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Editor's Choice – Association Between Peri-OPerative Aspirin ResisTance and CardioVascular Outcome (POPART-CVO): a Prospective Non-Interventional Cohort Study

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WHAT THIS PAPER ADDS

New onset aspirin resistance during or after surgery is observed in up to 30% of vascular surgery patients and has been linked to a post-operative rise in troponin. However, whether peri-operative aspirin resistance in vascular surgery patients is associated with adverse cardiovascular events has not been assessed in a prospective study. The present study has demonstrated that aspirin resistance in vascular surgery patients is not associated with myocardial injury after non-cardiac surgery. Measuring peri-operative platelet function using the Multiplate analyser to identify and potentially prevent or treat peri-operative aspirin resistance in vascular and endovascular surgery is dispensable.

Objective: New onset aspirin resistance during surgery, known as peri-operative aspirin resistance, is observed in up to 30% of vascular surgery patients and is associated with post-operative myocardial damage; questioning aspirin effectiveness towards peri-operative cardiovascular events. The objective of this study was to prospectively evaluate whether peri-operative aspirin resistance in vascular surgery is associated with an adverse cardiovascular outcome.

Methods: Based on a sample size calculation, 194 adult elective vascular or endovascular surgery patients receiving aspirin were analysed in this prospective, single centred, non-interventional cohort study. Platelet function was measured before surgery, one hour after incision, four hours post-operatively, and on the morning of the first and second post-operative days using the Multiplate analyser. The primary outcome was myocardial injury after non-cardiac surgery (MINS). Secondary outcomes included major bleeding, admission to intensive care unit, length of hospital stay, and major adverse cardiac and cerebrovascular events. Subgroup analyses were performed for patients with different cardiovascular risk and for patients who underwent endovascular surgery.

Results: Peri-operative aspirin resistance was observed in 27.8% of patients but was not associated with MINS (27.8% *vs.* 32.1%, aspirin resistance *vs.* no aspirin resistance, OR 0.812, 95% CI 0.406 − 1.624, $p = .56$) or with any of the secondary endpoints (all $p > .050$). In nine of the 10 subgroup analyses, aspirin resistance was not associated with a difference in MINS rate. However, in patients with a low cardiovascular risk profile (RCRI 0−2), MINS occurred more frequently in patients without aspirin resistance ($p = .049$).

Conclusion: This study confirmed previous reports demonstrating that peri-operative aspirin resistance is common in patients undergoing vascular or endovascular surgery. However, in patients who continue aspirin throughout the peri-operative period, aspirin resistance is a phenomenon, which does not appear to be related to MINS. Measuring peri-operative platelet function using the Multiplate analyser with the intention to identify and potentially prevent or treat peri-operative aspirin resistance seems to be dispensable.

Keywords: Cardiovascular outcome, Peri-operative aspirin resistance, Vascular surgery
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INTRODUCTION

In patients with cardiovascular diseases, aspirin (acetylsalicylic acid) is widely used for secondary prevention after myocardial infarction and other cardiovascular events.[1,2] In high risk populations, aspirin is used for primary

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prevention.[3,4] By deactivating platelet cyclooxygenase (COX), aspirin irreversibly blocks formation of thromboxane-A2, thereby preventing platelet aggregation and reducing thrombotic events. Continuation *vs.* discontinuation of aspirin during surgery has been under debate,[5] and current guidelines recommend weighing bleeding risk against the risk of thrombotic complications.[6] In vascular surgery, medication with aspirin is mostly continued throughout surgery. However, the Peri-Operative ISchemic Evaluation-2 trial demonstrated that peri-operative continuation of aspirin did not reduce the incidence of cardiovascular events but increased major bleeding.[5] This was also confirmed for the subgroup of vascular surgery patients.[7]

In patients with pre-existing cardiovascular diseases, the incidence rate of peri-operative cardiovascular events including acute peri-operative myocardial injury is up to 35% depending on cardiac troponin T (cTnT) assay, cutoff value, as well as type of surgery.[8,9] Putative mechanisms underlying peri-operative cardiovascular events include an oxygen supply/demand mismatch following hypotension or anaemia and atherosclerotic plaque destabilisation mediated by peri-operative stress.[10,11] Peri-operative death following myocardial injury after non-cardiac surgery (MINS) is 9% and is comparable with mortality after peri-operative myocardial infarction (MI).[12]

Laboratory aspirin resistance is the inability of aspirin to reduce platelet production of thromboxane-A2, resulting in failure to prevent platelet activation and aggregation.[13,14] Possible causes of aspirin resistance include genetic causes such as COX-1 polymorphisms, and non-genetic causes such as inadequate dosing, medication non-adherence, drug interactions (e.g., with proton pump inhibitors), non-platelet sources of thromboxane, inflammation, and increased platelet turnover.[13,15,16] Clinical aspirin resistance includes patients who experience thrombo-embolic events despite continuous antiplatelet therapy.[14,17,18] Laboratory aspirin resistance can be measured in several ways, for example, by whole blood aggregometry, light transmission aggregometry, or platelet function analyser.[14] In addition, there is the possibility to perform gene analyses to detect gene polymorphisms.[19] However, a meta-analysis of 19 025 patients with coronary heart disease (CHD) demonstrated that laboratory detected aspirin resistance is more predictive of a poor clinical outcome than genetically detected gene polymorphisms associated with aspirin resistance.[19]

New onset of aspirin resistance during or after surgery, known as peri-operative aspirin resistance, is observed in up to 30% of cardiac[20,21] and vascular surgery patients.[22,23] Vascular surgery patients with post-operative myocardial damage identified by a rise in troponin have an increased rate of non-response to aspirin peri-operatively,[24] suggesting that such an inadequate peri-operative response to aspirin might promote an adverse cardiovascular outcome. The objective of the current study was to examine whether peri-operative aspirin resistance is associated with MINS, major bleeding, other cardiovascular endpoints, admission to intensive care unit, or length of hospital stay in vascular surgery patients.

METHODS

Study design and participants

This was a single centre, prospective, non-interventional cohort study in patients receiving oral aspirin undergoing elective vascular surgery at Heidelberg University Hospital, Heidelberg, Germany. The study protocol conformed to the principles of the Declaration of Helsinki,[25] and was approved by the Ethics Committee of the Medical Faculty of the Ruprecht-Karls University Heidelberg (S-468/2019, 15 July 2019). The study was registered prior to patient enrolment at clinicaltrials.gov (NCT04053894, Principal investigator: J.L., Date of registration: 13 August 2019) and was conducted according to the Principles of Good Clinical Practice.[26] This report follows the STROBE recommendations for observational studies.[27]

From September 2019 to November 2020, consecutive adult patients with a history of at least 14 days of aspirin undergoing elective vascular or endovascular surgery with an expected three day minimum hospital stay were enrolled after written informed consent. Exclusion criteria were pregnancy, breastfeeding, congenital or acquired platelet malfunction, platelet count $<$ 100 000/μL, regular administration of non-steroidal anti-inflammatory drugs, elevated liver enzymes (serum aspartate transaminase [AST] $>$ 74 U/L / alanine transaminase [ALT] $>$ 70 U/L), elevated creatinine levels (serum creatinine $>$ 2 mg/dL), anaemia (haemoglobin (Hb) $<$ 10 g/dL), or primary aspirin resistance identified pre-operatively by Multiplate analysis. Patients were excluded if they had experienced one of the cardiovascular complications listed as study endpoints within the 28 days before enrolment or if a diagnostic angiogram without surgical intervention was the planned procedure. Surgical procedures, general anaesthesia, monitored anaesthesia care, or regional anaesthesia were performed according to standard operating procedures. According to departmental standards, aspirin was continued peri-operatively including the day of surgery.

Outcome analysis

The primary endpoint MINS was chosen as the most sensitive measure for cardiac complications.[28] Follow up was performed until day 30. The secondary endpoints were major bleeding complications, major adverse cardiac and cerebrovascular events (MACCE) defined as composite of cardiovascular death, MI, acute on chronic limb ischaemia, mesenteric ischaemia and stroke, individual components of the composite endpoint, admission to intensive care unit, and length of hospital stay. Pre-specified subgroup analyses were performed for patients with i) coronary heart disease, ii) diabetes mellitus, and iii) different cardiovascular risk profiles (revised cardiac risk index [RCRI] 0—2 *vs.* 3—5). RCRI is a classification system to estimate the patient's risk of post-operative cardiac complications based on pre-operative risk.[29]

Post hoc additional subgroup analyses were conducted for patients iv) on statins, and v) with endovascular surgery. A post-operative 12 lead electrocardiogram (ECG) was

recorded on post-operative day (POD) 3, patient charts were screened and if discharged prior to day 30, study participants or their family doctors participated in a scripted telephone interview at the end of follow up.

Data collection

Collected demographic data were pre-existing diseases including previous cardiovascular events, peripheral arterial disease according to the Rutherford classification,[30] heart failure according to the NYHA (New York Heart Association) classification,[31] and current medication. Creatinine, AST, and ALT values, the estimated glomerular filtration rate (eGFR using Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]), platelet count, leukocyte count, haemoglobin, and high sensitive cTnT were documented before surgery. A baseline 12 lead ECG was recorded.

Blood collection, platelet function testing, laboratory, and electrocardiogram analysis

Blood for platelet function analysis was collected in hirudin tubes (Sarstedt, Nümbrecht, Germany) before and one hour after incision, four hours post-operatively and on the morning of POD1 and POD2 before patients received their aspirin medication. Samples were processed immediately, and platelet aggregation was assessed using the Multiplate analyser (Roche Diagnostics, Rotkreuz, Switzerland). Blood samples were stimulated with arachidonic acid 15 mM. The Multiplate analyser ASPI test was used to detect an aspirin induced inhibition of platelets' COX. Aspirin resistance was defined according to the manufacturer's instructions resulting in an area under the curve (AUC) in the ASPI test over 40. Platelet sensitivity to aspirin *ex vivo* was determined by addition of aspirin to hirudin tubes (final concentrations 20 and 100 μM). Hs-cTnT was determined in lithium heparinised (Sarstedt, Nümbrecht, Germany) blood pre-operatively and daily on POD1—3. Hs-cTnT (Cobas E4111, Roche Diagnostics, Mannheim, Germany) measurements were performed in the central laboratory of the University Hospital. ECGs were analysed by two independent physicians unaware of the clinical or flow cytometry data. All disagreements were discussed with a third physician and were resolved by consensus.

Detailed definitions of outcome variables

MINS was defined as any post-operative peak hs-cTnT $\geq$ 20 ng/L and $<$ 65 ng/L with an increase of $\geq$ 5 ng/L or any new hs-cTnT $\geq$ 65 ng/L with peak hs-cTnT post-operatively [12]. Cardiac death was defined as any death presumed to be of cardiac origin. Criteria for MI followed the fourth universal definition of MI.[32] Stroke was diagnosed as new focal neurological deficit with radiological or angiographic evidence of embolic or thrombotic cause.[33] Peripheral arterial occlusion was confirmed by angiography. Major bleeding was recorded using the International Society on Thrombosis and Haemostasis definition (ISTH).[34]

Sample size calculation

Peri-operative aspirin resistance was observed in approximately one third of the relevant patient population.[20—22] The expected rate for the primary endpoint was derived from the preceding LeukoCAPE-2 study.[35] Here, 82 of the recruited patients underwent vascular surgery. Within 30 days, 31 patients (37%) suffered MINS. Therefore, it was assumed that peri-operative aspirin resistance will occur in one third of patients. It was expected that 50% of these patients will experience MINS compared with 30% in the group without aspirin resistance. To find a difference in the rate of the primary endpoint at the expected group ratio of 1:2 at a two sided significance level of 5% with a statistical power of 0.8 using the likelihood chi square test and expecting 6% dropouts, it was estimated that recruitment of 220 patients should be sufficient.

Statistical analysis

The MINS rate was compared for patients suffering peri-operative aspirin resistance *vs.* patients with an adequate aspirin response using a chi square test. If patients were discharged before the POD3 visit, hs-cTnT data were imputed (last observation carried forward analysis). Logistic regression models were calculated to examine the influence of platelet aggregation for MINS considering the influencing variables age, gender, statin, diabetes, RCRI (0—2 *vs.* 3—5), and CHD. Because the cutoff value specified for the Multiplate assay[36] was derived from individuals not undergoing surgery, the diagnostic accuracy of intra-operative platelet aggregation value was examined for this peri-operative population using receiver operating curves (ROC), calculation of AUCs, as well as sensitivity and specificity. A cutoff suitable for the patient population under investigation with regard to the occurrence of MINS (yes/no) was identified using Youden's J statistic and compared with the published value of 40 for this assay. Time to event analyses were performed using log rank tests and Cox proportional hazards regression models. Descriptive analyses comprised calculation of mean, standard deviation (SD), minimum, maximum, median, first and third quartile for continuous variables, and absolute and relative proportions for categorical variables. Continuous variables between patients exhibiting peri-operative aspirin resistance *vs.* patients with an adequate aspirin response were compared using the *t* test or Mann—Whitney *U* test and categorical variables using the Boschloo test, or chi square test. Statistical analyses were performed using R version 4.0.5 (The R Foundation for Statistical Computing, Vienna, Austria) and SAS 9.4 (Statistical Analysis System, Heidelberg, Germany).

RESULTS

From patients scheduled for elective vascular or endovascular surgery taking aspirin as part of their permanent medication, 357 were screened. Of those, 220 patients were enrolled into the study; 137 patients were not enrolled

because they did not fulfil the inclusion criteria ($n = 12$), they did not meet the exclusion criteria ($n = 99$), or because no surgery was conducted ($n = 26$). Twenty of the included patients were discharged prior to the POD3 visit and three patients were discharged before the POD2 visit. Three patients withdrew consent and were excluded. In 21 (9.5%) patients, pre-operative aspirin resistance was identified and in two patients, angiograms without surgical intervention were performed. The final analysis set comprised 194 individuals (Fig. 1).

Patient characteristics

The main clinical and demographical baseline characteristics are presented in Table 1 and Supplementary Table S1. Peri-operative aspirin resistance was observed in 54 (27.8%) of 194 patients. The mean age was 69 ± 9 years, and seventy six per cent of the participants were male. Patients experiencing peri-operative aspirin resistance were lesslikely to be active smokers, were more likely to have diabetes mellitus controlled by oral medication, and had higher leukocyte counts. Furthermore, peri-operative aspirin resistance was more common in open surgery than in endovascular surgery. There was no difference regarding other baseline characteristics.

Myocardial injury after non-cardiac surgery

In total, 60 patients (30.9%) experienced the primary endpoint of MINS during the 30 day follow up. Peri-operative aspirin resistance did not correlate with the rate of MINS (27.8% *vs.* 32.1%, aspirin resistance *vs.* no aspirin resistance, OR 0.812, 95% CI 0.406 — 1.624, $p = .56$). Logistic regression for the dependent variable MINS identified age, sex, and RCRI to have an influence on the occurrence of MINS. In contrast, steady platelet aggregation level, statin medication, diabetes mellitus, and CHD did not (Table 2).

As there were more dropouts than expected, 194 patients were analysed instead of 207. Therefore, two additional analyses were conducted assuming extreme scenarios in which it was assumed that i) all of the 13 "missing" patients experienced aspirin resistance or it was assumed that ii) none of the 13 missing patients experienced aspirin resistance. No association between aspirin resistance and MINS was observed in either of the extreme scenarios (all $p > .050$).

Secondary endpoints and ex vivo experiments

Major bleeding occurred in nine patients (4.6%). Peri-operative aspirin resistance did not affect the incidence of major bleeding (Table 3).

Within 30 days of surgery, three patients (1.5%) suffered cardiovascular death. MI occurred in nine patients (4.6%) and three patients (1.5%) suffered stroke. Sixteen patients (8.2%) experienced MACCE. Acute peripheral arterial occlusion and mesenteric artery thrombosis each occurred in two patients (1%). Peri-operative aspirin resistance did not affect the incidence of cardiovascular complications (Table 3).

The mean duration of hospital stay was 10.1 ± 6.73 days and did not differ between groups. Patients with peri-operative aspirin resistance were not treated more frequently in intensive care (Table 3).

In the *ex vivo* experiments, a reduction of platelet aggregation was achieved by the addition of aspirin (Supplementary Table S2, Supplementary Fig. S1).

Subgroup analysis

In the subgroup of patients with a RCRI of 0 — 2, patients with peri-operative aspirin resistance less frequently suffered MINS (9% *vs.* 25%, aspirin resistance *vs.* no aspirin resistance, OR 0.296, 95% CI 0.083 — 1.052, $p = .049$). With regard to the other subgroups, peri-operative aspirin resistance did not influence the occurrence of MINS (Table 4).

ASPI test cutoff value optimised for peri-operative vascular and endovascular surgery patients

The median AUC value of the ASPI test in patients without MINS was 30 (Q1 — Q3: 20 — 41). Patients who suffered

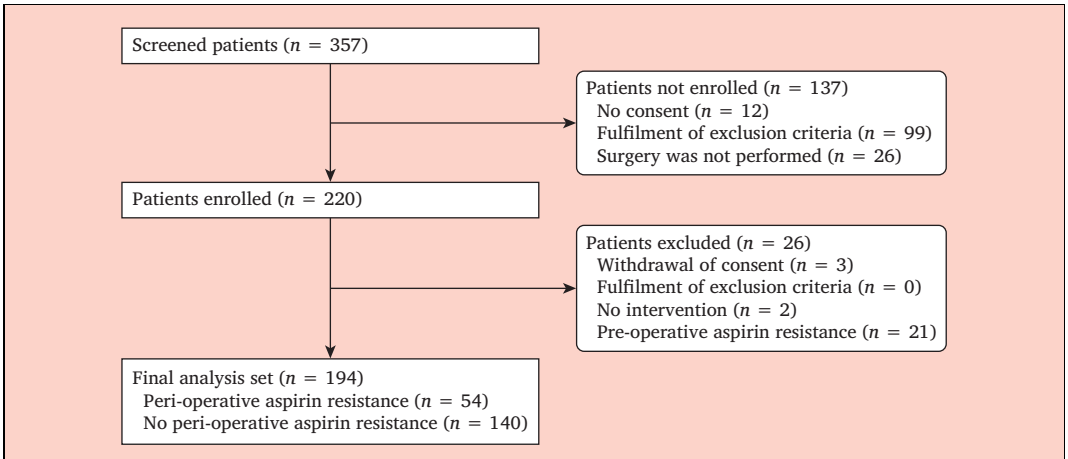

Figure 1. Participant flow chart of a prospective non-interventional cohort study Peri-operative Aspirin resistance and CardioVascular Outcome (POPART-CVO).

Table 1. Clinical baseline characteristics of the study cohort of 194 elective adult vascular or endovascular surgery patients studied for aspirin resistance during surgery

Variable	Analysis set (n = 194)	Peri-operative aspirin resistance (n = 54)	No peri-operative aspirin resistance (n = 140)	p value
Age − y	69.3 ± 8.70	69.4 ± 8.48	69.3 ± 8.81	.93
Male	147 (75.8)	42 (77.8)	105 (75.0)	.83
BMI − kg/m^2	26.2 ± 4.76	27.0 ± 4.85	25.9 ± 4.70	.13
Smokers	154 (79.4)	37 (68.5)	117 (83.6)	.024
Active	69 (35.6)	11 (20.4)	58 (41.4)	.009
Previous	85 (43.8)	26 (48.1)	59 (42.1)	
ASA status				
2	36 (18.6)	12 (22.2)	24 (17.1)	.44
3	154 (79.4)	42 (77.8)	112 (80.0)	
4	4 (2.1)	0 (0.0)	4 (2.9)	
RCRI	1.7 ± 1.22	1.9 ± 1.25	1.6 ± 1.20	.084
RCRI				
0	41 (21.1)	8 (14.8)	33 (23.6)	.33
1	48 (24.7)	13 (24.1)	35 (25.0)	
2	47 (24.2)	12 (22.2)	35 (25.0)	
3	47 (24.2)	17 (31.5)	30 (21.4)	
4	10 (5.2)	3 (5.6)	7 (5.0)	
5	1 (0.5)	1 (1.9)	0 (0.0)	
Surgical risk classification *				
Low risk	3 (1.5)	0 (0.0)	3 (2.1)	.28
Intermediate risk	117 (60.3)	29 (53.7)	88 (62.9)	
High risk	74 (38.1)	25 (46.3)	49 (35.0)	
Type of surgery				
Open surgery	138 (71.1)	46 (85.1)	92 (65.7)	.007
Endovascular surgery	56 (28.9)	8 (14.8)	48 (34.3)	
Aortic surgery	32 (16.5)	14 (25.9)	18 (12.9)	.21
Carotid surgery	66 (34.0)	23 (42.6)	43 (30.7)	
Lower limb surgery	37 (19.1)	9 (16.7)	28 (20)	
Others	3 (1.5)	0 (0)	3 (2.1)	
Endovascular aortic surgery	33 (17.0)	4 (7.4)	29 (20.7)	.58
Percutaneous transluminal angioplasty	23 (11.9)	4 (7.4)	19 (13.6)	
Hypertension	172 (88.7)	49 (90.7)	123 (87.9)	.76
Diabetes mellitus	48 (24.7)	18 (33.3)	30 (21.4)	.084
Oral medication	33 (17.0)	15 (27.8)	18 (12.9)	.016
Insulin dependent	10 (5.2)	5 (9.3)	5 (3.6)	.13
Congestive heart failure	108 (55.7)	35 (64.8)	73 (52.1)	.13
NYHA °1	58 (29.9)	18 (33.3)	40 (28.6)	.24
NYHA °2	40 (20.6)	12 (22.2)	28 (20.0)	
NYHA °3	10 (5.2)	5 (9.3)	5 (3.6)	
NYHA °4	0 (0)	0 (0)	0 (0)	
Coronary heart disease	93 (47.9)	30 (55.6)	63 (45.0)	.19
Medical treatment	93 (47.9)	30 (55.6)	63 (45.0)	.19
History of PCI	46 (23.7)	17 (31.5)	29 (20.7)	.12
History of CABG	28 (14.4)	8 (14.8)	20 (14.3)	1.0
Peripheral artery disease	84 (43.3)	20 (37.0)	64 (45.7)	.31
Rutherford 0	5 (2.6)	2 (3.7)	3 (2.1)	.34
Rutherford 1−3	59 (30.4)	11 (20.4)	48 (34.3)	
Rutherford 4	8 (4.1)	2 (3.7)	6 (4.3)	
Rutherford 5−6	12 (6.2)	5 (9.3)	7 (5.0)	
History of myocardial infarction	35 (18.0)	8 (14.8)	27 (19.3)	.52
History of stroke	37 (19.1)	8 (14.8)	29 (20.7)	.40
History of acute decompensated heart failure	8 (4.1)	1 (1.9)	7 (5.0)	.42
Cardiac dysrhythmia	23 (11.9)	6 (11.1)	17 (12.1)	1.0
Anaesthesia				
General anaesthesia	111 (57.2)	29 (53.7)	82 (58.6)	.61
Analgosedation	73 (37.6)	23 (42.6)	50 (35.7)	.39
Peridural anaesthesia	27 (13.9)	8 (14.8)	19 (13.6)	.79
Spinal anaesthesia	10 (5.2)	0 (0.0)	10 (7.1)	.055
Regional anaesthesia	64 (33.0)	24 (44.4)	40 (28.6)	.037

Data are presented as n (%) or mean ± standard deviation. Continuous data were compared using t test and Mann−Whitney U test. Categorial variables were compared using Boschloo test, Fisher exact test, or chi square test. BMI = body mass index; ASA = risk classification according to the American Society of Anesthesiologists; RCRI = revised cardiac risk index; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting.

* Surgical risk classification according to the American College of Cardiology and American Heart Association.

Table 2. Effect of platelet function on myocardial injury after non-cardiac surgery (MINS) in 194 elective adult vascular or endovascular surgery patients

Variable	Odds ratio (95% CI)	*p* value
Maximum ASPI	0.984 (0.958–1.009)	.22
Age	1.13 (1.077–1.193)	<.001
Male	3.422 (1.37–9.553)	.012
Statin medication	0.809 (0.276–2.511)	.70
Diabetes mellitus	1.086 (0.469–2.456)	.84
RCRI (3–5)	7.507 (2.748–22.402)	<.001
CHD	0.944 (0.357–2.399)	.91

Odds ratio estimated from the logistic regression. Continuous variables were compared using the *t* test or Mann–Whitney *U* test and categorical variables using the Boschloo test or chi square test. ASPI = platelet response to aspirin for arachidonic acid mediated aggregation; CI = confidence intervals; MINS = myocardial injury after non-cardiac surgery; CHD = coronary heart disease; OR = odds ratio; RCRI = revised cardiac risk index.

MINS had a median AUC value of 26.5 (Q1 — Q3: 21 — 39.5).

The optimised threshold for the AUC value of the ASPI test to best predict MINS was 32.5. This cutoff value had a specificity of 0.45 and a sensitivity of 0.7 (Fig. 2).

DISCUSSION

In this study, peri-operative aspirin resistance during vascular or endovascular surgery was not associated with MINS or with any of the pre-specified secondary endpoints. In nine of the 10 subgroup analyses, aspirin resistance was not associated with a difference in MINS rates. However, in patients with a low cardiovascular risk profile, MINS occurred more frequently in patients without aspirin resistance. An ASPI test cutoff value specifically derived for peri-operative vascular and endovascular surgery patients had a low specificity and medium sensitivity for prediction of MINS.

Aspirin resistance, independent of surgical intervention, has been shown to be associated with cardiac complications, more severe stroke, more pronounced atherosclerotic burden, and a higher rate of hospitalised cardiovascular events.[37–40] Testing for aspirin resistance is not routinely recommended but is often performed in symptomatic patients receiving aspirin therapy.[41–43] Until now, no clinical guidelines have been implemented to manage aspirin resistance.[1,44] Increasing aspirin dosage is one possible strategy to treat aspirin resistance.[38,45] Previous reports were confirmed[20–22] that transient aspirin resistance is a common phenomenon in peri-operative patients. In this study, 27.8% of vascular or endovascular surgery patients suffered aspirin resistance during surgery or within POD1 and POD2. This finding is in line with previous studies reporting 27.5% of patients with aspirin resistance in a cohort of vascular surgery patients on POD1.[23] Potential underlying mechanisms include an increased platelet turnover which has been found during cardiac surgery, infection, and inflammation.[46] Due to the short half life of aspirin, the result is an increased proportion of aspirin naive platelets during the 24 hour dosing interval.[46] The severity of surgical trauma also appears to influence the incidence of peri-operative aspirin resistance. Potentially, more severe trauma leads to increased mobilisation of aspirin naive platelets from the bone marrow. Consistently, patients undergoing endovascular surgery were less likely to experience peri-operative aspirin resistance. Reasons for peri-operative aspirin resistance might be transient. That aspirin resistance was reversible during the observation period in the majority of patients may be the reason that cardiovascular outcome was not affected. To date, it is unclear whether the aspirin resistance observed by the present authors and others is clinically relevant. Rajagopalan *et al.* demonstrated, that patients with elevated post-operative cardiac troponin I (cTnI) had a higher incidence of non-response to aspirin compared with patients without cTnI elevation.[24] They assessed platelet aggregation in 136

Table 3. Secondary endpoints in 194 elective adult vascular or endovascular surgery patients studied for aspirin resistance during surgery

Variable	Peri-operative aspirin resistance (*n* = 54)	No peri-operative aspirin resistance (*n* = 140)	Odds ratio (95% CI)	*p* value
Major bleeding	2 (3.7)	7 (5)	0.731 (0.147–3.633)	.70
Cardiovascular death	1 (1.9)	2 (1.4)	1.302 (0.116–14.659)	.83
Myocardial infarction	1 (1.9)	8 (5.7)	0.311 (0.038–2.550)	.25
Stroke	2 (3.7)	1 (0.7)	5.346 (0.475–60.213)	.13
Acute on chronic limb ischaemia	0 (0)	2 (1.4)	0.986 (0.966–1.006)	1.0
Mesenteric artery thrombosis	0 (0)	2 (1.4)	0.986 (0.966–1.006)	1.0
MACCE	4 (7.4)	12 (8.6)	0.853 (0.263–2.771)	.79
Length of hospital stay – d				
Mean ± SD	10.7 ± 6.74	9.9 ± 6.74		
Median (IQR)	10 (5–14)	7 (5–12)		
Range	2–32	2–32		
Admission to intensive care unit	16 (29.6)	38 (27.1)	1.130 (0.565–2.260)	.73

Data are presented as *n* (%) unless stated otherwise. *p* values refer to the distribution of the patients in the four field tables and were calculated using chi square test. CI = confidence intervals; MACCE = major adverse cardiac and cerebrovascular events; ICU = intensive care unit; SD = standard deviation; IQR = interquartile range.

Table 4. Subgroup analysis of 194 elective adult vascular or endovascular surgery patients studied for aspirin resistance during surgery

Patient subgroup	Peri-operative aspirin resistance (n = 54)		No peri-operative aspirin resistance (n = 140)		Odds ratio (95% CI)	p value
	n	MINS	n	MINS		
Patients with CHD	30	12 (40)	63	27 (43)	0.889 (0.367–2.153)	.79
Subgroup of patients without CHD	24	1 (2)	77	8 (6)	0.468 (0.125–1.753)	
Subgroup of patients with DM	18	6 (33)	30	13 (43)	0.654 (0.194–2.209)	.49
Subgroup of patients without DM	36	9 (25)	110	32 (29)	0.813 (0.344–1.919)	.64
Subgroup of patients with RCRI 3–5	21	12 (57)	37	19 (51)	1.263 (0.430–3.713)	.67
Subgroup of patients with RCRI 0–2	33	3 (9)	103	26 (25)	0.296 (0.083–1.052)	.049
Subgroup of patients with open surgery	46	14 (30)	92	29 (32)	0.950 (0.442–2.046)	.90
Subgroup of patients with endovascular surgery	8	1 (13)	48	16 (33)	0.286 (0.032–2.526)	.24
Subgroup of patients with statin medication	45	14 (31)	118	38 (32)	0.951 (0.454–1.992)	.89
Subgroup of patients without statin medication	9	1 (11)	22	7 (32)	0.268 (0.028–2.578)	.23

Data are presented as n (%) unless stated otherwise. p values refer to the distribution of the patients in the four field tables and were calculated using chi square test. CHD = coronary heart disease; CI = confidence intervals; DM = diabetes mellitus; RCRI = revised cardiac risk index; MINS = myocardial injury after non-cardiac surgery.

patients undergoing major vascular surgery at the following timepoints: pre-operatively, immediately after surgery, and on POD1, 2, 3, and 5. As in the present study, Rajagopalan *et al.* continued aspirin use throughout the peri-operative period. Pre-operatively, non-response to aspirin for arachidonic acid mediated aggregation was observed in 22% of the patients who subsequently had a rise in troponin compared with 14% in patients without a troponin increase.[24] Post-operatively, the rate of non-response to aspirin increased to a maximum of 48% in troponin positive patients compared with 26% in the patients without troponin elevation on POD2.[24] In addition to the observed troponin kinetics, five patients had significant ischaemic changes in ECG recordings.[24] This work raised fears that peri-operative aspirin resistance might lead to adverse cardiovascular outcome and that preventive measures such as dual platelet inhibition might be warranted in high risk patients.

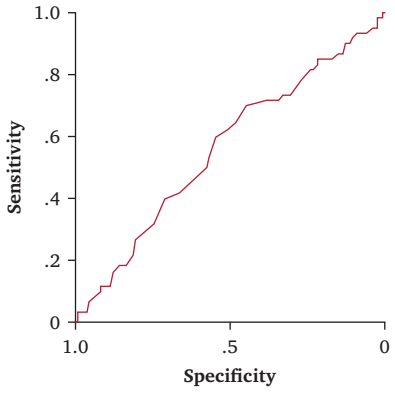

Figure 2. Receiver operating characteristics curve of the ability of the Multiplate analyser ASPI test to predict occurrence of myocardial injury after non-cardiac surgery (MINS) in 194 elective adult vascular or endovascular surgery patients. The new optimised threshold for the area under the curve value was 32.5, which accomplished a specificity of .45 and a sensitivity of .70.

Therefore, in the current study, the hypothesis was tested that patients with peri-operative aspirin resistance are at increased risk of the primary endpoint MINS or cardiovascular complications documented as secondary endpoints. No effects were observed on MINS or any of the secondary endpoints. Also, aspirin resistance was not associated with MINS in nine of 10 subgroup analyses. However, in the subgroup of patients with a low RCRI, patients with peri-operative aspirin resistance suffered MINS less frequently. The present authors cannot offer a reasonable underlying mechanism that could explain this surprising finding; it might be just a random observation.

The present study has some limitations that need to be addressed. About 10% of patients were discharged before POD3, accordingly, the observation period was shortened and data had to be imputed. It is unclear whether factors that differ between aspirin resistant patients and patients without aspirin resistance might interfere with the assay. However, the present authors are not aware of any literature demonstrating that diabetes, leukocyte counts, or smoking would affect the precision of the multiplate assay. Because there were more dropouts than expected, the study did not reach the intended sample size. However, neither a best case nor a worst case scenario, assuming all of the 13 “missing” patients to be in one or the other group, respectively, found a statistically significant association between aspirin resistance and MINS.

In conclusion, this study has demonstrated that peri-operative aspirin resistance occurred in 27.8% of patients undergoing vascular or endovascular surgery. However, peri-operative aspirin resistance is a phenomenon that does not appear to be related to MINS. Therefore, in patients who continue aspirin medication throughout vascular and endovascular surgery, potential aspirin resistance seems not to be relevant to peri-operative cardiovascular outcome. According to the present results, measuring peri-operative platelet function using the Multiplate analyser with the

intention to identify and potentially prevent or treat perioperative aspirin resistance in vascular and endovascular surgery seems to be dispensable.

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CONFLICT OF INTEREST

None.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2022.07.050.

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