



# Correlation of Abnormal Response to Acetylsalicylic Acid and the Phenomenon of Carotid Artery Restenosis

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## Abstract

The purpose of carotid endarterectomy and long-term administration of acetylsalicylic acid to a group of patients suffering from carotid arteries stenosis is to reduce the risk of ischemic stroke of the central nervous system. However, the long-term effects of the treatment process are adversely impacted by the phenomenon of re-stenosis of the unclogged artery (carotid artery restenosis), as well as the widely discussed in literature lack of a proper response to the antiplatelet effect of acetylsalicylic acid (i.e. aspirin resistance). The authors of this study have attempted to investigate the correlation of both pathologies.

The study was conducted in the years 2011-2013 at the Vascular Surgery and Angiology Clinic in Warsaw (at the Centrum Medyczne Kształcenia Podyplomowego, Medical Postgraduate Training Centre). Qualified for the study were 181 patients, with the mean age of 68 years, of whom 70% were male and whose average body weight was that of 76 kg (167.2 lbs); the patients were administered 75 mg/day of Acetylsalicylic Acid (ASA). Control group was formed from 36 patients. Restenosis was defined as a reduction in vessel diameter by a minimum of 50% (75% of the surface area), as confirmed by a Doppler Duplex ultrasound examination where the peak systolic velocity ( $V_{max}$ )  $>125$  cm/sec or peak systolic ratio (ICA/CCA)  $>2$ . Platelet reactivity was measured using the method of impedance aggregometry (Multiplate Dynabyte, Munich Germany). The average observation period was 18 months since the time of the operation.

Parameters characterizing the study group were described using the standard statistical tools: average values and standard deviation, medians, and quarters or frequency tables. The relationships between selected pairs of variables were examined respectively by using the chi square or Student's t-test, with possible amendments to unequal variances.

With the help of multivariate logistic regression models, a study was performed on the effect of some factors on the likelihood of resistance to antiplatelet effects of aspirin. The models take into account the following factors: blood biochemical parameters, co-morbidities, use of other drugs. Using stepwise elimination, some statistically significant variables selected were at 0.05, wherein it is assumed that the model preserves variables for which the test does not exceed the level of 0.1. The predictive value of the models was evaluated using the ROC curve graph. The area under the curve shows the predictive value of the model: the area can take values from the interval (0,1); the closer to 1.0 the greater the predictive value. Statistical significance was set at 0.05. All the performed tests were two-tailed. Calculations were performed using Stata 7.0. No statistical significance between the abnormal response to acetylsalicylic acid and restenosis was evidenced. Out of 14 (8%) patients within correct reactions to ASA only one (7%) was distinguished as showing signs of carotid restenosis. However, among the 167 (92%) ASA-responsive patients, the group suffering from restenosis consisted of 20 (12%) patients. The level of aggregation rate did not vary significantly between the two groups.

The lack of inadequate response to the antiplatelet effect of acetylsalicylic acid is a complex phenomenon which has not been fully investigated. The phenomenon of inadequate response to acetylsalicylic acid has no impact on the development of carotid restenosis.

## Introduction

Stroke is the third leading cause of death in developed countries. It is assumed that approximately 75% to 80% of all strokes are ischemic strokes, including about 20% being caused by various conditions affecting the extra cranial carotid arteries. In 2 out of every 3 patients with symptoms of cerebral circulatory disorders, these changes can be removed surgically, because in most cases the

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**Table 1:** Inclusion and exclusion criteria applied in the study.

Inclusion criteria	Exclusion criteria
Administration of ASA 75 mg/24 hr	Receiving thienopyridines, including clopidogrel
Internal carotid artery endarterectomy in the last 18 months	Acute coronary event $\leq$ 30 days or Percutaneous Coronary Intervention (PCI) $\leq$ 6 weeks or Coronary Artery Bypass Graft (CABG) $\leq$ 3 months
	ASA intolerance
	Chronic intake of NSAIDs
	Receiving Low Molecular Weight Heparin (LMWH) in the last 24 hours prior to the markings
	Abnormal blood clotting patterns, as stated in anamnesis
	Haemoglobin levels $<$ 8 g/dl
	Creatinine levels $>$ 4 mg/dl
	Surgical procedures undergone during the last week prior to the examination
	An expected lack of cooperation from the patient and the absence of a written consent to participate in the program
	Platelet count $<$ 150 k/ml or $>$ 450 k/ml

cause of stenoses and occlusions is atherosclerosis.

In accordance with the instructions of the consensus presented by the National Stroke Association (NSA) – and also recommended by the American Heart Association (AHA) - endarterectomy of the internal carotid artery is recommended in patients with symptomatic stenosis of  $>$ 70% [1]. The effectiveness of this type of surgery as a means of primary prevention of ischemic stroke study has been demonstrated by the ECST (European Carotid Surgery Trial) and NASCET (North American Symptomatic Carotid Endarterectomy Trial) trials [2,3].

The known and accepted long-term effect of carotid artery endarterectomy for the prevention of stroke is adversely affected by the phenomenon of re-narrowing of the treated artery (the so-called restenosis). The international medical reference literature often discusses the phenomenon of carotid restenosis [4]. It is believed that in symptomatic patients prior to the surgery the restenosis of the treated artery appears from 0.6% to 3.6%, while the population of asymptomatic patients shows proportion ranges from 8.8% to 19% [5]. The overall risk of carotid artery restenosis is defined at 10% during the first year following the surgery, 3% in the second year and 1% for a further period of follow-up observation [6]. Carotid restenosis is more rarely the cause of stroke when compared to patients with primary stenosis. However, despite this fact, counteracting the process of re-formation of atherosclerotic plaque is an important component of patient care.

It is believed that a major role in the process of reformation of arterial restenosis is played by a number of factors, such as risk factors for atherosclerosis development, tobacco use, hypercholesterolemia and arterial hypertension. Therefore, an adequate control of these risk factors is of a great importance for the prevention of restenosis. At the core of this study is the development of restenosis preceded by the formation of a thrombus in place the undergone surgery caused to uncover the deep layers of the vessel wall. This phenomenon is also supported by a progressive focal inflammation. It seems understandable that Acetylsalicylic Acid (ASA) having both antiplatelet and anti-inflammatory effect may yield a potential effect on the inhibition of the de novo stenosis [7]. Thus, an extensive use of this medicine - well-known since the time of Hippocrates –can also be justified in the prevention of carotid artery restenosis [8]. However, international reference literature tackles the problem of an incomplete response to acetylsalicylic acid and the inter-individual variability

of platelet response with increasing regularity. The weakening of platelet responsiveness is a phenomenon which, as of yet, has not been identified in full [9]. In some patients, despite prophylactic ASA intake, clinical manifestations of an incomplete response to aspirin supply occur in the form of complications [10]. This biochemical phenomenon is expressed by an insufficient inhibition of platelet function, as evaluated in laboratory studies [11].

Impedance aggregometry chosen in this study as a method of a valuating platelet function was first described by Cardinal and Fowler in 1980 and has since been widely used to evaluate the reactivity of platelets in the blood. Platelets show a lack of reactivity in the "dormant" state. However, when activated, the cell surface receptors are also mobilized which enables adhesion to the damaged vessel wall or the artificial surface of the test apparatus. Platelet adhesion to the electrodes of the device triggers an enhancement in the electric resistance between them and the phenomenon is recorded continuously. The principle of operation of the Multiplate apparatus is based on the very fact of platelet aggregation on an artificial surface, which causes the impedance method to significantly differ from the method based on Born's aggregometry or from the principle of a single platelet count. In these aggregometric methods, the platelets aggregate suspended in a solution; this process occurs rarely *in vivo* and in very specific clinical conditions, such as: Heparin-Induced Thrombocytopenia (HIT) or Disseminated Intravascular Coagulation (DIC). Platelet aggregation takes place in the body most often on the surfaces of the damaged blood vessels, on the endothelium, whether atherosclerotically affected or simply inflamed. The Multiplate device seems to be most reliable in reproducing the above-mentioned processes occurring *in vivo*, which is why impedance aggregometry is recommended as a reference method used to measure the reactivity of platelets.

There are many hypotheses as to the reason for the inadequate response to ASA. One of them pertains to a turbulent blood flow caused by atherosclerotic plaques leading to increased shear forces which, in turn, results in increased platelet activation. The location in the carotid artery which sustained endarterectomy also shows a certain predisposition to the formation of blood clots due to the exposure of deep atherogenic layers of the vessel. Serving as a consequence of this is the formation of a thrombus at the site of surgical intervention, which contributes to episodes of central nervous system ischemia [12].

**Table 2:** Characteristics of the study group.

Age	68 ± 10
Gender - male	127 (70%)
Weight [kg]	76 [20]
Tobacco use	40 (22%)
Responsive to aspirin	167 (92%)
Restenosis	21 (12%)
Arterial hypertension	124 (69%)
Diabetes	49 (27%)
Stroke	22 (12%)
Cardiac condition	37 (20%)

Depending on the population studied and the measurement methods used, the frequency of the phenomenon of the lack of expected response to ASA is not uniform and its percentage ranges from a few to over a dozen percentiles [13]. The vast majority of studies pertain to cases which entailed the use of aspirin in patients with coronary heart disease, while acetylsalicylic acid is also used as thrombotic prevention in patients with carotid atherosclerosis undergoing endarterectomy in order to prevent an occurrence of a stroke of the central nervous system.

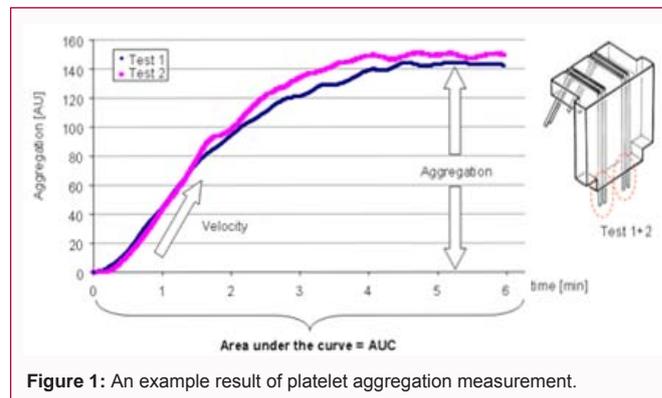
Publications on this group of patients are scarce. Accordingly, in the light of the numerous studies concerning the absence of the expected platelet response to acetylsalicylic acid, which is most often described in the population of cardiac patients, what seems to pose quite an interesting problem is the evaluation of the potential effect of incomplete ASA responsively on the formation of carotid restenosis following an endarterectomy (performed on the same artery). For we assume - according to the current state of medical knowledge - that underlying the progression of re-narrowing of the unclogged vessel is the aggregation process coupled with the local development of inflammation. Therefore, regular intake of ASA could hypothetically lead to a reduction in restenosis development dynamics. In contrast, patients who respond incorrectly to acetylsalicylic acid may belong to a group which is more susceptible to the development of a restenosis of the operated vessel.

## Material and Methods

The studies were conducted in the years 2011 to 2013 at the Vascular Surgery and Angiology Clinic in Warsaw (at the Centrum Medyczne Kształcenia Podyplomowego, Medical Postgraduate Training Centre). Qualified for the study were 181 patients, with the mean age of 68 years, of whom 70% were male and whose average body weight was that of 76 kg (167.2 lbs); the patients were administered 75 mg/day of Acetylsalicylic Acid (ASA). Restenosis was defined as a reduction in vessel diameter by a minimum of 50% (75% of the surface area), as confirmed by a Doppler Duplex ultrasound examination where the peak systolic velocity ( $V_{max}$ ) >125 cm/sec or peak systolic ratio (ICA/CCA) >2. Platelet reactivity was measured using the method of impedance aggregometry (Multiplate Dynabyte, Munich Germany). The average duration of the follow-up observation period was 18 months. Inclusion and exclusion criteria have been presented in Table 1.

The characteristics of the study group are presented in Table 2.

Platelet reactivity was tested using the method of impedance aggregometry - with the Multiplate Dynabyte apparatus, Munich,

**Figure 1:** An example result of platelet aggregation measurement.

Germany.

The measurement results have been given as the area under the aggregation curve (AU min, where AU - Aggregation Unit), as such a depiction shows both the total increase in impedance and the aggregation kinetics (Figure 1).

The analysis pertained to the size of the area under the AUC curve, with the referral of the results to the values of blood platelet aggregation, as recorded in healthy subjects not administered the medicine: AUC 790 - 1410.

In patients administered acetylsalicylic acid, considered as an indication of a normal reaction of platelets were AUC values below the lower limit in healthy people not taking ASA. Patients were believed to show abnormal platelet response to aspirin when, despite taking the medicine their platelet reactivity was within the normal range in healthy subjects not administered acetylsalicylic acid, i.e. 790 - 1410.

## Results

Out of the total 181 patients enrolled in the study, 14 (8%) were isolated as having an abnormal response to acetylsalicylic acid. The variation in the response to ASA has been shown in Figure 2.

Out of the 14 (8%) patients who were classified as abnormally responsive to ASA, only 1 (7%) developed restenosis during the unimmediate follow-up period. Out of the 167 patients properly responsive to aspirin, 20 (12%) suffered restenosis. The level of aggregation rate did not vary significantly between the patients who did or did not develop restenosis. No statistically significant correlation was observed between abnormal reaction to acetylsalicylic acid and the phenomenon of carotid artery restenosis. Figure 3 shows a graphical distribution of the aggregation rate in both groups.

The black bar indicates the median value, the box: the below and above points, which amount for 25% of the observations (the first and third quartile), while the shorter lines: the minimum and maximum values. The differences between the distributions were not statistically significant.

## Discussion

The purposefulness and effectiveness of carotid artery endarterectomies have been demonstrated by numerous multicentre and randomized studies [2,3]. Unfortunately, over longer follow-up periods, the phenomenon of a restenosis of the location of the surgical intervention worsens the obtained results [12,14]. In the meta-analysis performed by Lattimer and Burnand [1,15] on the

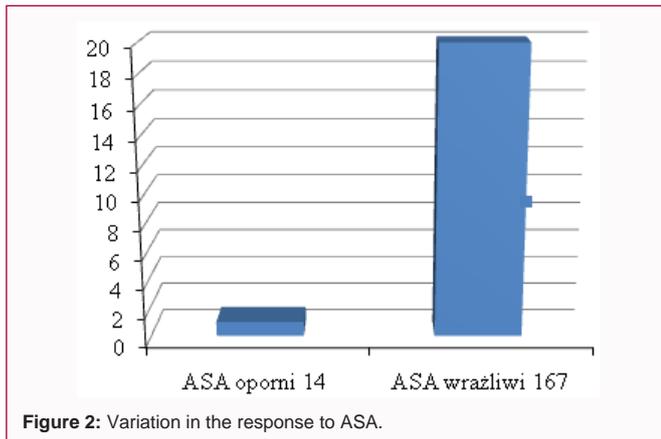


Figure 2: Variation in the response to ASA.

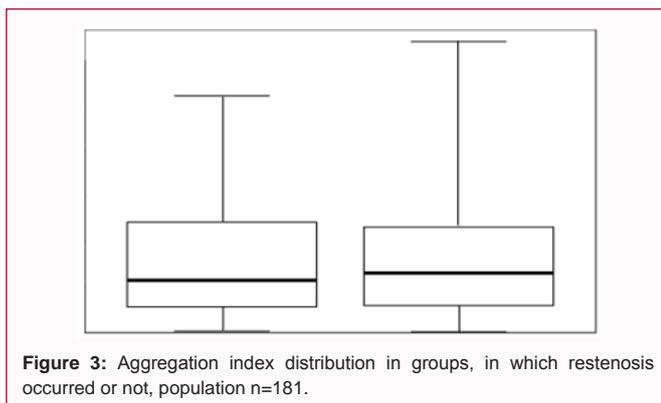


Figure 3: Aggregation index distribution in groups, in which restenosis occurred or not, population n=181.

basis of 55 publications pertaining to this issue, the authors provide a wide range of percentiles of restenosis rate fluctuating 1% to 37% over the observation period lasting from 1 years to 9 years. Such a wide range of the results obtained is conditioned by a non-heterogeneous definition of the phenomenon of carotid artery restenosis, the chosen method of diagnosis and length of follow-up observation of patients who underwent a surgical procedure, as is also shown in his work by Civil ID et al. [12,14]. In this study, the percentage of carotid artery restenosis in the value of 12% (22 patients) remains in correlation with the results obtained in the world literature. There are many reports on the co-occurrence of arterial hypertension, tobacco use, diabetes, age, gender and hyperlipidemia with the development of a postoperative stenosis of the carotid artery. However, the role of these factors in the process of restenosis has not been demonstrated clearly although it may appear that smoking can be a significant cause of the development of this phenomenon [1,15-17]. A number of researchers also emphasize the significant value of the female gender, as a negative factor correlating with restenosis. This is explained by the fact that blood vessels in females are of a smaller diameter and the potential possibility of the existence of differences in platelet reactivity in women [17]. The aim of this study was not a comparative analysis of the correlation of selected risk factors for the occurrence of restenosis; however, the authors did not note a statistically significant coincidence of these parameters with the phenomenon in question.

Recently, more and more emphasis is laid on the local processes that can affect the development of restenosis in the surgically invaded site, which are assisted by the infiltration of inflammatory cells (i.e. wall shear stress). Gnasso et al. drew attention to the importance of the local expanding forces acting on the vessel wall following the procedure, and their directly proportional relation to the velocity of

blood flow and inversely proportional to the diameter of the stented vessel. This promotes the migration of inflammatory process cells, proteoglycans and a focal development of a thrombus, resulting in hyperplasia of smooth muscle cells of the vessel wall exposed during the surgical procedure. It is believed that this complex local process is the basis of restenosis in the postoperative period [18]. Considering the fact of antiplatelet and anti-inflammatory effects of acetylsalicylic acid, it seems that its regular administration can promote the prevention of restenosis. However, as already mentioned, there is the population for which a long-term effect of antiplatelet administration is not satisfactory. Thus, it seems that these patients should bear a larger risk of developing restenosis, particularly in light of the meta-analyses which show that patients with an improper response to ASA are highly susceptible to cardiovascular and cerebrovascular complications, as well as death [19]. This was also confirmed by Poston et al. in a study on patients who have undergone Coronary Artery Bypass Graft Surgery (CABG), where an independent factor co-present with the graft occlusion was an incorrect response to antiplatelet activity of aspirin [20]. Given the fact that the method of optical aggregometry. As a so-called "golden standard" for measuring platelet reactivity is subject to many inconveniences, such as the need to obtain platelet-rich plasma, high expertise of the laboratory team, high price, and high volume of laboratory sample required materials and the long duration of the procedure this study made use of the advantages of impedance aggregometry (Multiplate - Dynabyte, Munich, Germany). This method is now widely used and recommended in the world literature, precisely owing to the fact that it eliminates the aforesaid drawbacks [21,22]. The authors observed an abnormal reaction to ASA in 14 (8%) patients. This result correlated with the number of reports in the world literature where the above-described method of platelet reactivity in cardiac patients was implemented [23]. On the other hand, the number of reports on the discussed issues that would be elaborated on a homogenous population of patients following a surgical procedure of unblocking carotid arteries is rather limited. In our study we failed to trace a significant correlation between the occurrence of abnormal platelet response and restenosis of the unblocked carotid artery. As already mentioned, there are no studies tackling the subject of the concurrence of the two phenomena and, in one of the earliest papers describing the relation between an abnormal reaction to ASA intake with the incidence of vascular events, the relative risk of vascular complications in this group was estimated at 9.1 [23]. In subsequent studies, the odds ratio of ischemic events incidence in patients with ASA resistance was estimated at 4.1. It was also shown that in people with an incorrect response to acetylsalicylic acid, the odds ratio for myocardial infarction was that of 2.0, while the risk of death from conditions of the cardiovascular system was estimated at 3.5, as compared with those responding correctly to ASA [9]. In the view of the large number of reports on concurrence of the lack of the expected reaction to anti-platelet medications with vascular and ischemic complications, this study blends into the current exchange of views within this background.

## Conclusions

1. The lack of inadequate response to the antiplatelet effect of acetylsalicylic acid is a complex phenomenon which has not been fully investigated.
2. The phenomenon of inadequate response to acetylsalicylic acid has no impact on the development of carotid restenosis.

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