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Kopjar, Tomislav; Petričević, Mate; Gašparović, Hrvoje; Svetina, Lucija; Miličić, Davor; Biočina, Bojan

Source / Izvornik: **Annals of Thoracic Surgery, 2015, 100, 1704 - 1711**

Journal article, Accepted version
Rad u časopisu, Završna verzija rukopisa prihvaćena za objavljivanje (postprint)

https://doi.org/10.1016/j.athoracsur.2015.05.001

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:105:932871

Postoperative Atrial Fibrillation is Associated with High On-Aspirin Platelet Reactivity

Running Head: POAF and Platelet Aggregability

Tomislav Kopjar MD, PhD[1]*, Mate Petricevic MD, PhD[1]*, Hrvoje Gasparovic MD, PhD[1], Lucija Svetina MD[1], Davor Milicic MD, PhD [2], Bojan Biocina MD, PhD [1]

[1] University of Zagreb School of Medicine, Department of Cardiac Surgery, University Hospital Center Zagreb, Kispaticeva 12, 10000 Zagreb, Croatia

[2] University of Zagreb School of Medicine, Department of Cardiovascular Diseases, University Hospital Center Zagreb, Kispaticeva 12, 10000 Zagreb, Croatia

*Drs Kopjar and Petricevic are co-first authors.

Keywords: Coronary artery bypass grafts, CABG; Atrial fibrillation (AF), flutter; Platelets.

Manuscript word count: 4763.

Correspondence:

Tomislav Kopjar, MD, PhD

University of Zagreb School of Medicine

Department of Cardiac Surgery

University Hospital Centre Zagreb

Kispaticeva 12, 10000 Zagreb, Croatia

E-mail: tkopjar@gmail.com

Work/Fax: +385 1 2367 531

GSM: +385 99 7055 543

Abstract

BACKGROUND: Atrial fibrillation contributes to a prothrombotic state through platelet activation. It is unclear whether increased platelet aggregability in patients with atrial fibrillation is due to the underlying cardiovascular conditions rather than the arrhythmia *per se*. We investigated the effect of postoperative atrial fibrillation (POAF) on platelet reactivity following coronary artery bypass grafting (CABG).

METHODS: The study is a *post hoc* analysis from a randomized controlled trial NCT01159639 based on elective primary CABG patients. Patients were dichotomized depending on POAF. Postoperative platelet function testing with arachidonic acid as platelet agonist (ASPI test) was used to define high on-aspirin platelet reactivity (HAPR). ΔASPI presented the difference between pre- and postoperative ASPI test values. To account for the isolated effect of POAF on platelet reactivity a propensity-score analysis was applied.

RESULTS: Overall incidence of POAF was 23% (92/398). HAPR was detected in 54% (214/398) of patients. HAPR was more prevalent amongst POAF when compared to No POAF patients (64.1% versus 50.7%; OR 1.74, 95% CI [1.08 – 2.82]; P=0.023). The propensity-score model produced a subcohort of patients that were well balanced for comorbidities. POAF when compared to matched No POAF group remained more prevalent for HAPR (64.1% versus 45.7%; OR 2.13, 95% CI [1.18 – 3.85]; P=0.012) and had greater ΔASPI (15.0 [0.0 – 36.0] versus 8.0 [-5.5 – 19.5]; P=0.030).

CONCLUSIONS: The main finding of our study indicates there is added platelet activation in patients with POAF following CABG before and after controlling for pathologies through propensity matching. The present study does not prove a causal association between POAF and HAPR.

Introduction

In spite of all the prophylactic measures, postoperative atrial fibrillation (POAF) still occurs in about 15-30% of coronary artery bypass grafting (CABG) patients (1-4). It is associated with increased risk-adjusted mortality, hospital costs, and readmission rates (4) as well as late mortality (1,2). Proper and timely treatment may reduce the risk of stroke and mortality associated with POAF.

There is a strong correlation between atrial fibrillation (AF) and thromboembolic sequelae. The precise mechanism behind the increased thromboembolic risk has not been fully elucidated. Abnormalities in cardiac blood flow combined with endothelial disturbances are partly responsible for the hypercoagulable state in AF. Other possible mechanisms that have been proposed include inflammatory response reaction (5) and neuroendocrine activation (6). Increased expression of platelet activation markers has been shown to be associated with AF (7,8).

There is an excess of platelet activation in AF when compared with healthy control subjects (7), although no significant difference between AF patients and disease control subjects in sinus rhythm has been established (7). What remains unclear is whether the underlying AF-associated cardiovascular conditions, rather than the arrhythmia *per se*, cause platelet activation noted in those patients. The aim of the present study is to determine whether an increase in platelet reactivity might be associated with AF following CABG. We hypothesize that an increase of on-aspirin platelet reactivity in patients with new-onset POAF is associated with the arrhythmia *per se* regardless of the cardiovascular conditions associated with AF. Data available from a randomized study (NCT01159639) were utilized for this post hoc analysis. Although patients that formed the basis for this analysis did have underlying AF-associated cardiovascular conditions, pathologies were controlled for through propensity matching in order to explain the additional effect of the arrhythmia. The disease control group was formed out of subjects without POAF from the matched patient subcohort.

Patients and Methods

The present study is a *post hoc* analysis from a randomized controlled trial (NCT01159639). It is a retrospective analysis of prospectively collected data from a single-center randomized trial. Details of

the study design, eligibility, and exclusion criteria have been published previously (9). Briefly, adult patients scheduled to undergo elective primary CABG were eligible for the randomized study. On postoperative day (POD) 4, patients underwent platelet function testing (PFT). Patients found to have high on-aspirin platelet reactivity (HAPR) on POD4 were randomized to 75 mg of clopidogrel and 300 mg of aspirin, or 300 mg of aspirin. Patients who had adequate platelet reactivity (No HAPR) were excluded from the randomized analysis but were included in the follow up. Results comparing the incidence of major adverse cardiac and cerebrovascular events (MACCE) at 6 months have already been published (10). An exploratory analysis from the randomized trial showing 6-month MACCE outcome comparing No HAPR patients to HAPR patients only on aspirin have been published more recently (11). For the purpose of this analysis both HAPR and No HAPR patients were included and dichotomized to either POAF or No POAF group.

Patients

All patients were treated with equal antiplatelet therapy during the first 4 days following surgery (aspirin 300 mg/day). The only additional exclusion criteria in this analysis not accounted for in the original randomized trial is history of previous AF. Flowchart of the study is shown in Figure 1. The POAF status in this analysis represents all patients who had a recorded episode of AF lasting for 10 min or more. Most of these patients were medically converted to sinus rhythm. The POAF status was established regardless of medical or spontaneous conversion.

Perioperative Management

Perioperative management as previously described (9) consisted of our standard hospital protocol for elective CABG patients. Preoperative antiplatelet therapy, 100 mg of aspirin was continued up to the day of surgery. Clopidogrel in the preoperative period was discontinued 4 to 5 days prior to procedure. Patients receiving preoperative beta blockers (B-blocker) were given their normal dose on the morning of surgery. Angiotensin-converting enzyme (ACE) inhibitors were discontinued on the day of admission, usually two days before the procedure. The anesthetic, intraoperative and early postoperative protocols were described in the randomized trial (9).

Detection, Prophylaxis and Management of Atrial Fibrillation

Patients were continuously monitored with telemetry (Nihon Kohden WEP-4208, Tokyo, Japan) until POD5. Routine initiation of B-blocker started on POD1 or once inotropic support had been suspended with daily dosing escalation. Postoperative medication typically included a B-blocker, a hydroxy-methyl-glutaryl-CoA reductase inhibitor, proton pump inhibitor for peptic ulcer prophylaxis and a diuretic. An ACE-inhibitor was usually not instituted before discharge. Atypical opioid analgesics (like Tramadol) were used for pain relief. Non-steroidal anti-inflammatory drugs were generally not administered in the early postoperative period. Magnesium and potassium supplements were administered to maintain high normal levels. POAF was treated with amiodarone.

Platelet Function Testing

Blood samples for PFT were obtained on the morning before surgery (POD0) and on POD4 using venipuncture. Blood was collected in 4 ml heparin (lithium heparin 68 IU) coated plastic tubes. The test was performed 30 minutes after blood sampling. Multiple electrode aggregometry (Multiplate® analyzer, Roche Diagnostics International Ltd, Mannheim, Germany) was used. Platelet aggregation, as evaluated by multiple electrode aggregometry, accounts for the variability in sensor wire impedances (12). Increase in impedance is expressed in arbitrary area under the curve (AUC) units. Arachidonic acid (0.5 mM) and adenosine diphosphate (ADP, 6.4 μM) were utilized as platelet agonists for conducting the ASPI and ADP tests, respectively. The blood samples were incubated for 3 min and platelet aggregation was measured 6 min after stimulation with platelet agonist. The ASPI test evaluates cyclooxygenase-1-dependent platelet aggregation in response to aspirin. The cut-off point for HAPR of patients on aspirin was defined with an ASPI test value exceeding 30 AUC (13). This definition was verified using data from another source (14). Change in PFT measurements for each patient is presented as delta (Δ), ΔASPI = ASPI POD4 – ASPI POD0 and ΔADP = ADP POD4 – ADP POD0. The phenomenon of “aspirin resistance”, a terminology previously used by our group, has a wide prevalence in previously published reports (15) with HAPR being more appropriate.

Propensity Score Model and Matching

A number of significant, or near significant, differences were observed between the study groups. Such differences confounded the outcome comparisons in observational comparison groups. To minimize such confounding variables, we used propensity score matching to derive the risk factor matched subcohort. The propensity score represents the probability that a given patient would develop POAF. It was derived in a standard fashion for each patient from a logistic multivariate regression model that considered POAF status as the dependent outcome variable. Risk factors presented in Table 1 were entered in the propensity score calculation model. In order to indicate the level of discrimination C-statistic was calculated for the propensity model. Once generated the propensity score was employed for propensity-score matching. The algorithm for patient matching consisted of single (1-to-1) matching to the nearest counterpart without replacement. After matching, standardized mean differences were used to assess the adequacy of matching. A high degree of imbalance was reflected by a standardized mean difference of >25%. Differences were displayed for the entire unmatched and matched population. After generating risk factor balanced subcohorts through propensity-score matching, analysis for estimating the impact of POAF on HAPR was performed.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation, or median with interquartile range, whereas categorical variables are described with frequencies and percentages. Comparisons of POAF and No POAF groups before and after matching were performed using the unpaired *t* test or Mann-Whitney rank test for continuous, and the Pearson chi-square test for categorical variables. Longitudinal comparisons between samples of the same subject were analyzed using the Wilcoxon matched pair test. Odds ratios (OR) were used as a measure of the association between POAF and HAPR. The respective 95% confidence intervals (CI) were provided. All tests were two-sided and statistical significance was set at 5%. Box plots presented in Figure 2 were developed with BoxPlotR, a web-tool for generation of box plots (available at http://boxplot.tyerslab.com). Analyses were performed using the Statistical Package for Social Sciences software, version 21.0 (IBM, Somers, New York, USA).

Results

All patients

Three hundred and nighty eight patients formed the cohort for this analysis (Figure 1). The incidence of POAF was 23% (92/398). PFT on POD4 revealed 54% (214/398) of patients had HAPR. Baseline demographic, clinical characteristics and perioperative data of patients before matching are presented in Table 1. POAF patients were generally older, more prone to hypertension, hyperlipidemia and complex coronary pathology. They also had longer cardiopulmonary bypass duration, higher troponin T values on POD1 and lower fibrinogen levels on POD4. Finally, patients with POAF had higher incidence of postoperative HAPR (64.1% versus 50.7%; OR 1.74, 95% CI [1.08 – 2.82]; P=0.023). There was no difference in preoperative HAPR (POAF versus No POAF; 69.6% versus 65.7%; OR 1.19, 95% CI [0.72 – 1.97]; P=0.489).

Results of PFT in relation to surgery and stratified by groups are presented in Table 2. No difference was noted in preoperative PFT between groups. POAF patients had higher postoperative ASPI and lower ADP test values. When compared to baseline, PFT values on POD4 revealed increased platelet activation in POAF and No POAF patients. ΔASPI and ΔADP per group are displayed in Figure 2. POAF patients had higher ΔASPI when compared to No POAF (15.0 [0.0 – 36.0] versus 7.5 [-7.0 – 23.0]; P=0.019).

Propensity-Matched Patients

A propensity-score model was constructed by adjusting for the variables outlined in Table 1. The resulting propensity scores were significantly different (POAF versus No POAF; 0.33±0.15 versus 0.20±0.14; P<0.000). The corresponding C-statistic value 0.85 (95% CI [0.81 – 0.89]; P<0.001) indicates good discrimination. The model produced a subcohort of 184 patients. Overall, 92 patients with POAF were matched to 92 without. All of the 25 variables included in the model were well balanced, with relatively small standardized mean differences, and no statistically significant differences in means (Table 3). In the subcohort analysis patients with POAF had higher incidence of postoperative HAPR (64.1% versus 45.7%; OR 2.13, 95% CI [1.18 – 3.85]; P=0.012). There was no

difference in preoperative HAPR (POAF versus No POAF; 69.6% versus 64.1%; OR 1.28, 95% CI [0.69 – 2.37]; P=0.434). Inverse correlation of postoperative ADP and POAF noted previously was not detectable in the matched subcohort while maintaining higher postoperative ASPI test values (Table 2). Likewise, POAF patients maintained higher ΔASPI (15.0 [0.0 – 36.0] versus 8.0 [-5.5 – 19.5]; P=0.030) (Figure 2).

Comment

The main finding of our study indicates that there is an excess platelet activation in patients with POAF regardless of the underlying AF-associated cardiovascular conditions. From the multivariate analysis we found that new-onset POAF has an independent association with HAPR in patients receiving 300 mg/day of aspirin early after CABG (Online Supplement). Higher preoperative ASPI and ADP test values were also independently associated with postoperative HAPR showing consistent PFT analysis results with the Multiplate® analyzer. In order to account for the underlying AF-associated cardiovascular conditions we controlled for pathologies through propensity matching. The propensity-matched analysis corroborated a subcohort of patients that were well-balanced for comorbidities. From matched patient analysis higher postoperative ASPI test values and a greater increase in platelet reactivity was demonstrated through ΔASPI in on-treatment POAF patients when compared to those without POAF thus confirming our hypothesis. To our knowledge this is the first study to assess and show a correlation between AF and platelet function with multiple electrode aggregometry and Multiplate® analyzer.

It is a well-known fact that platelet activation is strongest at the location of vascular intimal injury and is essential in the process of thrombus formation. Patients with AF and thrombus formations have increased plasma concentrations of markers of platelet activation and thrombogenesis, as well as evidence of endothelial dysfunction (16). Platelet surface expression of CD62P (P-selectin) is enhanced in activated platelets, while soluble P-selectin is a plasma marker of platelet activation (17). However, studies of soluble P-selectin levels in AF have shown conflicting results. Within 12 hours of arrhythmia onset patients with paroxysmal AF have detectable P-selection levels (18). While excess platelet activation in AF compared with healthy control subjects is significant, no significant

difference between AF patients and disease control subjects in sinus rhythm was detected (7). When considering the findings from the study of *Choudhury et al* we performed the present analysis and found that new-onset POAF is independently associated with HAPR in patients following CABG. Platelet activity measured from peripheral blood samples is enhanced in the setting of paroxysmal AF after 3 to 12 hours (18,19). Return to "normal" levels of platelet activity can be detected 24 hours after successful cardioversion (19). Due to the lack of data describing the time point when POAF occurred after CABG in our analysis, one could argue against our hypothesis of an association between POAF and HAPR. When analyzing the available data on the time association of POAF and open-heart surgery, most reports indicate the highest incidence within the first 4 days following the procedure, peaking around the second day (3,20). Therefore, if the timing of postoperative PFT was synchronized with the timing of POAF, the association effect of POAF and HAPR could only have been stronger.

Pathogenesis of POAF might be explained by increased inflammatory activity and endothelial dysfunction. Significant associations between dense spontaneous echo contrast and the 2 indexes, C-reactive protein and soluble P-selection, support the hypothesis of increased inflammatory activity for thrombogenesis in AF (5). Inflammatory markers play an important role in the development of AF, although the results are not consistent (3). An association of preoperative platelet activity and POAF has been shown previously (21,22). In the study of *Antoniades et al* preoperative soluble CD40 ligand level, a marker of platelet activation was found to be a risk factor for POAF independent of systemic endothelial function, vascular redox state, and systemic inflammation in patients undergoing off-pump coronary bypass surgery.

ACE-inhibitors have been shown to have a beneficial clinical outcome in patients with AF for hypertension treatment (23). The renin-angiotensin-aldosterone system could be mechanistically implicated in the initiation and perpetuation of atrial fibrillation, as well as providing the link to other mechanisms promoting the prothrombotic state in atrial fibrillation (24). Interestingly, the results of our analysis also illustrated that long-term preoperative ACE-inhibitor therapy has an inverse correlation with early postoperative HAPR in the setting of an elective CABG population.

Dual antiplatelet therapy with aspirin and thienopyridines reduces the risk of ischemic events in patients with acute coronary syndrome (25,26). However, it was shown not to be more effective than aspirin alone among patients with stable cardiovascular disease in a broader population of patients (27). While pronounced platelet inhibition reduces the risk of ischemic events it comes at a cost of moderate-to-sever bleeding (25-27). Clopidogrel and aspirin versus aspirin alone, showed to be beneficial in reducing the rate of major vascular events among patients with AF who were unsuitable for vitamin K antagonists (28). Considering the beneficial effect shown with stronger platelet inhibition in the ACTIVE A trial (28) and the association of POAF and HAPR we found in the present analysis, forthcoming larger longitudinal trials might reveal the potential clinical benefit of PFT tailored antiplatelet therapy in CABG patients with POAF.

Some limitations of this study should be noted. First, it is subject to limitations inherent to any retrospective analysis. The present study does not prove a causal association between POAF and HAPR. We used ECG and telemetry monitoring to detect POAF and did not use ECG-Holter monitoring. Duration and timing of POAF were not documented and therefore the effect could not be analyzed. The small sample size gives little room to address the clinical implications of the results. Platelet response to aspirin is also influenced by other unaccounted factors such as concomitant therapy and genotype. Genetic testing was not part of the protocol in the NCT01159639 trial. Even though there is no evidence linking amiodarone to increased platelet aggregability, the lack of consideration of treatment affect, particularly amiodarone is another limitation in our study.

In summary, there is an independent association of new-onset POAF and an additional excess platelet activation in patients following CABG, regardless of the underlying AF-associated cardiovascular conditions. Considering that various markers involved in the inflammatory hypothesis for thrombogenesis in AF play a key role in the etiology of arrhythmia it is hard to explain the cause-and-effect association between arrhythmia burden and platelet activation. Partial understanding of mechanisms underlying AF-induced thrombogenesis requires further research. To establish whether platelet activation is the key feature in the mechanism of POAF thrombogenesis, it will be important for future studies to include other more specific measures of platelet activity and to account for other factors in the process of AF-induced thrombus formation.

Acknowledgments and Disclosures

The authors have no conflicts of interest to disclose.

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Table 1. Baseline demographic, clinical characteristics and perioperative data of patients before propensity matching stratified by postoperative atrial fibrillation

	No POAF (n=306)	**POAF (n=92)**	***P*-value**	**Std. Diff. (%)**
Age (years)	62.9±8.7	67.1±7.1	<0.001	58.1
Male gender	234 (76%)	75 (82%)	0.308	12.9
BMI (kg/m^2)	28.8±4.1	29.2±4.2	0.494	9.0
EuroSCORE (%)	3.2±3.1	3.3±2.5	0.221	2.4
LVEF (%)	55±11	55±9	0.895	0.9
Hyperlipidemia	287 (94%)	91 (99%)	0.049	49.1
Diabetes mellitus	108 (35%)	33 (36%)	0.919	1.2
Hypertension	291 (95%)	92 (100%)	0.030	inf
Chronic kidney disease*	11 (4%)	7 (8%)	0.104	15.1
Smoker	122 (40%)	28 (30%)	0.102	-20.4
Left main narrowing	125 (41%)	44 (48%)	0.235	13.9
Three-vessel disease	222 (73%)	77 (84%)	0.030	30.0
Preoperative medication				
Statin	286 (93%)	90 (98%)	0.108	29.7
Aspirin	276 (90%)	85 (92%)	0.525	8.2
B-blocker	247 (81%)	79 (86%)	0.260	14.7
ACE-inhibitor	212 (69%)	66 (72%)	0.652	5.4
Clopidogrel	94 (31%)	26 (28%)	0.652	-5.4
Perioperative data				

LIMA use	288 (94%)	84 (91%)	0.338	-9.9
X-clamp time (min)	55±20	60±24	0.082	17.5
CPB time (min)	83±25	91±29	0.006	30.4
Ventilation time (h)	8.0 (6.0-11.0)	8.5 (7.0-12.8)	0.171	20.7
Postoperative inotropes	86 (28%)	30 (33%)	0.405	9.6
Troponin T POD1 (µg/L)	0.54 (0.32-0.90)	0.63 (0.40-1.40)	0.023	21.0
Hematocrit POD4 (%)	28±4	27±3	0.123	-23.4
Fibrinogen POD4 (g/L)	6.9±1.4	6.6±1.5	0.029	-21.3

ACE-inhibitor=angiotensin-converting enzyme inhibitor; B-blocker=beta blocker; BMI=body mass index; CPB=cardiopulmonary bypass; EuroSCORE=European System for Cardiac Operative Risk Evaluation; HAPR=high on-aspirin platelet reactivity; inf=infinity; LIMA=left internal mammary artery; LVEF=left ventricular ejection fraction; POAF=postoperative atrial fibrillation; POD=postoperative day; Std. Diff.=standardized mean difference, X-clamp=aortic cross-clamp

[*] Chronic kidney disease was defined as preoperative serum creatinine >200 µmol/L or renal replacement therapy

Table 2. Platelet function testing

	All patients			Matched patients		
	No POAF	**POAF**	***P*-value**	**No POAF**	**POAF**	***P*-value**
ASPI POD0	31±26	28±26	0.263	30±25	28±26	0.602
ADP POD0	75±28	70±25	0.074	72±28	70±25	0.622
ASPI POD4	38±27	43±27	0.033	36±29	43±27	0.010
ADP POD4	93±35	82±33	0.006	85±37	82±33	0.478
P-value[a]	<0.001	<0.001		0.009	<0.001	
P-value[b]	<0.001	<0.001		0.003	<0.001	

ADP=adenosine diphosphate dependent platelet aggregation; ASPI=cyclooxygenase dependent platelet aggregation; POAF=postoperative atrial fibrillation; POD=postoperative day

[a] *P*-value for ASPI POD0 versus ASPI POD4

[b] *P*-value for ADP POD0 versus ADP POD4

Table 3. Baseline demographic, clinical characteristics and perioperative data of patients after propensity matching stratified by postoperative atrial fibrillation

	No POAF (n=92)	**POAF (n=92)**	***P*-value**	**Std. Diff. (%)**
Age (years)	66.7±7.5	67.1±7.1	0.717	5.5
Male gender	79 (86%)	75 (82%)	0.425	-11.1
BMI (kg/m^2)	29.2±4.4	29.2±4.2	0.846	0.4
EuroSCORE (%)	3.3±2.6	3.3±2.5	0.883	-0.6
LVEF (%)	54±10	55±9	0.932	3.7
Hyperlipidemia	89 (97%)	91 (99%)	0.312	20.9
Diabetes mellitus	30 (33%)	33 (36%)	0.641	6.8
Hypertension	92 (100%)	92 (100%)	1.000	NaN
Chronic kidney disease*	8 (9%)	7 (8%)	0.788	-4.1
Smoker	29 (32%)	28 (30%)	0.873	-2.3
Left main narrowing	44 (48%)	44 (48%)	1.000	0.0
Three-vessel disease	78 (85%)	77 (84%)	0.840	-2.9
Preoperative medication				
Statin	89 (97%)	90 (98%)	0.650	7.4
Aspirin	84 (91%)	85 (92%)	0.788	4.1
B-blocker	74 (80%)	79 (86%)	0.325	15.5
ACE-inhibitor	65 (71%)	66 (72%)	0.871	2.4
Clopidogrel	31 (34%)	26 (28%)	0.425	-12.0
Perioperative data				

LIMA use	84 (91%)	84 (91%)	1.000	0.0
X-clamp time (min)	58±21	60±24	0.833	4.8
CPB time (min)	91±28	91±29	0.933	1.3
Ventilation time (h)	8.0 (7.0-10.5)	8.5 (7.0-12.8)	0.440	20.5
Postoperative inotropes	25 (27%)	30 (33%)	0.421	11.5
Troponin T POD1 (µg/L)	0.60 (0.32-1.00)	0.63 (0.40-1.40)	0.372	5.0
Hematocrit POD4 (%)	0.27±0.03	0.27±0.03	0.812	-3.7
Fibrinogen POD4 (g/L)	6.7±1.4	6.6±1.5	0.305	-7.7

ACE-inhibitor=angiotensin-converting enzyme inhibitor; B-blocker=beta blocker; BMI=body mass index; CPB=cardiopulmonary bypass; EuroSCORE=European System for Cardiac Operative Risk Evaluation; HAPR=high on-aspirin platelet reactivity; LIMA=left internal mammary artery; LVEF=left ventricular ejection fraction; NaN=number not available; POAF=postoperative atrial fibrillation; POD=postoperative day; Std. Diff.=standardized mean difference, X-clamp=aortic cross-clamp

* Chronic kidney disease was defined as preoperative serum creatinine >200 µmol/L or renal replacement therapy

Figure legends

Figure 1. Study flowchart showing patient eligibility and study protocol. Previous publications from the same trial (NCT01159639) have likewise been noted. AF=atrial fibrillation; CABG=coronary artery bypass grafting; dAPT=dual antiplatelet therapy; HAPR=high on-aspirin platelet reactivity; MI=myocardial infarction; PCI=percutaneous coronary intervention; PFT=platelet function testing; POAF=postoperative atrial fibrillation; POD=postoperative day, PVD=peripheral vascular disease; TEA=thrombendarterectomy.

Figure 2. Box-and-whisker plots showing differences (ΔASPI and ΔADP) between preoperative and postoperative platelet function measurements for all and propensity-matched subcohort of patients stratified according to postoperative atrial fibrillation (POAF) status. ADP=adenosine diphosphate dependent platelet aggregation; ASPI=cyclooxygenase dependent platelet aggregation; AUC=area under the curve; POAF=postoperative atrial fibrillation.

Abbreviations

ACE – angiotensin-converting enzyme

ADP – adenosine diphosphate dependent platelet aggregation

AF – atrial fibrillation

ASPI – cyclooxygenase dependent platelet aggregation

AUC – area under the curve

CABG – coronary artery bypass grafting

HAPR – high on-aspirin platelet reactivity

CI – confidence interval

MACCE – major adverse cardiac and cardiovascular event

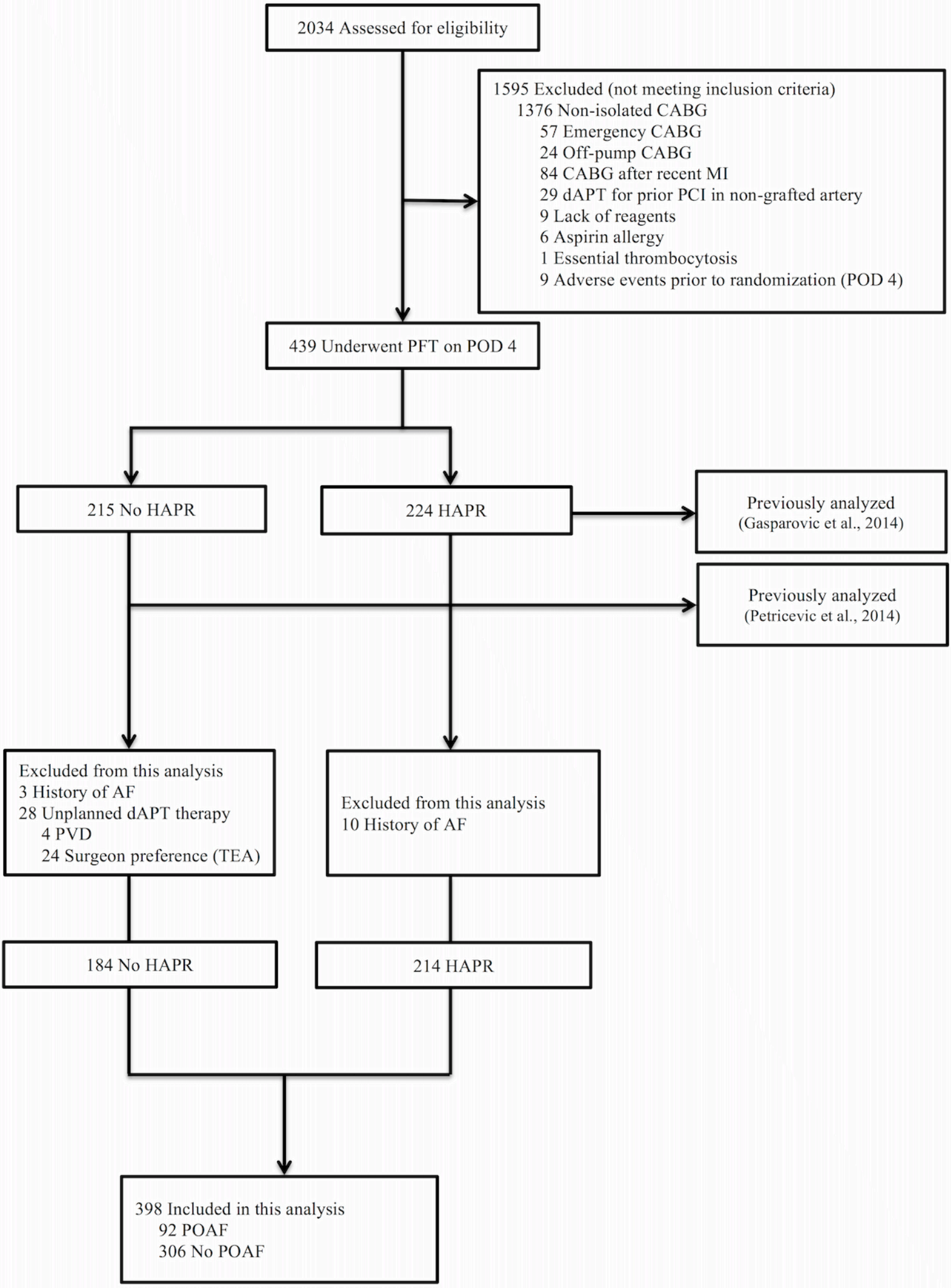
OR – odds ratio

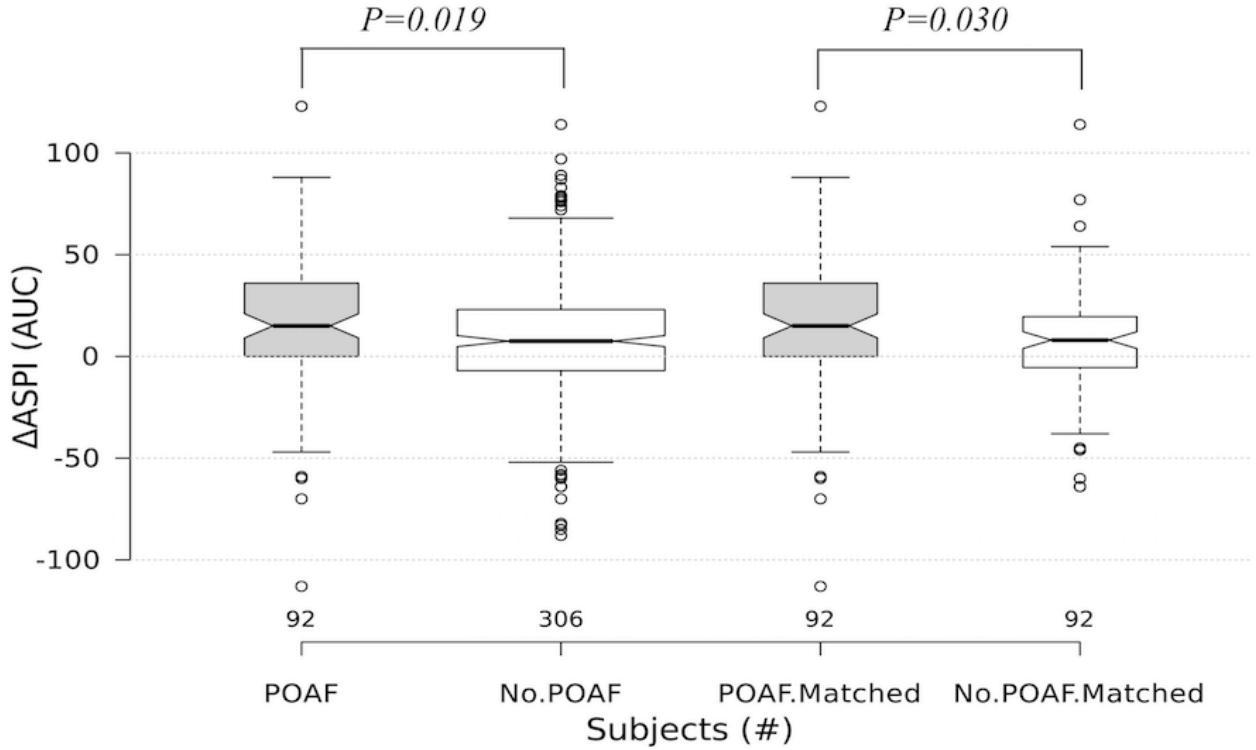
PFT – platelet function testing

POAF – postoperative atrial fibrillation

POD – postoperative day

Δ – delta


2034 Assessed for eligibility
1595 Excluded (not meeting inclusion criteria)
1376 Non-isolated CABG
57 Emergency CABG
24 Off-pump CABG
84 CABG after recent MI
29 dAPT for prior PCI in non-grafted artery
9 Lack of reagents
6 Aspirin allergy
1 Essential thrombocytosis
9 Adverse events prior to randomization (POD 4)
439 Underwent PFT on POD 4
215 No HAPR
224 HAPR
Previously analyzed
(Gasparovic et al., 2014)
Previously analyzed
(Petricevic et al., 2014)
Excluded from this analysis
3 History of AF
28 Unplanned dAPT therapy
4 PVD
24 Surgeon preference (TEA)
Excluded from this analysis
10 History of AF
184 No HAPR
214 HAPR
398 Included in this analysis
92 POAF
306 No POAF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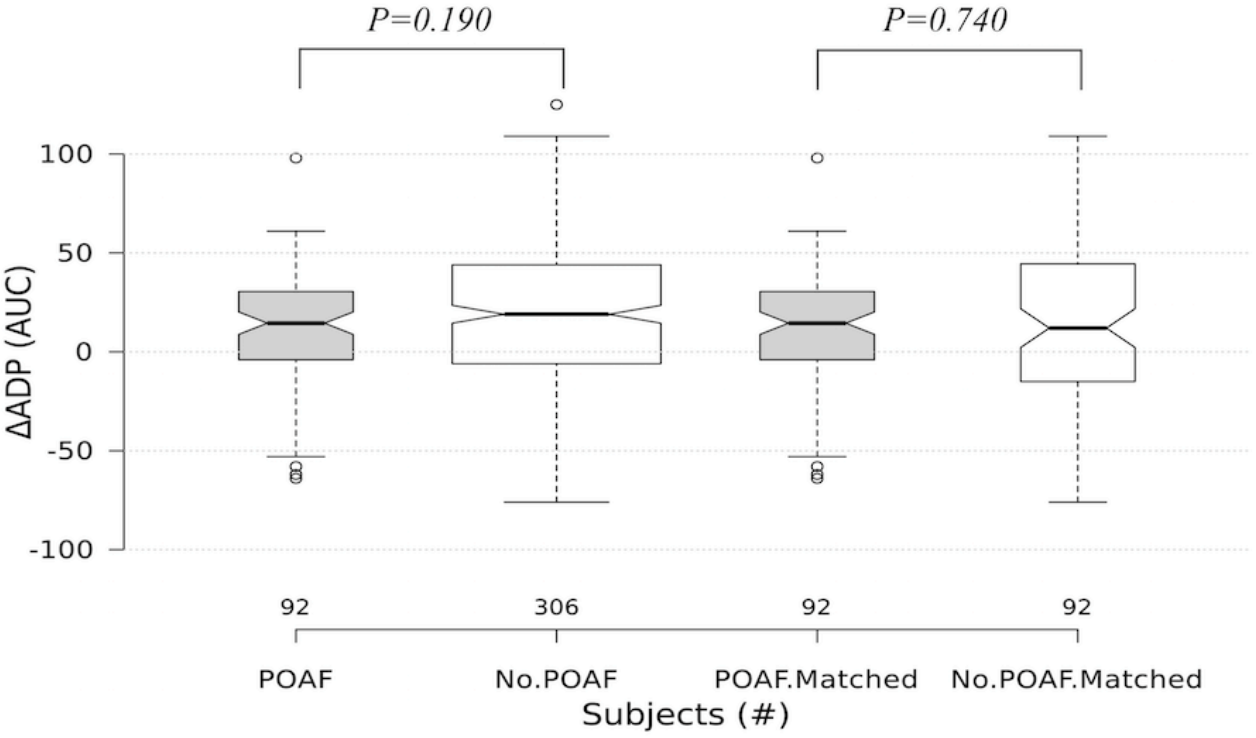
P=0.030
100
50
0
-50
-100
ΔASPI (AUC)
92
306
92
92
POAF
No.POAF
POAF.Matched
No.POAF.Matched
Subjects (#)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P=0.740
100
50
0
-50
-100
ΔADP (AUC)
92
306
92
92
POAF
No.POAF
POAF.Matched
No.POAF.Matched
Subjects (#)

Multivariate logistic regression

Stepwise multivariate logistic regression analysis was performed to assess independence of correlation between POAF and postoperative HAPR. Postoperative HAPR status was the dependent variable in the multivariate regression analysis. Variables presented in Supplement Table 2 were included as independent variables in the multivariate regression analysis. For multivariate regression, variables with a probability value of >0.1 were removed. Odds ratios (OR) were used as a measure of the association between independent variables and HAPR. The respective 95% confidence intervals (CI) were provided. Multivariate logistic regression analysis with postoperative HAPR status as the dependent variable showed an independent association with POAF (overall model R^2=0.297, P<0.001).

Supplement Table 1. Multivariate logistic regression analysis results showing predictors of postoperative high on-aspirin platelet reactivity (all patients, N = 398)

	OR	**95% CI**	***P* Value**
Age (years)	1.05	1.02 – 1.08	0.002
Left main narrowing	1.73	1.09 – 2.75	0.020
POAF	1.81	1.04 – 3.15	0.035
Preoperative medication			
ACE-inhibitor	0.18	0.11 – 0.31	<0.001
Statin	5.93	1.97 – 17.84	0.002
Preoperative platelet function testing (POD 0)			
ASPI test values (AUC)	1.02	1.01 – 1.03	<0.001
ADP test values (AUC)	1.01	1.00 – 1.02	0.026

ACE-inhibitor=angiotensin-converting enzyme inhibitor; ADP=adenosine diphosphate dependent platelet aggregation; ASPI=cyclooxygenase dependent platelet aggregation; CI=confidence interval; OR=odds ratio; POAF=postoperative atrial fibrillation; POD=postoperative day

Supplement Table 2. Baseline demographic, clinical characteristics and perioperative data of patients stratified by high on-aspirin platelet reactivity

	No HAPR (n=184)	**HAPR (n=214)**	***P* Value**
Age (years)	62.7±8.1	64.9±8.8	0.012
Male gender	148 (80%)	161 (75%)	0.214
BMI (kg/m^2)	28.6±4.3	29.2±3.9	0.158
EuroSCORE (%)	2.8±2.3	3.6±3.4	0.011
LVEF (%)	54.8±10.5	54.4±10.3	0.775
Hyperlipidemia	172 (93%)	206 (96%)	0.205
Diabetes mellitus	64 (35%)	77 (36%)	0.803
Hypertension	178 (97%)	205 (96%)	0.622
Chronic kidney disease*	6 (3%)	12 (6%)	0.261
Smoker	71 (39%)	79 (37%)	0.732
Left main narrowing	66 (36%)	103 (48%)	0.014
Three-vessel disease	135 (73%)	164 (77%)	0.452
Preoperative platelet function testing (POD 0)			
ASPI test values (AUC)	23.8±20.6	35.6±28.7	<0.001
ADP test values (AUC)	68.5±27.9	78.8±25.9	<0.001
Preoperative medication			
Statin	168 (91%)	208 (97%)	0.010
Aspirin	170 (92%)	191 (89%)	0.282
B-blocker	148 (80%)	178 (83%)	0.478
ACE-inhibitor	156 (85%)	122 (57%)	<0.001
Clopidogrel	58 (32%)	62 (29%)	0.581

	Perioperative data		
LIMA use	172 (94%)	200 (93%)	0.993
X-clamp time (min)	55.1±20.8	57.3±21.1	0.147
CPB time (min)	82.5±27.1	86.4±26.0	0.078
Ventilation time (h)	9.9±9.7	10.5±6.9	0.021
Postoperative inotropes	49 (27%)	67 (31%)	0.306
Troponin T POD 1 (μg/L)	0.54 (0.31 – 0.90)	0.60 (0.35 – 1.11)	0.203
Hematocrit POD 4 (%)	0.28±0.03	0.28±0.03	0.820
Fibrinogen POD 4 (g/L)	6.9±1.6	6.8±1.4	0.514
	Postoperative platelet function testing (POD 4)		
ASPI test values (AUC)[a]	20.1±6.3	56.3±26.1	<0.001
ADP test values (AUC)[a]	84.8±35.9	95.3±32.4	0.002

ACE-inhibitor=angiotensin-converting enzyme inhibitor; ADP=adenosine diphosphate dependent platelet aggregation; ASPI=cyclooxygenase dependent platelet aggregation; AUC=area under the curve; B-blocker=beta blocker; BMI=body mass index; CPB=cardiopulmonary bypass; EuroSCORE=European System for Cardiac Operative Risk Evaluation; HAPR=high on-aspirin platelet reactivity; LIMA=left internal mammary artery; LVEF=left ventricular ejection fraction; POD=postoperative day; X-clamp=aortic cross-clamp

[*] Chronic kidney disease was defined as preoperative serum creatinine >200 μmol/L or renal replacement therapy

[a] Not included in the multivariate logistic regression analysis