrel induced platelet dysfunction was measured using ADP (adenosine diphosphate) and PGE1 (prostaglandin E1), thrombin receptor activating peptides as activating agonists. The results were expressed in Plavix Reaction Units (PRU). Patients were considered biochemical resistant to aspirin if platelet aggregation was ≥550 ARU, whereas biochemical clopidogrel resistance was defined when platelet inhibition was > 230 PRU. The demographic data, comorbidities (diabetes mellitus (DM), arterial hypertension (AH), coronary artery disease (CAD), congestive heart failure (CHF), oncology, atrial fibrillation (AF), peripheral artery disease (PAD) and cerebrovascular events), vascular risk factors, previously administrated medications were obtained from patient's medical records and recorded on a standardized form.

Informed consent was obtained from all participants of the study. Ethical permission was granted by the University of Latvia Ethics Committee.

Descriptive statistics were used to analyze the demographics and clinical characteristics of the population. The normal distribution of data was tested with the Kolmogorov-Smirnov test. Categorical variables were presented as counts and percentages. Continuous variables were described as the median and interquartile range (IQR). To explore an association between categorical variables the Chi-square test was performed. Continuous variables were compared with the Mann-Whitney U test. A two-sided p-value < 0.05 was considered statistically significant. To understand whether differences

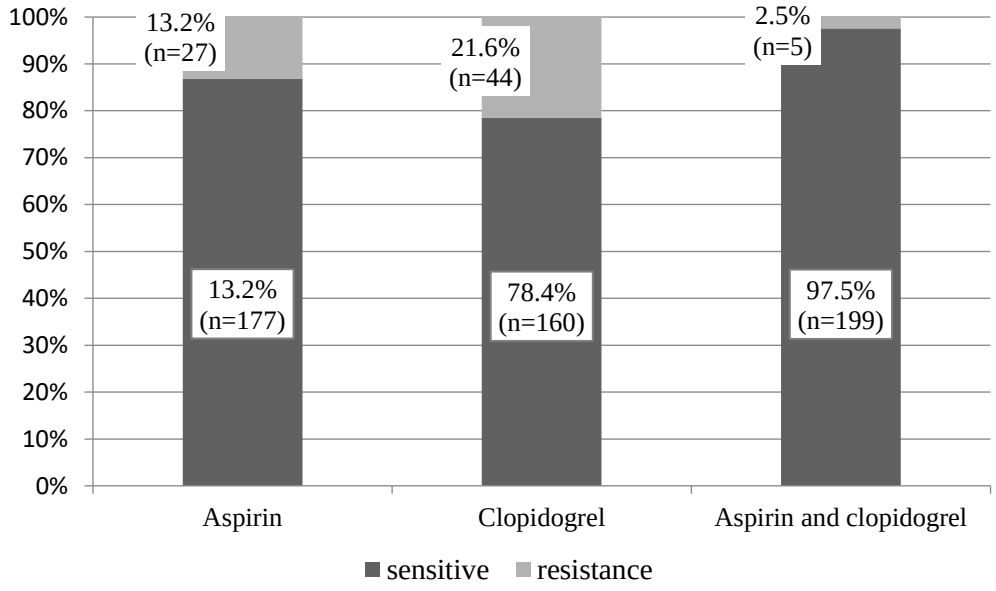
were statistically meaningful, Cramer's V (<0.3=small effect size, 0.3 - 0.5 = medium effect size, >0.5=large effect size) for Pearson Chi-square test and r (<0.3=small effect size, 0.3-0.5=medium effect size, >0.5=large effect size) for Mann-Whitney U test were used. Statistical analyses were performed using IBM SPSS Statistics (version 23 for Windows, IBM Corp., Somers, NY, USA).

Results

Frequency of aspirin and clopidogrel resistance.

A total of 204 patients with an ischemic stroke or transient ischemic attack (TIA) were studied. There were33% (n=68) females, median age of the study population was 72 (IQR 61-80) years. Biochemical aspirin resistance was found in 27 patients (13%), whereas clopidogrel resistance - in 44 patients (22%). Five patients (2%) had resistance to both antiplatelet drugs. The frequency of aspirin and clopidogrel resistance is shown in Figure1.

Figure 1: Frequency of aspirin and clopidogrel resistance.



Source: Authors

Risk factors associated with aspirin resistance.

The proportion of gender distribution in aspirin resistant and sensitive groups were equal. Although patients were older in the aspirin resistant group than in the aspirin sensitive group (Me 76 vs. Me 67, p=0.005), the effect size of statistical significance was small (r=0.2). Analyzing frequencies of comorbidities (DM, AH, CAD, CHF, oncology, AF, PAD and cerebrovascular events) in both groups, there was no significant difference between aspirin sensitive and resistant groups. Demographic and clinical characteristics of aspirin sensitive and resistant patients are listed in Table1.

Table 1: Demographic and clinical characteristics of aspirin sensitive and resistant patients

	Aspirin sensitive (n=177)	**Aspirin resistant** (n=27)	***p* value**	**Effect size**
Age, years, median (IQR)	67 (61-76)	76 (68-78)	0.005*	r=0.2
Male, n, %	118 (67%)	18 (67%)	>0.999	Cramer's V<0.001
Female, n, %	59 (33%)	9 (33%)		
Prior TIA	7 (4%)	2 (7.4%)	0.339	Cramer's V=0.057
Prior stroke	61 (34.5%)	8 (29.6%)	0.621	Cramer's V=0.035
Acute TIA	27 (15.3%)	5 (18.5%)	0.776	Cramer's V=0.03
Acute stroke	145 (81.9%)	22 (81.5%)	>0.999	Cramer's V=0.004

IQR, interquartile range; TIA - transient ischemic attack; * p<0.05

Source: Authors

In the analysis of biochemical blood parameters - lipid profile, glycosylated hemoglobin (HbA1c), C-reactive protein (CRP) and white blood cells count (WBC) - none were associated with aspirin resistance, except the level of triglycerides. Patients who were resistant to aspirin showed lower levels of triglycerides (p=0.001; r=0.26) (Table 2). Severity of carotid artery stenosis in our study was not associated with aspirin biochemical resistance (p=0.65; *Cramer V*=0,131). The frequency of carotid artery occlusion was higher in aspirin resistant group, but the difference was not statistically significant (15.8% and 22.2%, p=0.52). Laboratory data of aspirin sensitive and resistant patients are listed in Table 2.

Table 2: Laboratory data of aspirin sensitive and resistant patients

	Aspirin sensitive (n=177)	**Aspirin resistant (n=27)**	***p* value**	**Effect size**
HbA1C, %	6.0 (5.5-6.8)	5.9 (5.5-6.3)	0.56	r=0.06
HDL, mmol/L	1.1 (0.9-1.4)	1.2 (1.0-1.5)	0.16	r=0.1
LDL, mmol/L	2.9 (2.1-3.9)	2.9 (2.2-3.9)	0.65	r=0.03
TG, mmol/L	1.5 (1.2-2.3)	1.1 (0.8-1.3)	0.001*	r=0.26*
Cholesterol, mmol/L	5.1 (4.1-6.0)	4.6 (3.8-6.0)	0.48	r=0.05
Troponin I, ng/L	10 (6-34)	9.5 (6-98.5)	0.392	r=0.06
CRP, mg/L	4 (1.4-12.3)	4.6 (0.76-12.98)	0.685	r=0.03
WBC, 10^9/L	7.8 (6.5-9.6)	7.9 (6.1-9.1)	0.498	r=0.05

Values are presented in as median (IQR, interquartile range);
HbA1C, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerids; CRP,C-reactive protein; WBC, white blood cells; * p<0.05

Source: Authors

In the analysis of previously and in a hospital setting used medications (angiotensin-converting-enzyme inhibitors (ACE-I), calcium channel antagonists, beta blockers, angiotensin II receptor blockers (ARBs), loop diuretics, proton pump inhibitors and diabetes medications), there was no statistically significant differences between aspirin sensitive and resistant patients (p>0.2).

Risk factors associated with clopidogrel resistance.

Comparing gender distribution between clopidogrel sensitive and clopidogrel resistant groups, there was no statistically significant difference between both groups. Median age was similar in both groups (Me 68.5 vs. Me 72.5, p>0.05). In the analysis of comorbidities (AH, CAD, CHF, oncology, AF, PAD and cerebrovascular events), patients with hypertension grade 3 were more prone to have resistance to clopidogrel than patients with hypertension grade 1 and 2, but the difference was not statistically significant (p>0.05). There was significant difference of DM prevalence where DM was more frequent in clopidogrel resistance group (15.6% vs. 40.9%; p=0.001; r=0.255). Demographic and clinical characteristics of clopidogrel sensitive and resistant patients are listed in Table 3.

Table 3: Demographic and clinical characteristics of clopidogrel sensitive and resistant patients

	Clopidogrel sensitive (n=160)	**Clopidogrel resistant (n=44)**	***p* value**	**Effect size**
Age, years, median (IQR)	68.5 (61-76)	72.5 (63.25-80)	0.103	r=0.11
Male, n, %	108 (67.5%)	28 (63.4%)	0.63	Cramer's V=0.034
Female, n, %	52 (32.5%)	16 (36.6%)		
Prior TIA	8 (5%)	1 (2.3%)	0.687	Cramer's V=0.055
Prior stroke	53 (33.1%)	16 (36.4%)	0.688	Cramer's V=0.028
Acute TIA	25 (15.6%)	7 (15.9%)	0.663	Cramer's V=0.004
Acute stroke	116 (72.5%)	35 (79.5%)	0.567	Cramer's V=0.035

IQR, interquartile range; TIA - transient ischemic attack;

Source: Authors

There were also higher levels of HbA1c in the clopidogrel resistant group (5.8 (5.5-6.4) vs. 6.7 (5.7-8.7), p=0.016; r=0.23). Apart from significant association between HbA1c and clopidogrel resistance, there was also association with lipid profile. Patients with a clopidogrel resistance had higher level of triglycerides (1.7 (1.3-2.6)) than patients sensitive to clopidogrel (1.4 (1.1-2.0), (p=0.033; r=0.16)). There was a tendency of slightly elevated high-density lipoprotein levels (1.2 (1.0-1.4) in resistant

compared to clopidogrel sensitive group (1.1 (0.8-1.3), (p=0.027; r=0.16)), however the effect size of statistical significance was small. Laboratory data of clopidogrel sensitive and resistant patients are listed in Table 4.

Table 4: Laboratory data of clopidogrel sensitive and resistant patients

	Clopidogrel sensitive (n=160)	**Clopidogrel resistant (n=44)**	***p* value**	**Effect size**
HbA1C, %	5.8 (5.5-6.4)	6.7 (5.7-8.7)	0.016*	r=0.23
HDL, mmol/L	1.2 (1.0-1.4)	1.1 (0.8-1.3)	0.027*	r=0.16
LDL, mmol/L	2.9 (2.2-3.9)	3.0 (2.0-3.7)	0.799	r=0.02
TG, mmol/L	1.4 (1.1-2.0)	1.7 (1.3-2.6)	0.033*	r=0.16
Cholesterol, mmol/L	4.9 (4.1-6.0)	5.0 (4.0-5.9)	0.879	r=0.01
Troponin I, ng/L	10 (6-41.5)	9.5 (6-33.3)	0.961	r=0.004
CRP, mg/L	4.3 (1.3-14.0)	2.9 (1.4-9.8)	0.491	r=0.05
WBC, 10^9/L	8.2 (6.6-9.6)	7.3 (6.0-8.9)	0.033*	r=0.15

Values are presented in as median (IQR, interquartile range);
HbA1C, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerids; CRP,C-reactive protein; WBC, white blood cells; * p<0.05

Source: Authors

Apart from drugs administered for DM, there were not any observed statistically significant differences between clopidogrel sensitive and resistant groups when previously used medications in outpatient setting were compared. In hospital settings, administration of insulin (5.6% vs 18.2%, p=0.013, Cramer's V=0.187) and gliclazide (0.6 vs 9.1%, p= 0.08; Cramer's V=0.225) was more frequent in the clopidogrel resistant group than in the sensitive group. Previously used medications which showed association with clopidogrel resistance was the diabetic drug - metformine which was more frequently used in the clopidogrel resistant group than the sensitive group (p=0.036).

Discussion

In our study aspirin resistance was confirmed in 27 (13% of 204) patients and clopidogrel resistance - in 44 (21.6%) patients. Using rough estimation, there could be approximately 250 147 clopidogrel and 407 647 aspirin resistant inhabitants in Latvia (United Nations, 2017). In previous studies, aspirin resistance varied from 5 to 60% (Kim et al., 2018; Zhang et al., 2017) and clopidogrel resistance - from 4 to 30% (Nguyen et al., 2005). Considering clinical and laboratory parameters being associated with resistance to aspirin, we haven't found any specific risk factors, except triglyceride levels (p= 0.001, r= 0.26). The association between aspirin resistance and triglyceride levels was previously described, although, the pathway is still unknown but it may be explained by diminished platelet membrane fluidity resulting in insufficient inhibition of platelets (Karepov, Tolpina, Kuliczkowski, &Serebruany, 2008). *Hovens et al.* (2007) also noticed that aspirin resistance was associated with higher triglyceride levels in diabetic patients. It has been suggested that there is a correlation between high triglyceride level and aspirin resistance (Karepov et al., 2008; Liu et al., 2011; Uzun et al.,2015). However, the results of our cohort showed a contrary association. There was association between lower triglyceride levels and aspirin resistance. The explanation of our results could be related to the administration of high dose statins in the aspirin resistant group where patients had more often severe carotid artery stenosis or occlusion. It has been established that statins significantly reduce triglyceride levels by 10-19% (Miller, n.d; Colhoun, et al.,2004; Scandinavian simvastatin survival study group, 1994; Ridker et al., 2008). Further investigations should be provided to confirm these statements.

In our study there was no association between gender and aspirin resistance (p=0.99), which is according to the findings from a study by *Becker et al.*(2006). Although the authors of the literature review concluded that women are less responsive to aspirin in myocardial infarction rates (Yerman, Gan, & Sin, 2007), they found that low dose aspirin decreased platelet activity equally in both genders, despite of the higher platelet activity on baseline and additional risk factors such as menopause and hormone therapy (Becker et al., 2006). However, mechanism of distinct aspirin effect on platelets in men and women remains unknown (Becker et al., 2006; Yerman et al., 2007). In our study, there was no significant difference of genders between clopidogrel resistant and sensitive groups as well, whereas in population-based studies female gender was more prone to increased risk of clopidogrel resistance (Su et al. 2017; Sakr, Alamri, Almoghairi, Alkhudair, & Al Masood, 2016). The

discrepancy of these results may be due to different population groups. Lately, it has been shown that genetic factors also have influence on resistance to clopidogrel, but significant association between gender and P2RY12 (Li et al., 2017) and ABCB1 gene rs1045642 (Su, Hu, & Li, 2015) polymorphisms haven't been found.

Some factors, that are associated with antiplatelet drug resistance such as non-compliance, absorption, dosage, drug interactions, need to be discussed in more detail. In this study the administration of antiplatelet drugs was closely monitored, therefore non-compliance was excluded. It is essential, because in another study patients who were estimated as "resistant" became sensitive to antiplatelet drugs after a controlled drug administration in hospital setting (Meen et al., 2008). In our study coated aspirin was used, which is absorbed in the duodenum. Based on available studies, during the exchange to other forms of aspirin (immediate-release aspirin or chewing enteric-coated aspirin), "pseudoaspirin" resistance may be observed by delayed and diminished drug absorption (Grosser et al, 2013; Cox et al., 2006).For safety reasons, the 100 mg aspirin dosage was used because studies have shown increased bleeding risk with higher aspirin doses (Kim et al., 2018; Antithrombotic Trialists' Collaboration, 2002; Rodrıguez & De Abajo, 2001). The association between aspirin dose and medication resistance was out of the scope of this study.

In our study association between antiplatelet resistance and interaction with other drugs such as proton pump inhibitors, beta blockers, ACE-Inhibitors, ARBs, diuretics, hypoglycemic drugs was not found, although it is known that cytochrome P450 3A4 agents (e.g. statins) can block the transformation of clopidogrel to its active metabolite (Grotta et al., 2016). Antiplatelet activity may be diminished by cytochrome P450 2C19 inhibitors (e.g. proton pump inhibitors) as well (Grotta et al., 2016). Mainly omeprazole and esomeprazole have a greater effect on clopidogrel metabolism by the reduction of antiplatelet activity, therefore proton pump inhibitors such as omeprazole should be avoided in co-administration with clopidogrel according to the recommendations by the USA Food and drug administration (Johnson, Chilton, & Liker, 2014; Rodrıguez et al., 2001; Food and Drug Administration, 2009). Furthermore, nonsteroidal anti-inflammatory drugs have suppressive effects on the antithrombotic action of aspirin by reversibly binding to COX -1 (Shibata, Akagi, Nozawa, Shimomura, & Aoyama, 2017).

In our cohort, patients with diabetes had a higher propensity towards biochemical clopidogrel resistance whereas association with aspirin resistance was not found. Diabetes, elevated Hb1Ac were previously found to be associated with increased prevalence of clopidogrel resistance (Sakr et al., 2016; Jung, Tantry, Gurbel, &Jeong, 2015). However, data of association between diabetes and aspirin resistance are controversial. *Tasdemir et al.*(2014) have found that the prevalence of aspirin resistance is similar in diabetic and non-diabetic patients, whereas there are several studies without similar findings (Gokalp, Tuzcu, Irmak, Bahceci, & Demirpence, 2014; Antithrombotic Trialists' Collaboration, 2002). Patients with DM have increased prothrombotic condition due to platelet dysfunction, platelet aggregation and activation, increased platelet turnover caused by oxidative stress, persistent thromboxane-dependent platelet activation, increased P2Y12 receptor signaling, insulin resistance and increased protein glycosylation (Du, Lin, & Wang, 2016; Prabhakaran, Wells, Lee, Flaherty, & Lopes, 2008). Although weight was not evaluated in our study, obesity is also associated with increased platelet activity, adhesiveness and diminished response to antiplatelet drugs (Du et al., 2016).

Conclusions

Biochemical aspirin and clopidogrel resistance are quite common in patients with cerebrovascular diseases in Latvia. Our study found that patients with diabetes and elevated glycosylated hemoglobin level were more prone to clopidogrel biochemical resistance while conclusions about the association between aspirin resistance and clinical and laboratory data remain inconclusive. It is not recommended to test patients routinely for antiplatelet resistance. However, it could provide some benefits in high cerebro- and cardio-vascular risk patients and in cases of recurrent atherothrombotic events. Laboratory tests for antiplatelet resistance could help to establish an individualized treatment plan for each patient. However, further studies are needed to determine whether there is a clinical correlation with biochemical antiplatelet resistance in a larger cohort of cerebrovascular disease patients.

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References

Antithrombotic Trialists' Collaboration. (2002). Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ, 324(7329), 71–86. https://doi.org/10.1136/bmj.324.7329.71

Badimon, L., Padró, T., Vilahur, G. (2012). Atherosclerosis, platelets and thrombosis in acute ischaemic heart disease. Eur Heart J Acute Cardiovasc Care, 1(1), 60-74. https://doi.org/10.1177/2048872612441582

Becker, D. M., Segal, J., Vaidya, D., Yanek, L. R., Herrera-Galeano, J. E., Bray, P. F., et al. (2006). Sex differences in platelet reactivity and response to low-dose aspirin therapy. J Am Med Assoc. 295(12), 1420–7. https://doi.org/10.1001/jama.295.12.1420

CAPRIE Steering Committee. (1996). A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events. Lancet, 348(9038),1329-39. https://doi.org/10.1016/S0140-6736(96)09457-3

Colhoun, H. M, Durrington, P. N., Hitman, G. A., Neil, H. A., Livingstone, S. J., Thomason, M. J., Mackness, M. I. , Charlton-Menys, V., Fuller, J. H., CARDS investigators BDJ, Colhoun, H. M., Betteridge, D. J., Durrington, P. N., Hitman, G. A., Neil, H. A. , et al. (2004). Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentrerandomised placebo-controlled trial. Lancet, 364(9435), 685-96. https://doi.org/10.1016/s0140-6736(04)16895-5

Cox, D., Maree, A. O., Dooley, M., Conroy, R., Byrne, M. F., Fitzgerald, D. J. (2006). Effect of enteric coating on antiplatelet activity of low-dose aspirin in healthy volunteers. Stroke, 37(8),2153–8. https://doi.org/10.1161/01.STR.0000231683.43347.ec

Du, G., Lin, Q., Wang, J. (2016). A brief review on the mechanisms of aspirin resistance. Int J Cardiol, 220, 21–26. https://doi.org/10.1016/j.ijcard.2016.06.104

European Observatory on Health Systems and Policies (OECD). (2017). Latvia: Country Health Profile 2017. State of Health in the EU. Brussels: OECD Publishing, Paris/European Observatory on Health Systems and Policies. Retrieved from https://doi.org/10.1787/9789264283466-en

Feher, G., Feher, A., Pusch, G., Koltai, K., Tibold, A., Gasztonyi, B., Papp, E., Szapary, L., Kesmarky. G., Toth, K. (2010). Clinical importance of aspirin and clopidogrel resistance. World J Cardiol, 2(7), 171-186. https://doi.org/10.4330/wjc.v2.i7.171

Fong, J., Cheng-Ching, E., Hussain, M. S., Katzan, I., Gupta, R. (2011). Predictors of biochemical aspirin and clopidogrel resistance in patients with ischemic stroke. J Stroke Cerebrovasc Dis, 20(3), 227–30. https://doi.org/10.1016/j.jstrokecerebrovasdis.2009.12.004

Gokalp, D., Tuzcu, A., Irmak, S., Bahceci, M., Demirpence, O. (2016). Frequency of Aspirin Resistance in Patients With Type 1 and 2 Diabetes Mellitus and Its Association With Metabolic Parameters. Int J Surg Med, 2(3), 122-26. https://doi.org/10.5455/ijsm.aspirin-resistance-diabetes

Grosser, T., Fries, S., Lawson, J. A., Kapoor, S. C., Grant, G. R., FitzGerald, G. A. (2013). Drug resistance and pseudoresistance: An unintended consequence of enteric coating aspirin. Circulation, 127(3):377–85. https://doi.org/10.1161/CIRCULATIONAHA.112.117283

Grotta, J. C. , Albers, G. W., Broderick, J. P., Kassner, S. E., Lo, E. H. , Mendelow, A. D., Sacco, R. L., Wong, L. K. S. (Ed.). (2016). Chapter 61, Antiplatelet Therapy for Secondary Prevention of Stroke. Stroke: Pathophysiology, Diagnosis, and Management 6th ed. Elsevier. Retrieved from https://www.elsevier.com/books/stroke/grotta/978-0-323-29544-4

Hovens, M. M. C., Snoep, J. D., Groeneveld, Y., Tamsma, J.T., Eikenboom, J. C. J., Huisman, M.V. (2007). High levels of low-density lipoprotein cholesterol and triglycerides and suboptimal glycemic control predict diminished ex vivo aspirin responsiveness in patients with Type 2 diabetes. J ThrombHaemost, 5(7), 1562–4. https://doi.org/10.1111/j.1538-7836.2007.02596.x

Johnson, D. A., Chilton, R., Liker, H. R. (2014). Proton-pump inhibitors in patients requiring antiplatelet therapy: New FDA labeling. Postgrad Med,126(3),239–45. https://doi.org/10.3810/pgm.2014.05.2772

Jung, J. H, Tantry, U. S., Gurbel, P. A., Jeong, Y. H.(2015). Current antiplatelet treatment strategy in patients with diabetes mellitus. Diabetes Metab J ,39(2), 95–113. https://doi.org/10.4093/dmj.2015.39.2.95

Karepov, V., Tolpina, G., Kuliczkowski, W., Serebruany, V. (2008). Plasma triglycerides as predictors of platelet responsiveness to aspirin in patients after first ischemic stroke. Cerebrovasc Dis., 26(3), 272–6. https://doi.org/10.1159/000147455

Kim, J. O., Kim, T., Kim, J. G., Sohn, S., Kim, D., Lee, S. J. (2018). Poor Response to Aspirin on Platelet Function Assay and the Associated Factors in Patients with Ischemic Stroke. EC Neurology, 9(2), 52–5. Retrieved from https://www.ecronicon.com/ecne/pdf/ECNE-09-00268.pdf

Li, M., Wang, H., Xuan, L., Shi, X., Zhou, T., Zhang, N, Miaonan Li, M. S., Hongju Wang, M. D., Ling Xuan, M. S., Xiaojun Shi, B. S., Tong Zhou, M. S., Ningru Zhang, M. S., Yuli Huang, M. S. (2017). Associations between P2RY12 gene polymorphisms and risks of clopidogrel resistance and adverse cardiovascular events after PCI in patients with acute coronary syndrome. Medicine, 96(14), e6553. https://doi.org/10.1097/MD.0000000000006553

Liu, L., Cao, J., Fan, L., Hu, G., Hu, Y., Zhu, B., et al. (2011). Prevalence and risk factors for aspirin resistance in elderly patients with type 2 diabetes. Int J Gerontol, 5(2), 112–6. https://doi.org/10.1016/j.ijge.2011.04.016

Meen, O., Brosstad, F., Khiabani, H., Gjertsen, H., Lauritsen, M. E., Pedersen, T. M., Bjørnsen, S., Schjelderup, N. M., Ameln, W., Ng, E. C., Wettergreen, M., Siddique, S. P., Erikssen, G. (2008). No case of COX-1-related aspirin resistance found in 289 patients with symptoms of stable CHD remitted for coronary angiography. Scand. J. Clin. Lab Invest, 68 (3), 185–19. https://doi.org/10.1080/00365510701601673

Mijajlovic, M. D., Shulga, O., Bloch, S., Covickovic-Sternic, N., Aleksic, V., Bornstein, N. M. (2013). Clinical consequences of aspirin and clopidogrel resistance: An overview. ActaNeurolScand, 128(4), 213–9. https://doi.org/10.1111/ane.12111

Miller, M. What Are the Effects of Statins on Triglycerides and What Are the Results of Major Outcomes Studies? Medscape. Retrieved from https://www.medscape.org/viewarticle/589010

Nguyen, T. A., Diodati, J. G., Pharand, C. (2005). Resistance to clopidogrel: A review of the evidence. J Am CollCardiol, 45(8), 1157–64. https://doi.org/10.1016/j.jacc.2005.01.034

Powers, W. J., Rabinstein, A. A., Ackerson, T., Adeoye, O. M., Bambakidis, N. C., Becker, K., Biller, J., Brown, M., Demaerschalk, B. M., Hoh, B., Jauch, E. C., Kidwell, C. S., Leslie-Mazwi, T. M., Ovbiagele, B., Scott, P. A., Sheth, K. N., Southerland, A. M., Summers, D. V., Tirschwell, D. L, American Heart Association Stroke Council.(2018). 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke, 49(3), e46-e110. https://doi.org/10.1161/STR.0000000000000158.

Prabhakaran, S., Wells, K. R., Lee, V. H., Flaherty, C. A., Lopes, D. K. (2008). Prevalence and risk factors for aspirin and clopidogrel resistance in cerebrovascular stenting. Am J Neuroradiol, 29(2), 281–5. https://doi.org/10.3174/ajnr.A0818

Resistance [Def. 2.1]. English Oxford Dictionary. Retrieved December 21, 2018, from https://en.oxforddictionaries.com/definition/resistance

Ridker, P. M., Danielson, E., Fonseca, F. A. H., Genest, J., Gotto, A. M., Kastelein, J. P., Glynn, R. J., Koenig, W., Libby, P., Lorenzatti, A. J., MacFadyen, J. G., Nordestgaard, B. G., Shepherd, J., Willerson, J. T., Glynn, R. J. (2008). Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein. New England Journal of Medicine, 359(21), 2195–2207. https://doi.org/10.1056/nejmoa0807646

Rodrıguez, L. A. G., De Abajo, F. J. (2001). Association between aspirin and upper gastrointestinal complications: Systematic review of epidemiologic studies. Br J ClinPharmacol, 52(5), 563–71. https://doi.org/10.1046/j.0306-5251.2001.01476.x

Sakr, H.I, Alamri, H. S., Almoghairi, A. M., Alkhudair, A. A., Al Masood, A. S. (2016). Prevalence and risk factors of clopidogrel non-response among Saudi patients undergoing coronary angiography. Saudi Med J, 37(2), 166–72. https://doi.org/10.15537/smj.2016.2.14263.

Scandinavian simvastatin survival study group. (1994). Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). The Lancet, 344(8934), 1283-89. https://doi.org/10.1016/s0140-6736(94)90566-5

Shibata, K., Akagi, Y., Nozawa, N., Shimomura, H., Aoyama, T. (2017). Influence of nonsteroidal anti-inflammatory drugs on aspirin's antiplatelet effects and suggestion of the most suitable time for administration of both agents without resulting in interaction. J Pharm Heal Care Sci Journal of Pharmaceutical Health Care and Science, 3(1):9. https://doi.org/10.1186/s40780-017-0078-7

Su, J. F., Hu, X. H., Li, C.Y. (2015). Risk factors for clopidogrel resistance in patients with ischemic cerebral infarction and the correlation with abcb1 gene rs1045642 polymorphism .ExpTher Med, 9(1), 267–71. https://doi.org/10.3892/etm.2014.2058

Su, J., Yu, Q., Zhu, H., Li, X., Cui, H., Du, W., et al. (2017). The risk of clopidogrel resistance is associated with ABCB1 polymorphisms but not promoter methylation in a Chinese Han population. PLoSOne, 12(3), 1–16. https://doi.org/10.1371/journal.pone.0174511

Tasdemir, E., Toptas, T., Demir, C., Esen, R., Atmaca, M. (2014). Aspirin resistance in patients with type II diabetes mellitus. Ups J Med Sci, 119(1), 25–31. https://doi.org/10.3109/03009734.2013.861549

United Nations. (2017). World Population Prospects: The 2017. Revision. 2017. Retrieved from https://population.un.org/wpp/DataQuery/

US Food and Drug Administration. (2009). FDA Announces New Warning on Plavix: Avoid Use with Prilosec/Prilosec OTC. Retrieved from https://wayback.archive-it.org/7993/20170113011724/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2009/ucm191169.htm

Uzun, F., Biyik, I., Akturk, I. F., Erturk, M., Yalcin, A. A., Surgit, O., et al. (2015). Antiplatelet resistance and the role of associated variables in stable patients treated with stenting. PostepyKardiolInterwencyjnej, 11(1), 19-25. https://doi.org/10.5114/pwki.2015.49180

World Health Organization. (2018). The top 10 causes of death. Geneva: World Health Organization. Retrieved from http://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death

Yerman, T., Gan, W. Q., Sin, D. D. (2007). The influence of gender on the effects of aspirin in preventing myocardial infarction. BMC Med, 5(29). https://doi.org/10.1186/1741-7015-5-29

Zhang, N., Wang, Z., Zhou, L. (2017). Aspirin resistance are associated with long-term recurrent stroke events after ischaemic stroke. Brain Res Bull, 134, 205–10. https://doi.org/10.1016/j.brainresbull.2017.08.012