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Impact of Dual Antiplatelet Therapy on Clinical Outcomes Among Aspirin-Resistant Patients Following Coronary Artery Bypass Grafting

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Brief title: Clopidogrel in Aspirin Resistant Patients

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ABSTRACT

Coronary artery bypass grafting (CABG) is pivotal in the contemporary management of complex coronary artery disease. Inter-patient variability to antiplatelet agents, however, harbors potential to compromise the revascularization benefit by increasing the incidence of adverse events. This study was designed to define the impact of dual antiplatelet therapy (dAPT) on clinical outcomes among aspirin-resistant patients who underwent coronary artery surgery. We randomly assigned 219 aspirin-resistant patients according to multiple electrode aggregometry to receive clopidogrel (75 mg) plus aspirin (300 mg) or aspirin-monotherapy (300 mg). The primary end-point was a composite outcome of all-cause death, non-fatal myocardial infarction, stroke or cardiovascular hospitalization assessed at 6 months postoperatively. The primary end-point occurred in 6% assigned to dAPT, and 10% of patients randomized to aspirin-monotherapy (relative risk [RR] 0.61 [95% CI 0.25-1.51]; p=0.33). No significant treatment effect was noted in the occurrence of the safety endpoint. The total incidence of bleeding events was 25% and 19% in the dAPT and aspirin-monotherapy groups, respectively (RR 1.34 [95% CI 0.80-2.23]; p=0.33). In the subgroup analysis dAPT led to lower rates of adverse events in patients with a body mass index >30 kg/m^2 (0% vs. 18%, p<0.01) and those younger than 65 years (0% vs. 10%, p=0.02). In conclusion, the addition of clopidogrel in patients found to be aspirin resistant after CABG did not reduce the incidence of adverse events, nor did it increase the number of recorded bleeding events. Dual antiplatelet therapy did, however, lower the incidence of the primary end-point in obese patients and those younger than 65 years.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT01159639

***Key words*—** aspirin, clopidogrel, antiplatelet resistance, coronary artery bypass surgery, major adverse events

INTRODUCTION

Coronary artery bypass grafting (CABG) remains the standard of care in the management of complex coronary artery disease.[1] Improvements in postoperative outcomes rely both upon technical refinements of the procedure and optimization of medical management. The long-term benefits of CABG depend upon the durability of non-obstructed flow through bypass grafts. Inhibition of platelet aggregability plays a crucial role in improving graft patency. Aspirin is currently the most commonly employed antiplatelet agent after CABG.[2] Dual anti-platelet therapy (dAPT) may improve venous graft patency[3], but this benefit has not been reliably reproduced in a wider clinical arena.[4] The combination of clopidogrel and aspirin results in cumulation of their individual antiaggregatory effects, since their individual mechanisms of antiplatelet activity differ.[5] Dual platelet inhibition may be of particular importance in patients exhibiting single antiplatelet drug resistances.[6] Defining the role of dAPT in the contemporary surgical practice is paramount before recommending it without reservations, however, as it may increase the incidence of bleeding.[7] The incidence of low-response to aspirin is not uniform across the available spectrum of platelet function tests. It has been reported to range from 1 to 45%.[8] While clear outlines of this phenomenon remain to be defined, its adverse clinical impact has been validated.[9] We hypothesized that augmentation of platelet inhibition with clopidogrel in patients with high postoperative on-aspirin platelet reactivity would lead to improvement in clinical outcomes. The convergence of the clinical impact of aspirin resistance with the beneficial effects of dAPT in other clinical scenarios was at the foundation of this trial's design. This is, to the best of our knowledge, the first prospective randomized study that selectively implemented dAPT after CABG in patients with aggregometry-documented aspirin resistance.

METHODS

The study was conducted at the University Hospital Center Zagreb in Zagreb, Croatia. Patient enrolment started in June 2010 and was completed in February 2013. Details of the study design, eligibility and exclusion criteria have been published previously.[10] Briefly, adult patients scheduled to undergo elective primary CABG were eligible for enrolment. Exclusion criteria included valvular pathology warranting surgical correction, off-pump CABG, requirement for dual antiplatelet

management, anticoagulation and critical condition prior to randomization. Patients undergoing CABG following a recent acute coronary syndrome were excluded, as there is data to suggest that they might benefit from dAPT.[11] On postoperative day (POD) 4 patients underwent an aggregometry-based assessment of their on-aspirin platelet reactivity. Patients found to be aspirin-responders were excluded from further analysis, while aspirin-resistant patients were randomized into either the control or intervention groups.

The trial was approved by the Ethics committee of the University Hospital Center Zagreb. Ethical standards in line with the Declaration of Helsinki were adhered to. Written informed consent was obtained from all patients prior to enrolment.

Multiple electrode aggregometry (MEA) was used for quantifying platelet reactivity in the study cohort (Multiplate, Dynabyte, Munich, Germany). Platelet aggregation, as evaluated by MEA, is responsible for variability in sensor wire impedances. The numerical MEA output describes the electrical resistance between sensor wires, which is proportional to platelet adherence.[12] Arachidonic acid (0.5 mM) and adenosine diphosphate (ADP, 6.4μM) were utilized as platelet agonists for conducting the ASPI and ADP tests, respectively.

The ASPI test evaluates COX-1 dependent platelet aggregation, and is therefore a surrogate for aspirin responsiveness. While aspirin response is better described as a continuous variable, dichotomizing patients into "responders" and "non-responders" is commonly utilized for research purposes.[8] Aspirin resistance in the present study was defined in line with previous reports stratifying individual patient responsiveness into quartiles.[13] Patients were classified as aspirin-resistant if their ASPI test values exceeded the population's 75th percentile cut-off point (area under the curve (AUC)≥30).[13] This definition was substantiated by data from multiple other sources.[14,15]
Having met the inclusion criteria for aspirin resistance on POD 4, patients scheduled for isolated CABG were randomly allocated into either continuation on 300 mg of aspirin (control group), or enhancement of platelet inhibition with 75 mg of clopidogrel plus 300 mg of aspirin (dAPT group). Randomization software was used for patient allocation into the control or intervention arms.[10]

Preoperative platelet inhibition with aspirin was maintained up to the day of surgery. Conversely, patients receiving preoperative clopidogrel had the drug discontinued approximately 5

days prior to the surgical procedure. Tepid cardiopulmonary bypass (CPB) and cardioplegic arrest were used in all study patients. Myocardial preservation was based on a combination of antegrade and retrograde cardioplegia. Postoperatively, patients typically received a beta-blocker, hydroxy-methyl-glutaryl-CoA reductase inhibitor, peptic ulcer prophylaxis and a diuretic. Angiotensin-converting-enzyme inhibitors were administered selectively, and titrated to effect. Aspirin was typically administered within the first six hours of surgery. In aspirin non-responders, the postoperative anti-platelet regime was then re-evaluated on POD 4 in line with the study protocol.

The primary efficacy end-point was the incidence of major adverse cardiac and cerebrovascular events (MACCE) at 6-months. MACCE was a composite outcome including all-cause mortality, non-fatal myocardial infarction, cerebrovascular accident and cardiovascular rehospitalization. The secondary outcomes were bleeding events and individual MACCE components. We adhered to the Bleeding Academic Research Consortium (BARC) definitions in presenting the safety end-point data.[16] The Joint European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation Task Force for the Redefinition of Myocardial Infarction (MI) was implemented in patients suspected to have ischemic myocardial injury.[16] Patients with new focal neurologic deficits lasting more than 24 hours, or those having an acute cerebral lesion on an imaging study were considered to have had a stroke.[17]

The study was designed to analyze the incidence of MACCE at 6-months, on an intention-to-treat basis, in aspirin-resistant patients randomized to either continue on aspirin monotherapy or receive dual inhibition of platelet aggregation. The sample size required to test the null hypothesis was determined by an exact binomial test power analysis.[18] The minimum effect size was 10%. Accounting for an estimated 10% loss to follow-up, a total of 219 patients were required to test the null hypothesis with an α value of 0.05 and a power of 0.8. An additional per-protocol analysis of the safety end-point was performed in patients adhering to the study protocol. The continuous data were presented as mean values with their standard deviation. Categorical variables were presented as absolute numbers with percentages. The Mann-Whitney U test was used to analyze continuous data between the control and intervention groups. Comparisons between categorical variables were performed with Fisher's exact test. Changes in platelet reactivity in response to surgery were evaluated with the Wilcoxon matched-

pairs test. Relative risks were used as a measure of the association between the intervention and clinical outcomes. The respective 95% confidence intervals were provided. A two-tailed p value <0.05 was considered to be statistically significant for all deployed calculations. Additional one-tailed *P* values were also obtained and provided for comparisons likely to result in one-directional relationships. The data were processed using the IBM SPSS Statistics software package (version 20.0; Somers, NY, USA) and Statpages.org.

RESULTS

During the recruitment period 2034 patients were screened for eligibility. A total of 224 aspirin resistant CABG patients were randomly assigned to receive aspirin only (n=110) or aspirin plus clopidogrel (n=114). An overview of the patient enrolment and randomization is presented in Figure 1. The baseline patient demographic and clinical profiles were well balanced between the two groups (Table 1). Approximately three quarters of patients were male and the majority had three-vessel disease, which is representative of the contemporary cardiac surgical practice. Beta-blockers were utilized more commonly in the dAPT group prior to surgery. The use of other preoperative medications, including anti-platelet agents, did not differ significantly between the groups (Table 1). Perioperative data are summarized in Table 2. Postoperative medication regimes did not differ between the groups with the notable exception of clopidogrel utilization, which was subject to the randomization protocol (Table 2).

There were no differences in preoperative platelet aggregability between the groups (Table 1). The ASPI test values evaluated on POD 4 were also comparable between the control and intervention groups (Table 2). Postoperative ASPI test values in both patient groups were well above the pre-defined 30 AUC cut-off point discriminating between aspirin response and resistance. Analogously, the postoperative ADP test values did not differ between the groups (Table 2). We have, however, documented a significant post-procedural rise in platelet reactivity in comparison to the respective preoperative values. The ASPI test values across the entire cohort increased from 36±29 to 57±26 AUC ($p<0.001$). This accelerated platelet aggregability was corroborated by an increase in the ADP values (preoperatively: 78±26; postoperatively: 96±33 AUC, $p<0.001$). Additional evidence for a

hypercoagulable state in the early postoperative period was found in the dynamics of fibrinogen levels. We documented a consistent and statistically significant increase in fibrinogen concentrations in response to the surgical procedure (4.1±1.3 vs. 6.8±1.4 g/L; $p<0.001$). The observed rise in platelet aggregability was seen in both groups, irrespective of the antiplatelet management strategy (Figure 2).

Six-month follow-up was completed in 107 (97%) and 112 (98%) patients in the aspirin monotherapy and dAPT groups, respectively. The study outcomes are summarized in Table 3. Freedom from MACCE at the completion of the follow-up period was 90% in the control group and 94% in the dAPT group. The overall incidence of the primary end-point was not affected by the different anti-platelet management protocols (6% vs. 10%; relative risk [RR]: 0.61 [95% CI: 0.25 to 1.51]; two-tailed p=0.33, one-tailed p=0.20). A non-significant 43% relative risk reduction in the composite endpoint of MI/stroke/cardiovascular death was observed with enhancement of platelet inhibition (two-tailed p=0.49, one-tailed p=0.34). The frequency of individual MACCE components was not affected by the anti-platelet management strategy (Table 3). The causes of death in the 4 control group patients were stroke, sepsis, necrotizing tracheitis and trauma. Two patients in the dAPT group died during follow-up. One suffered a stroke that eventually led to his death, while the other died of intractable respiratory failure induced by pneumonia.

An intention-to-treat analysis revealed no statistically significant differences in the incidence of bleeding events between the groups within any of the BARC strata (Table 3). A non-significant increase in the frequency of total bleeding events was noted with the post-procedural addition of clopidogrel to aspirin-resistant patients (25% vs. 19%; RR: 1.34 [95% CI: 0.80 to 2.23]; two-tailed p=0.33, one-tailed p=0.17). A post-hoc analysis excluding patients requiring anticoagulation during the follow-up period was also performed. The incidence of bleeding events in the per-protocol analysis did not differ significantly from the intention-to-treat analysis (24% in the dAPT group vs. 19% in the aspirin monotherapy group; RR: 1.28 [95% CI: 0.75 to 2.20]; two-tailed p=0.39, one-tailed p=0.23). The incidence of the primary end-point was analyzed in patient subgroups, stratified according to the presence or absence of individual comorbidities or clinical characteristics. We found a statistically significant reduction in the frequency of MACCE in patients aged less than 65 years (0% vs. 10%, p=0.02). Analogously, patients with a body mass index (BMI) >30 kg/m^2 were more likely to benefit

from platelet inhibition with clopidogrel on the background of aspirin therapy in the prevention of the composite adverse outcome. The incidences of MACCE among obese patients were 0% with the dAPT strategy vs. 18% in the aspirin-only arm ($p<0.01$). The subgroup analyses are presented in Table 4. Dual antiplatelet therapy did not increase the incidence of bleeding events in patients younger than 65 years (22% vs. 22%; RR: 0.99 [95% CI: 0.48 to 2.04]; two-tailed p=1.0, one-tailed p=0.61). Similarly, dAPT did not significantly increase bleeding among patients with a BMI>30 kg/m^2 (29% vs. 20%; RR: 1.46 [95% CI: 0.69 to 3.11]; two-tailed p=0.45, one-tailed p=0.23). Similar bleeding rates were noted in all other studied subgroups (all one- and two-tailed $p>0.05$).

DISCUSSION

The principal goal of this trial was to measure the impact of enhanced platelet inhibition with clopidogrel on the background of standard therapy in aspirin-resistant CABG patients on the incidence of adverse events. This is the first prospective randomized study to address the clinical impact of augmented anti-platelet therapy after CABG in patients with aggregometry-documented aspirin resistance.

Platelets are anuclear cell fragments harboring unique adhesion mechanisms that are as critical to arresting bleeding as they are to atherothrombosis.[19] They are at a junction between inflammatory and thrombotic cascades, playing an active part in both of them.[19] Suppressing platelet aggregability is an integral component in the management of coronary artery disease. The rationale for using clopidogrel in patients with a history of cardiac surgery has been validated in the Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study.[20] The relative risk reduction of 29% in the incidence of vascular death, stroke, MI or rehospitalization in the CABG subgroup exceeded the benefit seen in the general CAPRIE study population.[20] In the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial, clopidogrel proved superior to placebo in the prevention of MACCE.[21] The degree of risk reduction with dAPT paralleled the patient complexity, with the greatest benefit seen in higher risk subgroups.[21] The reduction in the frequency of MACCE with dAPT was also represented in the CABG subgroup (RR 0.89; 95% CI, 0.71 to 1.11).[22] The composite end-point of death and recurrent MI was also seen less frequently in a cohort of MI patients revascularized with

CABG who were taking clopidogrel.[11] Furthermore, graft patency was improved by the dAPT protocol in comparison to aspirin monotherapy.[3,23] Gao et al randomized CABG patients to receive either aspirin only (n=124), or aspirin plus clopidogrel (n=125).[3] Computed tomographic imaging revealed better SVG patency in the dual antiplatelet treatment arm.[3] In a similar study design, Sun et al suggested that, in the total of 79 patients that completed angiographic follow-up, clopidogrel was superior to placebo in preventing radial artery graft failure.[23] A caveat worth noting was that only a low maintenance aspirin dose was administered (81-100 mg) in the monotherapy arm in the latter trials,[3,23] which has been found to incompletely inhibit TxA2 production after CABG.[24] The impact of individual responsiveness to aspirin was not reported in these studies.[3,23] The combination of clopidogrel and aspirin also resulted in superior clinical outcomes in patients undergoing off-pump coronary artery bypass surgery (OPCAB).[25] The higher postoperative platelet responsiveness in OPCAB in comparison to conventional CABG patients, as determined by P-selectin expression, adds credibility to strategies intensifying platelet inhibition in this subpopulation.[26] The potential advantages of dual antiplatelet inhibition notwithstanding, its benefits have not been generally demonstrable in all trials investigating its impact. In the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial evaluating patients with stable cardiovascular disease dAPT was ineffective in reducing the composite endpoint of death, MI or stroke.[27]

Our study differed from the aforementioned trials in that it specifically targeted the CABG subpopulation that retained high platelet aggregability despite aspirin therapy. We found that 51% of patients undergoing elective CABG had incomplete inhibition of platelet reactivity with aspirin. The utilized aggregometry-based algorithm for discriminating between aspirin responders and non-responders had a distinct advantage in comparison to conventional coagulation tests. It used whole blood at the patient's own temperature for analysis, thereby measuring platelet activity within their physiological milieu. Similar incidences of post-CABG aspirin resistance were previously reported.[6] Our study revealed multiple facets of postoperative hypercoagulability. We found that the surgical procedure elicited an increase in both fibrinogen levels and platelet reactivity. While there is data to suggest that aspirin resistance postoperatively is a transient phenomenon,[28] this observed early

hypercoagulability may render the grafts particularly vulnerable during this period. The parallel and synergistic inhibitions of the COX-1 and ADP-mediated platelet activation pathways result in amplification of platelet inhibition,[5] which we hypothesized to be potentially useful in patients exhibiting single anti-platelet drug resistance. Our trial, however, did not prove that the combination of aspirin and clopidogrel was superior in reducing the frequency of the primary endpoint to aspirin monotherapy in aspirin-resistant CABG patients. These results mirror the observations from a retrospective analysis of propensity-matched cohorts, which also found no survival benefit for dAPT over aspirin after CABG.[29] Furthermore, one-year SVG intimal hyperplasia, as documented by intravascular ultrasound, in the Clopidogrel After Surgery for Coronary Artery DiseasE (CASCADE) study was not improved by dAPT (n=46) in comparison to an aspirin-only antiplatelet regime (n=44).[4] Our data did, however, suggest that patients younger than 65 years and those with a body mass index >30 kg/m^2 might benefit from dual antiplatelet therapy in the setting of aspirin resistance. This gain was not offset by increasing bleeding events in neither the entire study cohort nor any of the subgroups. We believe that a study evaluating the potential of these aspirin-resistant subgroups to capitalize on enhancement of anti-platelet therapy is warranted.

Our study has significant limitations. The estimation of the sample size required to test the null hypothesis was based on an exact binomial test power analysis.[18] We cannot reliably exclude the possibility that the study may have been underpowered. In point of fact, a non-significant 39% relative risk reduction in the primary end-point was noted with the addition of clopidogrel to aspirin in the context of aspirin resistance. Our results may provide an impetus for the conduct of a larger scale study of a similar design. Another potential drawback of our study stems from the lack of an unequivocal definition of aspirin resistance. Aggregometry in our study revealed a continuum in individual platelet inhibition responses to aspirin. The cut-off points of multiple platelet function tests differentiating between aspirin response and resistance are based on definition, rather than unambiguous clinical data supporting their relevance. Furthermore, different laboratory pathway descriptors of platelet function yield varying incidences of high on-therapy residual platelet reactivity. One should, therefore, resist extrapolating results based on one platelet assessment instrument onto a larger group of platelet function tests, until confirmation of interchangeability has been established.

In conclusion, this prospective randomized trial showed that enhancing platelet inhibition with clopidogrel in aspirin-resistant patients after CABG did not result in a reduction of major adverse cardiac and cerebrovascular events. However, our subgroup analysis showed that obese patients and those younger than 65 years experience a statistically significant benefit from dAPT in the prevention of MACCE.

DISCLOSURES

None.

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Figure 1. Patient eligibility, randomization and follow-up

CABG = coronary artery bypass grafting; MI = myocardial infarction; dAPT = dual antiplatelet therapy; PCI = percutaneous coronary intervention; POD = postoperative day; PFT = platelet function testing; BARC = Bleeding Academic Research Consortium

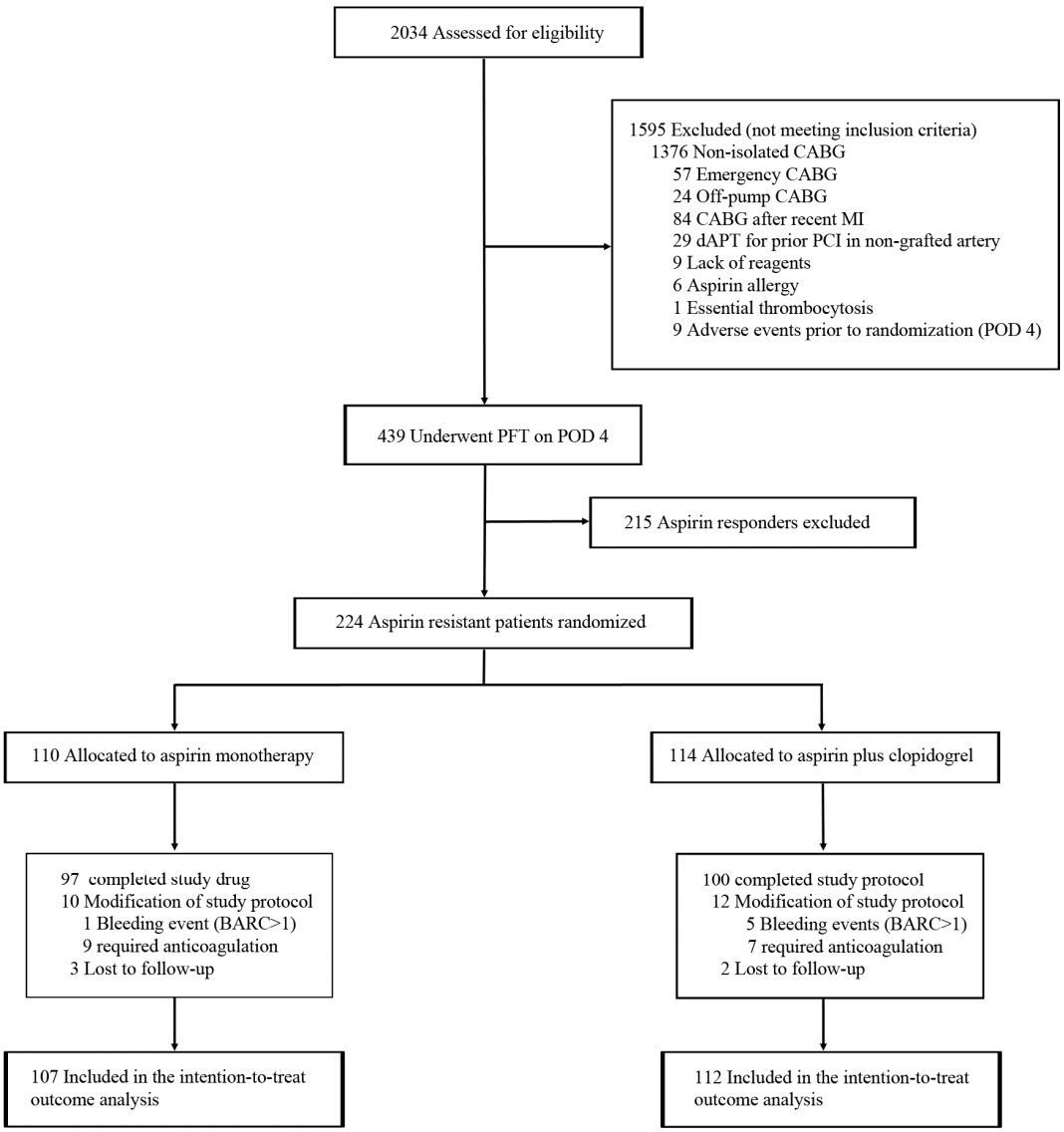
2034 Assessed for eligibility
1595 Excluded (not meeting inclusion criteria)
1376 Non-isolated CABG
57 Emergency CABG
24 Off-pump CABG
84 CABG after recent MI
29 dAPT for prior PCI in non-grafted artery
9 Lack of reagents
6 Aspirin allergy
1 Essential thrombocytosis
9 Adverse events prior to randomization (POD 4)
439 Underwent PFT on POD 4
215 Aspirin responders excluded
224 Aspirin resistant patients randomized
110 Allocated to aspirin monotherapy
114 Allocated to aspirin plus clopidogrel
97 completed study drug
10 Modification of study protocol
1 Bleeding event (BARC>1)
9 required anticoagulation
3 Lost to follow-up
100 completed study protocol
12 Modification of study protocol
5 Bleeding events (BARC>1)
7 required anticoagulation
2 Lost to follow-up
107 Included in the intention-to-treat outcome analysis
112 Included in the intention-to-treat outcome analysis

Figure 2. Increases in ASPI test values in the aspirin-monotherapy (A) and Dual APT groups (B) in response to surgery. Changes in ADP test values in the aspirin-monotherapy (C) and Dual APT groups (D) in response to surgery.

*Wilcoxon matched-pairs test

APT = antiplatelet therapy; ASPI = cyclooxygenase dependent platelet aggregation; ADP = adenosine diphosphate; Preop = preoperative; POD = postoperative day; AUC = area under the curve

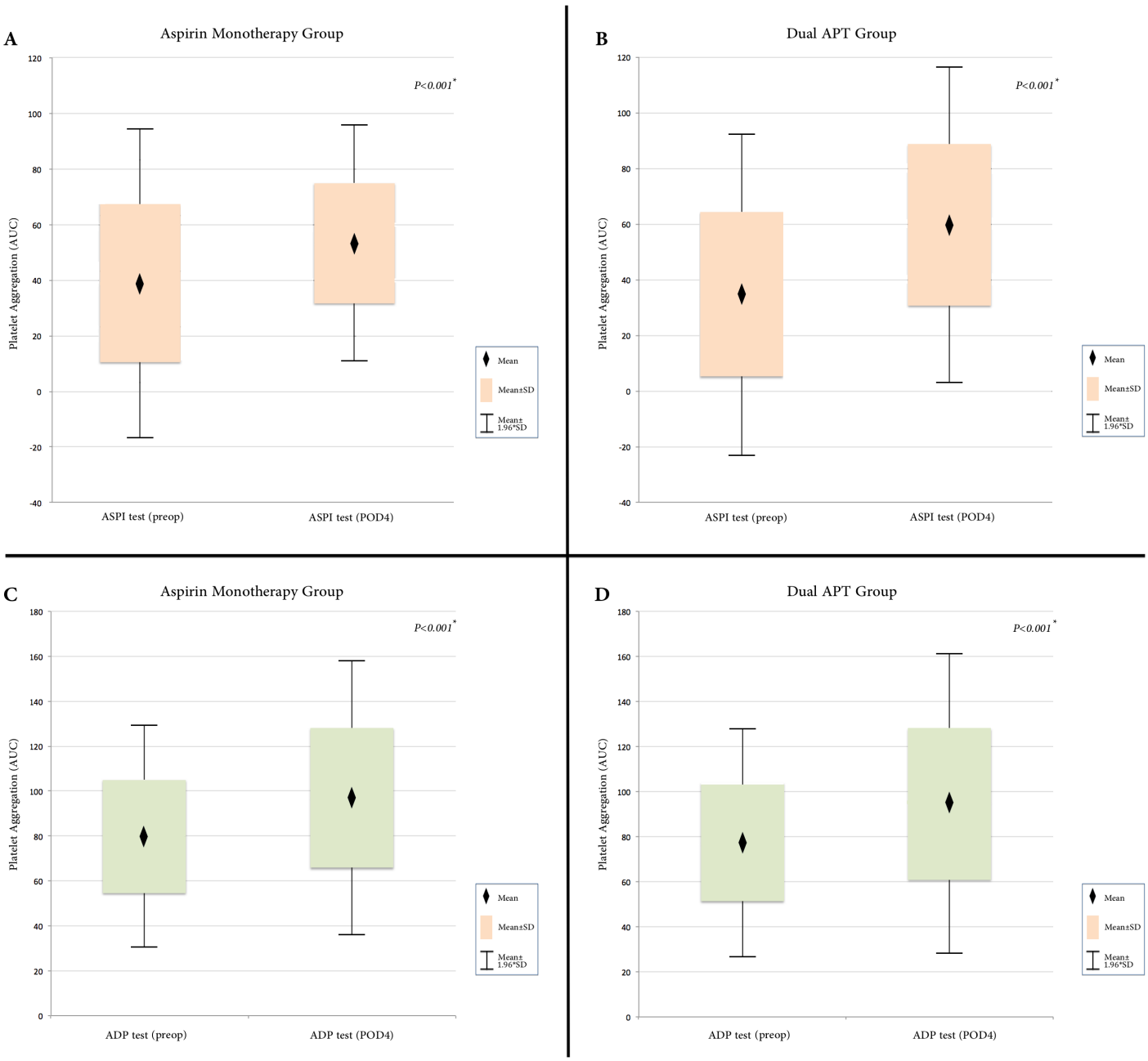
A
Aspirin Monotherapy Group
P<0.001*
Platelet Aggregation (AUC)
120
100
80
60
40
20
0
-20
-40
ASPI test (preop)
ASPI test (POD4)
Mean
Mean±SD
Mean± 1.96*SD
B
Dual APT Group
P<0.001*
Platelet Aggregation (AUC)
ASPI test (preop)
ASPI test (POD4)
Mean
Mean±SD
Mean± 1.96*SD
C
Aspirin Monotherapy Group
P<0.001*
Platelet Aggregation (AUC)
180
160
140
120
100
80
60
40
20
0
ADP test (preop)
ADP test (POD4)
Mean
Mean±SD
Mean± 1.96*SD
D
Dual APT Group
P<0.001*
Platelet Aggregation (AUC)
ADP test (preop)
ADP test (POD4)
Mean
Mean±SD
Mean± 1.96*SD

Table 1. Baseline Demographic and Clinical Profiles (N=219)

Variable	Aspirin Monotherapy (n=107)	Aspirin Plus Clopidogrel (n=112)	p*
Age (years)	65±9	65±8	0.69
Male gender	82 (77%)	83 (74%)	0.75
Body mass index (kg/m^2)	30±4	29±4	0.21
EuroSCORE	3.6±3.7	3.5±3.0	0.44
LVEF (%)	55±10	53±10	0.16
Hyperlipidemia†	103 (96%)	108 (96%)	1.00
Diabetes mellitus	41 (38%)	43 (38%)	1.00
Smoker	41 (38%)	38 (34%)	0.57
Hypertension‡	103 (96%)	108 (96%)	1.00
Left main narrowing	57 (53%)	48 (43%)	0.14
Three-vessel coronary disease	80 (75%)	88 (79%)	0.53
Preoperative platelet reactivity			
ASPI test values, AUC	38±28	35±30	0.27
ADP test values, AUC	80±25	77±26	0.47
Preoperative medications			
Clopidogrel	27 (25%)	37 (33%)	0.24
Aspirin	94 (88%)	100 (89%)	0.83
B-blocker	83 (78%)	101 (90%)	0.02
Angiotensin-converting enzyme inhibitor	67 (63%)	61 (54%)	0.27
Statin	104 (97%)	108 (96%)	1.00

* Two-tailed *p*

† Hyperlipidemia was defined as any of the following: history of hypercholesterolemia (LDL-cholesterol>3.4 mmol/l or total cholesterol>5.2 mmol/l), hypertriglyceridemia (>1.7 mmol/L), hyperchylomicronemia or use of lipid-lowering medications to achieve target lipid/lipoprotein values

‡ Hypertension was defined as 2 or more systolic blood pressure (BP) measurements ≥140 mmHg or diastolic BP readings ≥90 mmHg, or use of anti-hypertensive medications to achieve the desired BP values in patients with a history of high BP

EuroSCORE=European System for Cardiac Operative Risk Evaluation; LVEF=left ventricular ejection fraction; ASPI=cyclooxygenase dependent platelet aggregation; AUC=area under the curve; ADP=adenosine diphosphate

Table 2. Perioperative Details and Postoperative Medication Use

	Aspirin Monotherapy (n=107)	**Aspirin Plus Clopidogrel (n=112)**	**p***
Perioperative Data			
Left internal mammary use	101 (94%)	104 (93%)	0.78
Cross-clamp time (min)	57±22	59±22	0.45
CPB time (min)	86±25	87±28	0.62
Postoperative AF	27 (25%)	36 (32%)	0.30
Postoperative inotrope use	31 (29%)	36 (32%)	0.66
Postoperative Platelet Reactivity			
ASPI test values, AUC	53±22	60±29	0.19
ADP test values, AUC	97±31	95±34	0.89
Postoperative Medications			
Clopidogrel	0	112 (100%)	<0.01
Aspirin	107 (100%)	112 (100%)	1.00
Beta blocker	101 (94%)	101 (90%)	0.31
Angiotensin-converting enzyme inhibitor	12 (11%)	17 (15%)	0.43
Statin	100 (93%)	104 (93%)	1.00

*Two-tailed *p*

CPB=cardiopulmonary bypass; AF=atrial fibrillation; ASPI=cyclooxygenase dependent platelet aggregation; ADP=adenosine diphosphate; AUC=area under the curve

Table 3. Primary and Secondary Study Outcomes (Intention-to-Treat Analysis)

	Aspirin Monotherapy	**Aspirin Plus Clopidogrel**	**Relative Risk (95% CI)**	**p***
Efficacy End-points	**(n=107)**	**(n=112)**		
MACCE	11 (10%)	7 (6%)	0.61 (0.25-1.51)	0.33
All-cause death	4 (4%)	2 (2%)	0.48 (0.09-2.55)	0.44
Cardiovascular death	1 (1%)	1 (1%)	0.96 (0.06-15.08)	1.00
Stroke	4 (4%)	1 (1%)	0.24 (0.03-2.10)	0.20
Non-fatal MI	1 (1%)	1 (1%)	0.96 (0.06-15.08)	1.00
Composite MI or stroke or cardiovascular death	5 (5%)	3 (3%)	0.57 (0.14-2.34)	0.49
Cardiovascular hospitalization	3 (3%)	3 (3%)	0.96 (0.20-4.63)	1.00
Safety End-points				
Total bleeding events	20 (19%)	28 (25%)	1.34 (0.80-2.23)	0.33
BARC 1	19 (18%)	23 (21%)	1.16 (0.67-2.00)	0.61
BARC 2	0	1 (1%)	N/A	1.00
BARC 3	1 (1%)	4 (4%)	3.82 (0.43-33.65)	0.37
BARC 4	0	0	N/A	1.00
BARC 5	0	0	N/A	1.00

*Two-tailed *p*

CI=confidence intervals; MACCE=major adverse cardiac and cerebrovascular events; MI=myocardial infarction; BARC=Bleeding Academic Research Consortium

Table 4. Subgroup Analyses of the Primary End-Point

	***Aspirin* Monotherapy**	**Aspirin Plus Clopidogrel**	***Relative Risk (95% CI)***	**p***
Age, y				
≥65	6/58 (10%)	7/58 (12%)	1.17 (0.42-3.26)	1.00
<65	5/49 (10%)	0/54	N/A	0.02
Sex				
Male	7/82 (9%)	6/83 (7%)	0.85 (0.30-2.41)	0.78
Female	4/25 (16%)	1/29 (3%)	0.22 (0.03-1.81)	0.17
Body mass index, kg/m^2				
>30	8/45 (18%)	0/41	N/A	<0.01
≤30	3/62 (5%)	7/71 (10%)	2.04 (0.55-7.54)	0.34
EuroSCORE				
≥3	6/48 (13%)	5/48 (10%)	0.83 (0.27-2.55)	1.0
<3	5/59 (8%)	2/64 (3%)	0.37 (0.07-1.83)	0.26
LVEF				
>50%	5/66 (8%)	4/63 (6%)	0.84 (0.24-2.98)	1.0
≤50%	6/41 (15%)	3/49 (6%)	0.42 (0.11-1.57)	0.29
Diabetes mellitus				
Yes	7/41 (17%)	3/43 (7%)	0.41 (0.11-1.47)	0.19
No	4/66 (6%)	4/69 (6%)	0.96 (0.25-3.67)	1.0
Three vessel disease				
Yes	8/80 (10%)	6/88 (7%)	0.68 (0.25-1.88)	0.58
No	3/27 (11%)	1/24 (4%)	0.38 (0.04-3.37)	0.61
Left main disease				
Yes	8/57 (14%)	2/48 (4%)	0.30 (0.07-1.33)	0.11
No	3/50 (6%)	5/64 (8%)	1.30 (0.33-5.19)	1.0

*Two-tailed *p*

CI=confidence interval; EuroSCORE=European System for Cardiac Operative Risk Evaluation; LVEF=left ventricular ejection fraction