


The Pre- and Postoperative Prevalence and Risk Factors of ASA Nonresponse in Vascular Surgery

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Abstract

Background: An antiplatelet therapy with acetylsalicylic acid (ASA) is prescribed in the prevention of cardiovascular events, but around 24% of ASA takers are resistant to the treatment.

Aim: In this prospective, observational cohort study, we aimed to identify the prevalence and risk factors of ASA nonresponse in patients who underwent vascular surgery.

Methods: The study was conducted in the University hospital in Frankfurt am Main. In total, 70 patients were pre-treated with 100 mg of ASA per day and underwent either elective carotid thromboendarterectomy, femoral thromboendarterectomy or endovascular aneurysm repair of the abdominal aorta. The platelet function was measured on the first preoperative and the second or fourth postoperative day with the multiple electrode aggregometry by in-vitro stimulation with arachidonic acid (ASPItest) and thrombin receptor activating peptide 6 (TRAPtest). The primary end point was the in-vitro induced platelet aggregation in the ASPItest. If the ASPItest amounted ≥ 400 AU \times min, the patients were categorized as ASA nonresponders.

Results: The total prevalence of ASA nonresponse in our study was 20% preoperatively and 35.7% postoperatively ($p = 0.005$). As significant predictors for ASA nonresponse, we demonstrated the area under the aggregation curve in the TRAPtest preoperatively ($p = 0.04$) and postoperatively ($p = 0.02$), and the two comorbidities arterial hypertension ($P < .001$; $\rho 0.44$) and diabetes mellitus ($p = 0.04$; $\rho 0.39$), which are already well known to be associated with ASA nonresponse.

Conclusion: In conclusion, data of the study indicate a high incidence of perioperative, laboratory ASA nonresponse in patients undergoing vascular surgery.

Keywords

ASA nonresponse, Multiplate Analyzer, platelet aggregation, vascular surgery

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Introduction

In the primary prevention and secondary prophylaxis of cardiovascular events, an antiplatelet therapy with acetylsalicylic acid is decisive. Acetylsalicylic acid irreversibly inhibits the cyclooxygenase 1, and it reduces the synthesis of thromboxane A₂ and thus platelet activity.¹

However, many studies have demonstrated that ASA does not always fulfill its antithrombotic effect.^{2–5} Nowadays, two established terms describe ASA nonresponse: clinical nonresponse and laboratory nonresponse.² Clinical nonresponse happens to be when cardiovascular events occur even though the patient is

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under regular treatment with aspirin.³ Laboratory nonresponse is defined by tests with platelet function analyzers, for example, a multiple electrode aggregometry, resulting in ongoing platelet aggregation despite therapy with ASA.^{3,4} Depending on the method used, the aspirin nonresponse described in previous studies varied between <1% to 40 to 60%.^{1,5,6} Hovens et al.⁷ exhibited in a large meta-analysis including 42 trials that approximately 24% of aspirin takers are laboratory ASA nonresponders. It is also a known fact that laboratory ASA nonresponders are at higher risk of thromboembolic events.^{4,5,8,9}

The aim of our study was to investigate the pre- and postoperative prevalence and risk factors of ASA nonresponse in patients who undergo three different vascular surgical procedures (carotid thromboendarterectomy [group 1], femoral thromboendarterectomy [group 2] and endovascular aortic repair [group 3]) by using multiple electrode aggregometry. Our study was the first to compare these specific three types of vascular surgery towards ASA nonresponse.

Methods

Trial Design and Patients

Our study was undertaken at the University Hospital Frankfurt am Main, Germany and categorized as an observational, prospective, nonrandomized cohort study. The study was performed after approval by the ethics review board of the University Hospital Frankfurt am Main (approval numbers: 405/14) and obtaining written patient consent.

In total, 86 patients were initially enrolled from August 2016 to January 2019. Out of this initial cohort, 16 refused to participate postoperatively. Inclusion criteria were patients who underwent elective carotid thromboendarterectomy, femoral thromboendarterectomy and endovascular aneurysm repair of the abdominal aorta. They were pre-treated with 100 mg of ASA per day over a period of at least six weeks. If the patients did not take ASA over a period of at least 6 weeks before the trial, they were not concluded in our study. The perioperative adherence to treatment was also monitored as our proband were in-patient, so the treatment with ASA was given to them under controlled circumstances by the nurses. After taking the medicine, the taking was hacked down in the patients' electronic records data by the nurses. Exclusion criteria for the study were if the patients were under the age of 18 or allergic to ASA. According to the type of surgery they underwent, the patients were divided into three different groups. In the first group, we collected 30 patients who underwent a carotid thromboendarterectomy (CEA). The second group included 20 patients who underwent a femoral thromboendarterectomy, and the third group included 20 EVAR with abdominal aneurysm.

Our study was designed as all observational as we did not adjust the medication in ASA nonresponders. Demographic data, information concerning the surgical procedure, and pre-existing illness were collected from patients' electronic records at the hospital.

Sample Collection

To analyze the platelet function blood samples were taken on the first preoperative day and the second or fourth postoperative day. For this purpose, the blood was taken into a 2-mL heparin anticoagulated monovette (arterial blood gas monovette, Sarstedt AG & Co, Germany). Therefore, we used a central venous catheter (Vasofix Safety Braunüle, B. Braun Melsungen AG, Germany) which was placed preoperatively, or we punctured a vein one single time with a 21-G butterfly needle (Multifly; Sarstedt AG & Co, Germany). Additionally, blood samples were collected into a 4.7-mL EDTA tube (Sarstedt AG & Co, Germany) for hemoglobin and platelet count analyzes.

Multiple Electrode Aggregometry

Samples were evaluated within a maximum of 15 min with the help of the multiple electrode aggregometry (Multiplate® Analyzer, Roche Pharma AG, Grenzach-Wyhlen, Germany). This method works with impedance aggregometry, which results from platelet aggregation as described by Cardinal and Flower.¹⁰ For the measurement, 300 μ L of blood was diluted with 300 μ L of 0.9% sodium chloride in a test cell. After 3 min of incubation, the in-vitro platelet aggregation was started by 20 μ L of arachidonic acid (ASPItest) and 20 μ L of thrombin receptor activating peptide 6 (TRAPtest). The platelet aggregation was measured for 6 min.⁴ The area under the aggregation curve (AUC) indicated platelet aggregability. Therefore, the unit was named "aggregation units" (AU \times min). In our study, ASA nonresponse was defined as when a result was ≥ 400 AU \times min in the ASPItest whereas 790 to 1410 AU \times min for the ASPItest and 923 to 1509 AU \times min for the TRAPtest were considered as normal references by the manufacturer.

Primary End Point

The in-vitro induced platelet aggregation in the ASPItest was defined as primary end point (AU \times min). All the patients with an ASPItest of ≥ 400 AU \times min were classified as ASA nonresponders.

Secondary End Point

In-vitro induced platelet aggregation in the TRAPtest of MEA (AU \times min) was defined as a secondary end point.

Statistical Analyses

Statistical analyses were conducted in collaboration with the Institute for Biostatistics and Mathematical Modelling Department of Medicine, Goethe University Frankfurt, by using BiAS for Windows (Edition 11.10). The statistical analyses were performed two-sided, and a *P*-value of <.05 predicted statistical significance. We used the Kolmogorov-Smirnov-Lillifors test to evaluate the normal distribution of the parameters. If the data was not normally distributed, we used the

Wilcoxon matched-pair test. To compare the incidence of the ASA nonresponse in the total cohort, we used the Chi-squared test. The incidence of ASA nonresponse within one group was evaluated by the Chi-squared test or the Fisher exact test. The Wilcoxon-Mann-Whitney-test was used as a non-parametric test for the comparison of the aggregometric measurements. Multiple logistic regression analysis and the Spearman rank correlation test were used to investigate a potential correlation of the variables gender, age, platelet and hemoglobin count, and surgery time to ASA nonresponse. To compare three different surgical procedures, we used the unifactorial variance analysis (ANOVA).

Results

These 70 patients were divided into three different groups. The division into ASA response group and ASA nonresponse group resulted from cut-off values of $400 \text{ AU} \times \text{min}$ in the ASPItest of the Multiplate Analyzer. Patients with a score of $\geq 400 \text{ AU} \times \text{min}$ were called ASA nonresponders, whereas patients with a score $< 400 \text{ AU} \times \text{min}$ were called ASA responders. Overall, preoperatively 14 out of the 70 patients (20%) already showed ASA nonresponse. The nonresponder rate postoperatively increased significantly to 35.7% ($p = 0.005$, $n = 25$ of 70) in all patients. In the group of patients with carotid thromboendarterectomy, postoperatively, 10 out of 30 patients were classified as ASA nonresponders (33.3%, $p = 0.009$) while after femoral thromboendarterectomy 25% ASA nonresponders were identified ($n = 5$ out of 20 patients, $p = 0.06$). In the EVAR group, 50% of the patients showed an insufficient response to ASA ($n = 10$ out of 20 patients, $p = 0.04$) (Figure 1). In Table 1, the demographic data are displayed. Arterial hypertension and diabetes mellitus were defined according to the ESC

guidelines, so a blood pressure that was $> 140/90 \text{ mmHg}$ was calculated as arterial hypertension and $\text{HbA1c} > 6.5\%$ was the definition for diabetes mellitus.^{11,12} Arterial hypertension ($P < .001$, $\rho = 0.44$) and diabetes mellitus ($p = 0.04$, $\rho = 0.4$) significantly correlated with ASA nonresponse: 76% of the postoperative ASA nonresponders had arterial hypertension and 52% of them had diabetes mellitus. We also found that ASA nonresponders had preoperatively and postoperatively a higher platelet count and a lower hemoglobin level, but both findings were not significant. Table 2 shows AUC in the TRAPtest of the ASA nonresponders was preoperatively ($p = 0.03$) as well as postoperatively ($p = 0.02$) higher than the AUC in the TRAPtest of the ASA responders. Figures 2 and 3 demonstrate the aggregometric analyzes. ASA nonresponders, both pre- and postoperatively, showed lower means in the ASPItest but also in the TRAPtest. The surgical procedure did not influence the nonresponder rate ($p = 0.36$) (Figure 4).

Discussion

We here compared the prevalence of ASA nonresponse within a cohort of patients undergoing vascular surgery with the aim to identify risk factors for ASA nonresponse. To date, while most studies have investigated the incidence and outcomes of ASA nonresponse in coronary artery disease (CAD) fewer reports have described ASA response in patients with peripheral artery disease (PAD).⁶ In the meta-analysis of Hovens et al.,⁷ including a total of 42 studies, seven studies investigated the ASA nonresponders rate in PAD patients. Here they found that PAD patients had a mean nonresponder rate comparable to that of the CAD patients of approximately 24%.⁷ However, the range of ASA nonresponse differs widely in the literature between $< 1\%$ to 40 to 60%.^{6,7} The main reason for this

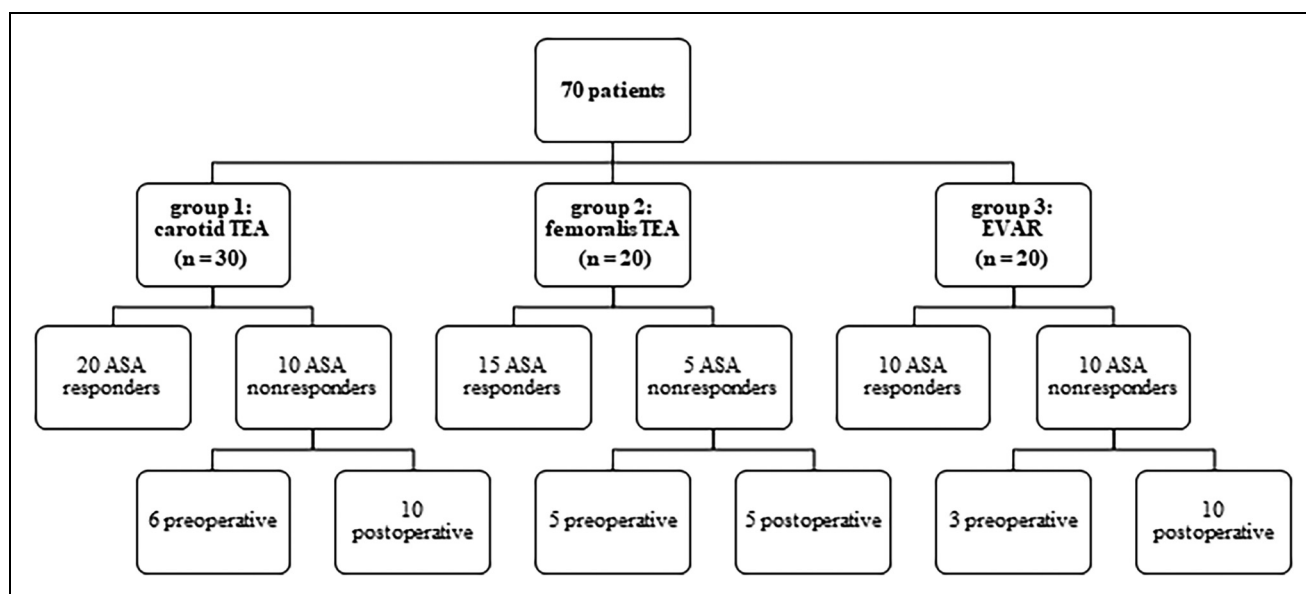


Figure 1. Overview of the trial design and patients. Patients were considered as ASA nonresponders if the AUC was $\geq 400 \text{ AU} \times \text{min}$ in the ASPItest of the Multiplate Analyzer.

Table 1. Demographic Data. The Data are Shown as Number (%) or Mean (SD). $p < .05$ Indicates Significant Difference. ρ = Correlation Coefficient. ASA Response and ASA Nonresponse was Defined on Second or Fourth Postoperative for this Table.

Parameters	ASA response (n = 45)	ASA nonresponse (n = 25)	P value
Gender [male, n (%)]	37 (82%)	20 (80%)	.86
Age [years (SD)]	71 (10)	68 (9)	.31
Arterial hypertension [n (%)] (total n = 53)	34 (75.6%)	19 (76%)	<.001 $\rho = 0.44$
Diabetes [n (%)] (total n = 28)	15 (33%)	13 (52%)	.04 $\rho = 0.39$
Platelet count postoperative [ng (SD)]	199 (76.4)	229.4 (87.7)	.15
Hemoglobin postoperative [g/dl (SD)]	10.6 (1.75)	10.4 (2.1)	.6
Total procedure time carotis TEA [min]	126 (23)	122 (23)	.3
Total procedure time femoral TEA [min]	179 (28)	179 (45)	.31
Total procedure time EVAR	191 (55)	182 (37)	.1

Table 2. Aggregometric Parameters as the Median. Here is the AU \times min for the ASPItest and the TRAPtest Demonstrated. ASA Response (n = 56 Preoperative, n = 45 Postoperative). ASA Nonresponse (n = 14 Preoperative, n = 25 Postoperative). $P < .05$ Indicates Statistical Significance. AUC in the TRAPtest of the ASA Nonresponders was Preoperatively ($p = 0.03$) as Well as Postoperatively ($p = 0.02$) Higher than the AUC in the TRAPtest of the ASA Responders.

Parameter	ASA response	ASA nonresponse	P value
ASPItest (preop) (AU \times min)	175	540	<.0001
ASPItest (postop) (AU \times min)	196	580	<.0001
TRAPtest (preop) (AU \times min)	915	1155	.04
TRAPtest (postop) (AU \times min)	866	1100	.02

spread may be that there are many different platelet function assays. The here used Multiplate Analyzer is a reliable and solid method for measuring the platelet function.^{4,6} Our cut-off values for ASA were defined as <400 AU \times min in the ASPItest. In our total cohort the prevalence of ASA nonresponders significantly increased from 20% to 35.7% ($p = 0.005$). The rate is influenced by the definition of the cut-off values. While there is no universal cut-off for ASA response and nonresponse in the Multiplate Analyzer cut-off values of <300 AU \times min in the ASPItest have been described for aspirin response, and results between 300-690 AU \times min are

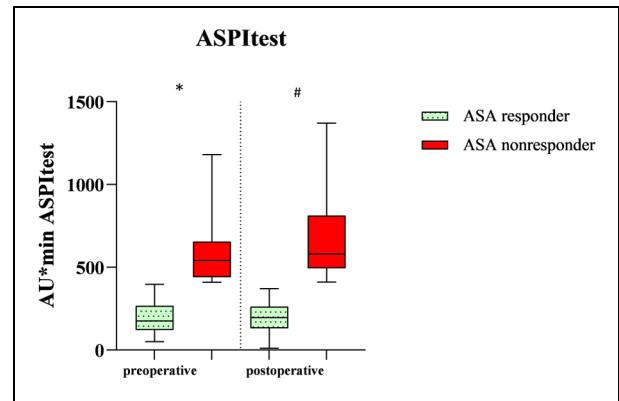


Figure 2. Demonstration of the in-vitro induced platelet aggregation of the total cohort after being stimulated with arachidonic acid (ASPItest) on the first preoperative and second or fourth postoperative day after vascular surgery. *A significant difference between the ASA responders and nonresponders on the first preoperative day ($P < .0001$). # A significant difference between the ASA responders and nonresponders on the second or fourth postoperative day ($P < .0001$). ASA response (n = 56 preoperative, n = 45 postoperative). ASA nonresponse (n = 14 preoperative, n = 25 postoperative).

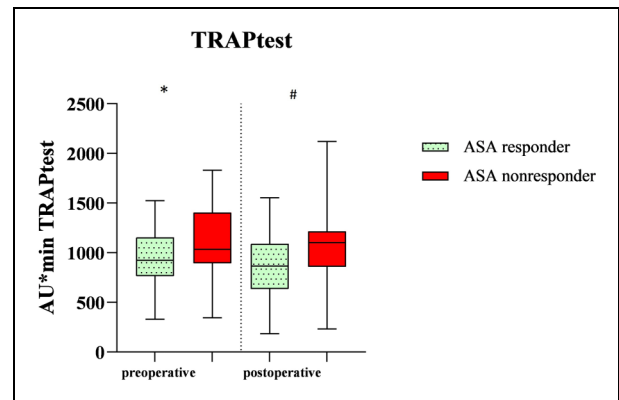


Figure 3. Demonstration of the in-vitro induced platelet aggregation of the total cohort after being stimulated with thrombin receptor activating peptide (TRAPtest) on the first preoperative and second or fourth postoperative day after vascular surgery. *A significant difference between the ASA responders and nonresponders on the first preoperative day ($p = 0.04$). # A significant difference between the ASA responders and nonresponders on the second or fourth postoperative day ($p = 0.02$). ASA response (n = 56 preoperative, n = 45 postoperative). ASA nonresponse (n = 14 preoperative, n = 25 postoperative).

categorized as a partial response whereas >690 AU \times min is called ASA nonresponse.^{2,13} So, if we here used a cut-off <300 AU \times min for our trial, we could expect an even higher amount of ASA nonresponse.

Wand et al.¹⁴ investigated 400 patients who underwent coronary artery bypass grafting (CABG) surgery. In their study 51.3% of patients on the third postoperative day and 71.3% of patients on the fifth postoperative day ($p = 0.0049$) were

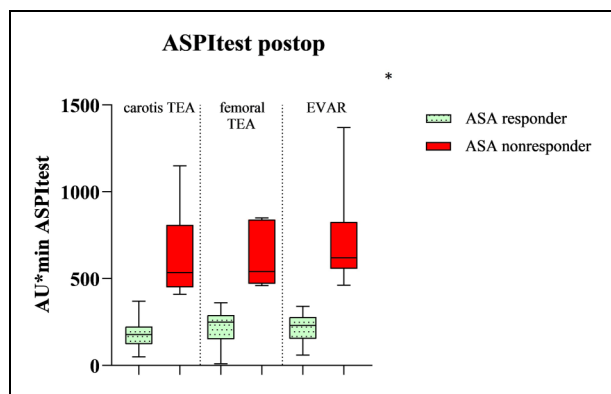


Figure 4. Comparison of the three groups in the in-vitro induced platelet aggregation after being stimulated with arachidonic acid (ASPItest) on the second or fourth postoperative day after vascular surgery. *no significant difference in the nonresponder rate between these 3 groups ($p = 0.36$). ASA response ($n = 45$). ASA nonresponse ($n = 10$ Carotis TEA, $n = 5$ femoral TEA, $n = 10$ EVAR).

ASA nonresponders according to their analysis using Multiplate Analyzer using a cut-off which was also located at $400 \text{ AU} \times \text{min}$. Their study presented a higher nonresponders rate as compared to our study. In alignment to our data, ASA non-response was significantly higher postoperatively. Indeed there is data that describes postoperative nonresponse.¹⁵ Postoperative nonresponse may be a temporary event. Payne et al.¹⁵ investigated 50 patients who underwent a carotid thromboendarterectomy (CEA). Blood samples were taken preoperatively, intraoperatively, and postoperatively. They concluded that in CEA patients the platelet aggregation was significantly greater towards the end of the operation than preoperatively. This may be caused by increased platelet activity during surgery because of the surgical trauma and the liberation of prothrombotic factors like thrombin.¹⁵ In concordance, we found a higher platelet aggregation in the TRAPtest postoperatively ($P < .0001$). A drawback of our data is that we did not measure ASA response intraoperatively. Another factor for this temporary ASA nonresponse may be the intraoperative administration of unfractionated heparin. Heparin indirectly leads to an increased level of arachidonic acid so that at the end, there is more arachidonic acid than ASA, and thus arachidonic acid can, to some extent, may escape from the inhibition through ASA.^{15,16} This may lead to a transient nonresponse postoperatively.

In contrast to Wand et al.¹⁴ we did not find a significant positive correlation between the surgical procedure time and nonresponder rate ($p = 0.65$). While the highest number of nonresponders was found in the EVAR group with the longest procedure time, the differences between the groups were not significant. As described above, vascular surgery implies vascular trauma which may result in higher platelet activity. This is relevant in carotid artery disease: Robless et al.¹⁷ and Nambi et al.¹⁸ also pointed out that in carotid disease, there is a higher level of P-selectin expression. This, in turn, leads to higher platelet aggregation, which further

induces the formation of chemokines and cytokines and thus indirectly perpetuates the atherosclerotic plaque. Temporary postoperative ASA nonresponse is clinically relevant since it may influence the rate of thromboembolic complications.^{19–21}

Lewszuk et al.²¹ investigated 66 patients who underwent a carotid endarterectomy and were pre-treated with ASA 75 mg/d. They measured platelet aggregation with the analyzer PFA-100 on the second day after the operation and identified a nonresponder rate of 32% (19 out of 66 patients). Moreover, they also reported a correlation with unstable carotid plaques and ASA nonresponse. This has further consequences as those patients are at higher risk of intracerebral micro-embolisms. Moreover, Mueller et al.²⁰ investigated 100 patients with peripheral arterial disease who were treated with 100 mg ASA daily and underwent elective percutaneous balloon angioplasty. They detected that vascular obliteration was 87% higher in ASA nonresponsive male patients. This points out that our laboratory ASA nonresponders are at higher risks of clinical thromboembolic outcomes.

A variety of factors can lead to ASA nonresponse. In concordance to other studies, we could find a significant correlation between ASA nonresponse and arterial hypertension.⁴ We demonstrated that 19 out of 25 nonresponders (75%) suffered from hypertension. A higher platelet reactivity in hypertensive patients is discussed through elevated shear stress, endothelial disorder, and arterial tone elevation.^{4,22} Jefferson et al.²³ investigated in a trial 330 patients with a history of myocardial infarction who were treated with a minimum of 81 mg ASA/d. Out of this number, 95 patients (29%) were ASA nonresponders. They discovered that ASA nonresponders were older, and they noticed a correlation between diabetes mellitus, lower HDL levels and ASA nonresponse ($p = 0.01$). We could also confirm a significant correlation between the existence of diabetes mellitus and ASA nonresponse ($p = 0.04$, $\rho = 0.39$) as 52% of our nonresponders had diabetes mellitus. No correlation could be found for the patient age. The postoperative analgesia regimen in our trial mainly included NSAIDs and the pyrazolone metamizole, which may have a supplement effect to the ASA nonresponder rate because of potential medical interference as they both practice their effect via the cyclooxygenase.¹⁴ Last but not least, the omnipresent problem of noncompliance is the most usual cause for ASA nonresponse.^{24,25}

Our study has several limitations. We had a relatively small cohort of patients from one single center. Moreover, we did not take any intraoperative blood samples to calculate the correlation of a higher intraoperative platelet turn. Furthermore, we did not evaluate the information of body weight of the patients. A 2018 metaanalysis from randomized trials evaluated the potential impact of body weight on ASA efficacy and safety which might be a potential confounder to ASA nonresponse.²⁶ As our study was merely observational without any long-term follow-up, we cannot conclude any direct clinical outcomes for our findings.

Despite the above-mentioned limitations, the present study is of clinical value because it demonstrated a high incidence of preoperative and postoperative ASA nonresponse in patients

who underwent vascular surgery. Our ASA nonresponder rate correlated to the known percentage of ASA nonresponders. A variety of factors (treatment adherence, increased postoperative platelet turnover, postoperative analgesia regimen and comorbidities like arterial hypertension and diabetes mellitus) can lead to ASA nonresponse. Though we may not have a direct clinical outcome due to the lack of a follow-up, our laboratory nonresponder rate lets us assume an indirect clinical effect in peripheral arterial disease patients with ASA nonresponse, as we know from the literature that those are at higher risk of cardiovascular events.²⁷ Our study emphasizes the demand to conduct further studies including a follow-up with peripheral arterial disease patients who are pre-treated with ASA to evaluate the ASA nonresponder rate and direct clinical outcomes.

Author Contributions

WM, MK and CW designed the study and contributed to the manuscript. AK performed the study and wrote the first draft of this manuscript.


Declaration of Conflicting Interests

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Appendix

List of Abbreviations

ASA	acetylsalicylic acid
CEA	carotid thromboendarterectomy
EVAR	endovascular aortic repair
MEA	Multiplate – multiple electrode aggregometry
ASPItest	arachidonic acid
TRAPtest	thrombin receptor activating peptide 6
CAD	coronary artery disease
PAD	peripheral artery disease
COX	cyclooxygenase
HDL	high-density lipoprotein
NSAID	non-steroidal anti-inflammatory drug
Preop	preoperative
Postop	postoperative