Impact of aspirin resistance on outcomes among patients following coronary artery bypass grafting: exploratory analysis from randomized controlled trial (NCT01159639)

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Abstract

Objectives: Individual variability in the response to aspirin, has been established by various platelet function assays, however, the clinical relevance of aspirin resistance (AR) in patients undergoing coronary artery bypass grafting (CABG) has to be evaluated.

Methods: Our working group conducted a randomized controlled trial (NCT01159639) with the aim to assess impact of dual antiplatelet therapy (APT) on outcomes among patients with AR following CABG. Patients that were aspirin resistant on fourth postoperative day (POD 4) were randomly assigned to receive either dual APT with clopidogrel (75mg) plus aspirin (300mg) – intervention arm or monotherapy with aspirin (300mg) – control arm. This exploratory analysis compares clinical outcomes between aspirin resistant patients allocated to control arm and patients that have had adequate platelet inhibitory response to aspirin at POD 4. Both groups were treated with 300 mg of aspirin per day following surgery. We sought to evaluate the impact of early postoperative AR on outcomes among patients following CABG.

Results: Exploratory analysis included a total number of 325 patients. Of those, 215 patients with adequate response to aspirin and 110 patients with AR allocated to aspirin monotherapy following randomization protocol. The primary efficacy end point (MACCEs - major adverse cardiac and cardiovascular events) occurred in 10% and 6% of patients with AR and with adequate aspirin response, respectively (p=0.27). Non-significant differences were observed in bleeding events occurrence. Subgroup analysis of the primary end point revealed that aspirin resistant patients with BMI > 30 kg/m^2 tend to have a higher occurrence of MACCEs 18% vs. 5% (relative risk 0.44 [95% CI 0.16-1.16]; p=0.05).

Conclusions: This exploratory analysis did not reveal significant impact of aspirin resistance on outcomes among patients undergoing CABG. Further, sufficiently powered studies are needed in order to evaluate clinical relevance of AR in patients undergoing CABG.

Keywords: Aspirin resistance; Multiple electrode aggregometry; Platelet aggregation inhibitors; Coronary artery bypass surgery; platelet function

Introduction

Clinical outcomes in coronary artery bypass grafting (CABG) surgery depend mainly on the patency of the graft vessels. Three distinct but interrelated pathological processes such as thrombosis, intimal hyperplasia and atherosclerosis[1] contribute to graft failure following CABG[1]. Early thrombosis is a major cause of graft failure during the first month after CABG[1, 2]. Beneficial effect of antiplatelet therapy (APT) in early postoperative phase is therefore important and has been reported in literature[3-5]. Aspirin is the most commonly prescribed antiplatelet drug following CABG[6]. When postoperatively administered, aspirin is associated with a 40% reduction in bypass graft occlusions occurence[6, 7]. Current guidelines on APT administration following CABG recommend initiation of 100 to 325 mg of aspirin starting within 6 hours of surgery[8, 9]. However, not all patients respond equally to APT, thus continuous refinement in postoperative APT management is warranted. Current guidelines[8] recommend the one-size fits-all strategy in administration of APT postoperatively, which certainly disregards wide variability in platelet inhibitory response to APT[8]. Even though there is no consensual definition of aspirin resistance (AR), literature reveals that up to 83.3% of patients inadequately respond to this drug based on *in vitro* platelet function testing[10]. Despite existing huge variability in platelet inhibitory response to aspirin, wide range in percentage of aspirin resistance prevalence dominantly stems in a lack of methodological consensus to define AR as well as in numeruous different tests available to quantify platelet function. Notably, the degree of agreement between the various assays to quantify platelet inhibitory response to aspirin is poor[10]. Clinical causes as well as pathophysiological mechanisms for AR onset are numerous. In addition to interindividual differences in platelet inhibitory response to aspirin, it is very important to stress out that antiplatelet effect of aspirin may vary intraindividually[11-13]. This is of particular relevance in patients undergoing CABG, as there is evidence that cardiopulmonary bypass contributes to hyperactivity onset in postoperative phase[2, 12, 14, 15]. Although there is evidence on AR prevalence in patients undergoing CABG, the clinical impact of AR on outcomes among patients following CABG remains elusive. The level of clinical relevance to which the term “aspirin resistance” may be attached remains unclear. The concept of AR has been debated since the 1980s[16] and the more recent literature evaluates the level of clinical relevance that may be attached to the term “aspirin resistance”[16].

Also it remains challenging to optimize postoperative APT management because individual variability in platelet inhibitory response to APT varies widely and is unpredictable. The aim of this exploratory analysis from the randomized trial (NCT01159639) was to evaluate the impact of AR presence detected with multiple electrode aggregometry (MEA) in early postoperative phase on outcomes among patients following CABG.

Materials and methods

Design of randomized controlled trial (NCT01159639)

NCT01159639 randomized controlled trial was a single-center randomized controlled trial that evaluated the addition of clopidogrel to aspirin on outcomes among patients found to have AR early postoperatively. Institutional review board approved the study and written informed consent was obtained for each patient considered for inclusion in the randomized controlled study. We adhered to ethical standards in line with the Declaration of Helsinki. Study design details and eligibility criteria have previously been published[17]. In brief, 2034 patients were initially assessed for eligibility and 439 patients underwent platelet function testing on the fourth postoperative day (POD 4). 224 out of 439 patients were found to be aspirin resistant at POD 4 and were randomly assigned to receive clopidogrel (75mg) plus aspirin (300mg) – *interventional arm* or aspirin-monotherapy (300mg) – *non-interventional (control) arm*[17]. Patients having adequate platelet inhibitory response to aspirin at POD 4 were initially excluded from the randomized controlled trial. These patients were included in the follow up as this exploratory analysis has been prospectively designed.

Patient selection

Study flowchart for this exploratory analysis is shown in Figure 1. A total number of 439 patients finally underwent platelet function testing at POD 4. Of those, 215 have had adequate platelet inhibitory response to aspirin therapy (aspirin responders) and continued to receive aspirin 300 mg/day postoperatively. Of 224 aspirin resistant patients that were randomized, 110 were allocated to aspirin monotherapy (control group) and continued to receive aspirin 300 mg/day postoperatively. 185 aspirin responders and 107 aspirin resistant patients allocated to aspirin monotherapy were finally included in the intention-to-treat analysis and were compared to each other with aim to evaluate clinical relevance of the AR among patients following CABG who continued to receive aspirin 300 mg/day monotherapy postoperatively.

Perioperative management

All patients had the same anesthetic and perfusion teams and were admitted at least 1 day before surgery. Surgery was performed in a single unit with standard surgical techniques. The critical components of the employed

cardiopulmonary circuit were the Medtronic Affinity Trillium membrane oxygenator, venous reservoir, PVC tubing (Medtronic, Minneapolis, MN, USA), and a Stoeckert III roller pump (Stoeckert, Munich, Germany). The ascending aorta and right atrium were cannulated for CPB. Myocardial protection consisted of both antegrade and retrograde cold blood cardioplegia. Systemic heparinization aiming at an activated clotting time >480 s was used, followed by full reversal with protamine after decannulation. A dose of 1 g tranexamic acid was given at the induction of anesthesia and after protamine administration. Distal coronary anastomoses were performed on an arrested heart during a single period of aortic cross-clamping. Weaning from CPB was initiated once the patient's rhythm had stabilized and normothermia had been achieved. Inotropic support was initiated in order to maintain a cardiac index greater than 2.2 l/min/m^2.

Blood sampling

Blood samples were obtained at POD 4 using venipuncture, and 4 ml blood was collected in 4 ml heparin (Lithium Heparin 68 IU) coated BD Vacutainer plastic tubes.

Multiple-electrode aggregometry (MEA)

Whole blood platelet aggregation was determined using MEA (Multiplate®, Verum Diagnostica GmbH and Dynabyte Informationssysteme GmbH, Munich, Germany)[18]. Increase in impedance is expressed in arbitrary area under the curve (AUC) units, highlighted as the parameter with the highest diagnostic power[18] . The samples were incubated for 3 min and platelet aggregation was measured 6 min after stimulation. Platelet aggregation was determined in response to stimulation with arachidonic acid with a final concentration of 0.5 mM (ASPI test designed to evaluate aspirin effect) and adenosine diphosphate (ADP) with a final concentration of 6.4 μM (ADP test designed to evaluate thienopyridines, such as clopidogrel, effect). The same person, not directly involved in patient care, performed all the measurements. Individuals processing the samples as well as individuals collecting follow up data were unaware of treatment group.

Primary and secondary outcome

More in detail data regarding primary and secondary outcomes have been already published[17,19]. Put briefly, the primary efficacy end point was the incidence of major adverse cardiac and cerebrovascular events (MACCEs) after 6

months follow up[19]. MACCE has been defined as a composite end point consisted of all-cause mortality, nonfatal myocardial infarction (MI), cerebrovascular accident, and cardiovascular rehospotalization. Individual MACCE components, as well as bleeding events characterized according to Bleeding Academic Research Consortium (BARC) definitions[20] (safety end point data) were considered as the secondary outcomes.

Statistical analysis

The continuous data were presented as mean values with their standard deviation. Categorical variables were presented as absolute numbers with percentages. A value of $p \leq 0.05$ was considered statistically significant. The Mann-Whitney U test was used to analyze continuous data between the two groups. Comparison between the categorical variables was performed with Fisher's exact test. Relative risks (RR) were used as a measure of the association between the response to aspirin and clinical outcomes. The respective 95% confidence intervals (CI) were provided. Changes in the platelet reactivity in response to surgery were evaluated with the Wilcoxon matched-pairs test. The data were processed using the IBM SPSS Statistics software package (version 20.0; Somers, New York)

Results

Baseline demographic and operative data

Baseline demographic and clinical profiles of the two compared groups are shown in Table 1. Significant differences were observed between the two groups in respect to age, body mass index, left main disease and angiotensin-converting enzyme inhibitor preoperative administration. We believe that those differences did not influence the clinical outcomes. Although age is one of the strongest predictors of adverse events, the fact is that 2 year difference may be of questionable significance. In addition to, EuroSCORE scoring system that accounts for age was not significantly different between groups. No differences were observed in perioperative details such as left internal mammary use, cross-clamp time (min), cardiopulmonary bypass time (CPB) and perioperative inotrope use (Table 2.).

Platelet function testing results

We observed significant differences in preoperative platelet aggregability between the groups (Table 1.). Aspirin resistant patients allocated to Aspirin monotherapy "control" arm have had higher value of ASPI test (38±28 vs. 23±20 AUC, $p<0.001$). The similar findings were found for the ADP test (80±25 vs. 68±28 AUC, $p<0.001$). The same trend of higher ASPI and ADP test values in aspirin resistant patients allocated to aspirin monotherapy comparing to aspirin responders was noted postoperatively (Table 2.). Of more importance, we observed significant difference in platelet reactivity turnover in response to surgery (Figure 2.). In aspirin resistant patients allocated to aspirin monotherapy we observed statistically significant increase of platelet aggregability in response to surgery for both the ASPI (38±28 vs. 53±22 AUC, $p<0.001$) and ADP (80±25 vs. 97±31 AUC, $p<0.001$) tests. Aspirin responders expressed a similar phenomenon for ADP test (68±28 vs 84±36 AUC, $p<0.001$). However, in aspirin responders group, there was no platelet aggregability increase in response to surgery for the ASPI test (23±20 vs. 20±6, $p = 0.857$). Hence, it seems that patients with adequate platelet inhibitory response to aspirin did not experience platelet reactivity turnover in response to surgery.

Clinical outcomes

Two groups were analyzed for differences in the primary and secondary study outcomes (Table 3.). The primary efficacy end point (MACCEs - major adverse cardiac and cardiovascular events) occurred in 10% and 6% in patients

with AR and with adequate aspirin response, respectively (p=0.27). All-cause death (4 vs. 2%), stroke (4 vs. 1%) and composite MI or stroke or cardiovascular death (3 vs. 2%) occurred more frequently in Aspirin resistant patients, however, those differences did not reach statistical significance. Non-significant differences were observed in bleeding events occurrence (Table 3.). Subgroup analysis of the primary end point (Table 4.) revealed that aspirin resistant patients with BMI > 30 kg/m2 tend to have a significantly higher occurrence of MACCEs 18% vs. 5% (RR 0.44 [95% CI (0.16-1.16); p=0.05).

Discussion

In this exploratory analysis of prospectively collected data within randomized controlled trial (NCT01159639) we sought to evaluate the impact of AR, detected by MEA, on clinical outcomes during the 6 month follow up period after CABG. Concerning efficacy end points, we observed that adverse events such as MACCEs (10 vs. 6%), all-cause death (4 vs. 2%), stroke (4 vs. 1%) as well as composite MI or stroke or cardiovasvular death (5 vs. 2%), occurred more frequently in patients with AR, however statistical significance has not been reached. Subgroup analysis of the primary end point revealed that AR may significantly affect clinical outcomes in patients with BMI > 30 kg/m^2 (Table 4.). Non-significant differences were observed in bleeding events occurrence. Considering the bleeding outcomes, previously we have conducted studies where the pronounced preoperative platelet inhibition reflected on the amount of early postoperative bleeding[21, 22]. In contrast to short term bleeding outcomes that correlated well with platelet function[21-23], we have found non-significant differences between aspirin sensitive and aspirin resistant patients in terms of bleeding outcomes, defined according to BARC[20] criteria and evaluated after six months of follow up. We found that 51% of patients undergoing isolated CABG were aspirin resistant in early postoperative phase[19]. These results are in line with those previously published by our working group[2] where we found that 46.5% of patients were aspirin resistant at POD 4[2]. Postoperatively registered increase of 15.2% in the proportion of patients with AR was found to be significant[2]. Very similar phenomenon was observed at the randomized controlled trial study cohort[19]. However, this exploratory analysis comparing aspirin resistant patients and patients with adequate platelet inhibitory response showed markedly different results[19]. In contrast to aspirin resistant patients where we observed significant increase of platelet aggregability in response to surgery (ASPI test, 38±28 vs. 53±22 AUC, $p<0.001$), in aspirin responders group, there was no platelet reactivity turnover in response to surgery for the ASPI test (23±20 vs. 20±6, $p = 0.857$). Hence, it seems that patients having adequate platelet inhibitory response to aspirin did not experience platelet hyperactivity turnover in response to surgery.

Extensive evidece describing the phenomenon of AR in patients undergoing cardiac surgery is available in literature[11, 24, 25]. Based on underlying mechanisms, we can assume that there are three types of aspirin resistance:

1) Pharmacokinetic AR where inadequate *in vivo* efficacy exists despite sufficient *in vitro* performance[24, 25]. In such a cases, patient non-compliance, inadequate absorption and drug to drug interactions should be considered[24, 25].
2) Pharmacodynamic AR may be considered in cases where is incomplete (cyclooxygenase-1) COX-1 inhibition presented in spite adequate plasma concentration[12]. Early postoperative increased platelet turnover and reactivity[12] as well as COX-1 polymorphism may be underlying cause for such a phenomenon[24, 25].
3) Pseudoresistance implies that adequate COX-1 inhibition is achieved, however platelet express activation via thromboxane independent pathways[24, 25]. This type of AR underlines the importance of comprehensive approach in management of AR. Drugs affecting other pathways of platelet activation should be considered in such cases. Not only aspirin resistant, but also patients with adequate platelet inhibitory response to aspirin may express at the same time platelet adenosine di-phosphate (ADP) receptor hyperactivity. In such a subgroup of patients with hyperactive ADP platelet receptors, thienopyridines should be considered. Moreover, platelet ADP receptor inhibitory response to thienopyridines should be quantified, as there is evidence that up to 30% of patients on clopidogrel may be considered as clopidogrel resistant[24, 26].

Optimal postoperative APT management certainly requires comprehensive approach. Assessment of platelet inhibitory response to aspirin therapy is representative of only one pathway of platelet reactivity. Therefore, it is difficult to expect that achievement of adequate platelet inhibition in only one platelet activation pathway may efficiently prevent adverse ischemic events in patients with CABG being performed. Significant number of patients treated with aspirin has major adverse, vascular related events every year[27]. Contrary to patients who benefit from aspirin therapy, patients that experience adverse ischemic events while on aspirin therapy may be labeled as “aspirin resistant”. Platelets of aspirin resistant patients generally do not achieve adequate platelet inhibitory response to aspirin. Notably, recent evidence suggests that clopidogrel improves aspirin response and dual antiplatelet therapy (aspirin plus clopidogrel) results with significantly lower incidence of AR comparing to aspirin monotherapy[28]. In patients labeled as aspirin resistant, aspirin dose increase or addition of other antiplatelet drug could be considered as a measure to overcome residual platelet reactivity. The Bochum CLopidogrel and Aspirin Plan (BOCLA-Plan)[29]

incorporating a “test and treat” strategy effectively eliminated AR by dose modification after subsequent platelet function testing being performed[29]. Notably, when considering increase of aspirin dosage up to 500 mg/day, it is important to understand that high-dose of aspirin may worsen endothelial mediated arterial dilatation[30]. In patients following CABG, the possible impact of each antiplatelet agent administered postoperatively should separately be assessed by drug specific platelet function testing[31] . Such an approach could distinguish patients with high residual on-treatment platelet reactivity, thus proclivity to ischemic events, from those with pronounced platelet inhibition, who are prone to bleeding events[31]. Personalized approach directed after drug specific platelet function test results could be considered in postoperative APT management[31]. Furthermore, platelet function testing could be performed repetitively in certain timeframes[31]. Recently, our working group performed randomized controlled trial with aim to evaluate the effect of serial clopidogrel dose adjustment based on MEA results on clinical outcomes of patients undergoing percutaneous coronary intervention[32]. Study showed that clopidogrel dose adjustment according to MEA results have led to better platelet inhibition in patients with initial high residual platelet reactivity. In addition, patients in the interventional group (drug dose adjustment targeted after MEA results) had a significantly better outcome and survival to an adverse event (ischemic or bleeding)[32]. Considering variability in platelet reactivity through time, we assume that longitudinal follow up based on repetitive MEA testing could target the therapeutic window of platelet reactivity which in turn could help to minimize both bleeding and ischemic events in patients following CABG. However, prospective randomized trials are needed to confirm this hypothesis.

Review of literature

There is shortage of literature evaluating the relation of AR and its impact on clinical outcomes following CABG. Gluckman et al evaluated effects of aspirin responsiveness and platelet reactivity on early vein graft thrombosis after CABG[33]. Thromboxane generation (increased levels of urinary 11-dehydro thromboxane B2) and shear-dependent platelet hyper-reactivity were independent risk factors for early saphenous vein graft thrombosis after CABG[33]. Investigator in the prevention of Coronary Artery Bypass Occlusion After CABG (CRYSSA trial) reported an alarming correlation between resistance to APT and graft occlusion (RR, 3.6; 95% CI, 2.5-6.9; $p<0.001$)[34]. Review

and meta-analysis published by Snoep et al[35] have shown that aspirin resistant patients are at increased risk of recurrent cardiovascular events compared with aspirin sensitive patients[35]. Similarly to Snoep et al[35], Krasopoulos et al[16] evaluated relation between AR and clinical outcomes in patients with cardiovascular disease[16]. Using systematic search, authors identified 20 studies, totaling 2930 patients[16]. Of those, 2120 were classified as aspirin sensitive and the remaining 810 (28%) as aspirin resistant[16]. These results[16] are in line with those published by our working group[2]. In prospective observational study evaluating perioperative changes in platelet reactivity in patients undergoing CABG[2], we have found that 31.3% of patients undergoing CABG were aspirin resistant preoperatively[2]. Therefore, one may expect that approximately one third of patients treated with aspirin may be aspirin resistant. Krasopoulos et al[16] have found that aspirin resistant patients were at greater risk of clinically important adverse cardiovascular events[16]. The odds ratio for increased mortality in aspirin resistant patients was 5.99 (2.28 to 15.72; $p<0.003$)[16]. Similarly to our findings from randomized controlled trial[19], authors reported[16] that concomitant therapy with other antiplatelet agent provided no benefit to those patients labeled as aspirin resistant[16].

Study limitations and methodological considerations

As we discussed ealier[19], we cannot exclude the possibility that the study may have been underpowered[19] despite the fact we performed initially sample size calculation based on exact binomial test power analysis[17, 19]. Further, similar designed, multicentric studies that would be sufficiently powered to assess the impact of AR on clinical outcomes. Furthermore, our trial has not initially been designed to estimate durability of AR, as MEA has been performed solely on POD 4 following CABG[17, 19]. In general, we may assume there is permanent as well as transient AR. Patients who were found to be aspirin resistant preoperatively are more likely to have permanent AR. In contrast to, patients that were aspirin resistant on POD 4, but did have adequate platelet inhibitory response preoperatively, are more likely to have temporary/transient AR. In this subgroup of patients it would be interesting to evaluate durability of AR by performing repetitively platelet function testing throughout follow up period. In this way it would be possible to assess the impact of AR presence as well as longevity of AR on clinical outcomes in patients following CABG. The design of randomized controlled study (NCT01159639)[17, 19] and subsequent exploratory analysis provide data insufficient to establish whether patients identified as aspirin resistant on POD 4 remained aspirin resistant or whether

patients identified as aspirin sensitive subsequently became aspirin resistant during the follow up period. Further studies should inevitably address this drawback by performing subsequently platelet function testing in predefined time intervals during the follow up.

Conclusion

In order to understand better the relation between AR and clinical outcome, further, sufficiently powered prospective multicenter studies are warranted. Adjustment of antiplatelet drug dosage, as well as duration of adjustment regimen could be directed according to platelet function test results. Longitudinal follow-up of platelet reactivity might be a useful adjunct to standard postoperative APT management protocol aiming to achieve more favorable patient outcomes by targeting therapeutic window for each antiplatelet drug being administered[6]. However, such a therapeutic approach requires further multicenter randomized controlled trial with a large study cohort that would allow for sufficiently powered data analysis and evaluation of such a treatment modality leading to meaningful conclusions.

References:

1. Zimmermann N, Gams E, Hohlfeld T. Aspirin in coronary artery bypass surgery: new aspects of and alternatives for an old antithrombotic agent. Eur J Cardiothorac Surg. 2008; 34(1): 93-108.

2. Petricevic M, Biocina B, Konosic S, Kopjar T, Kunac N, Gasparovic H. Assessment of platelet function by whole blood impedance aggregometry in coronary artery bypass grafting patients on acetylsalicylic acid treatment may prompt a switch to dual antiplatelet therapy. Heart Vessels. 2013; 28(1): 57-65.

3. Goldman S, Copeland J, Moritz T, Henderson W, Zadina K, Ovitt T, et al. Improvement in early saphenous vein graft patency after coronary artery bypass surgery with antiplatelet therapy: results of a Veterans Administration Cooperative Study. Circulation. 1988; 77(6): 1324-32.

4. Goldman S, Copeland J, Moritz T, Henderson W, Zadina K, Ovitt T, et al. Saphenous vein graft patency 1 year after coronary artery bypass surgery and effects of antiplatelet therapy. Results of a Veterans Administration Cooperative Study. Circulation. 1989; 80(5): 1190-7.

5. Goldman S, Copeland J, Moritz T, Henderson W, Zadina K, Ovitt T, et al. Long-term graft patency (3 years) after coronary artery surgery. Effects of aspirin: results of a VA Cooperative study. Circulation. 1994; 89(3): 1138-43.

6. Gasparovic H, Petricevic M, Biocina B. Management of antiplatelet therapy resistance in cardiac surgery. J Thorac Cardiovasc Surg. 2014; 147(3): 855-62.

7. Denko CW, Aponte J, Gabriel P, Petricevic M. beta-Endorphin, immunological and biochemical changes in synovial fluid in rheumatic disorders. Clin Rheumatol. 1986; 5(1): 25-32.

8. Dunning J, Versteegh M, Fabbri A, Pavie A, Kolh P, Lockowandt U, et al. Guideline on antiplatelet and anticoagulation management in cardiac surgery. Eur J Cardiothorac Surg. 2008; 34(1): 73-92.

9. Hillis LD, Smith PK, Anderson JL, Bittl JA, Bridges CR, Byrne JG, et al. 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for

Thoracic Surgery, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2011; 58(24): e123-210.

10. Lordkipanidze M, Pharand C, Schampaert E, Turgeon J, Palisaitis DA, Diodati JG. A comparison of six major platelet function tests to determine the prevalence of aspirin resistance in patients with stable coronary artery disease. Eur Heart J. 2007; 28(14): 1702-8.

11. Zimmermann N, Kienzle P, Weber AA, Winter J, Gams E, Schror K, et al. Aspirin resistance after coronary artery bypass grafting. J Thorac Cardiovasc Surg. 2001; 121(5): 982-4.

12. Zimmermann N, Kurt M, Wenk A, Winter J, Gams E, Hohlfeld T. Is cardiopulmonary bypass a reason for aspirin resistance after coronary artery bypass grafting? Eur J Cardiothorac Surg. 2005; 27(4): 606-10.

13. Zimmermann N, Kurt M, Winter J, Gams E, Wenzel F, Hohlfeld T. Detection and duration of aspirin resistance after coronary artery bypass grafting. J Thorac Cardiovasc Surg. 2008; 135(4): 947-8.

14. Kempfert J, Anger K, Rastan A, Krabbes S, Lehmann S, Garbade J, et al. Postoperative development of aspirin resistance following coronary artery bypass. Eur J Clin Invest. 2009; 39(9): 769-74.

15. Bednar F, Osmancik P, Hlavicka J, Jedlickova V, Paluch Z, Vanek T. Aspirin is insufficient in inhibition of platelet aggregation and thromboxane formation early after coronary artery bypass surgery. J Thromb Thrombolysis. 2009; 27(4): 394-9.

16. Krasopoulos G, Brister SJ, Beattie WS, Buchanan MR. Aspirin "resistance" and risk of cardiovascular morbidity: systematic review and meta-analysis. Bmj. 2008; 336(7637): 195-8.

17. Gasparovic H, Petricevic M, Kopjar T, Djuric Z, Svetina L, Biocina B. Dual antiplatelet therapy in patients with aspirin resistance following coronary artery bypass grafting: study protocol for a randomized controlled trial [NCT01159639]. Trials. 2012; 13(1): 148.

18. Toth O, Calatzis A, Penz S, Losonczy H, Siess W. Multiple electrode aggregometry: a new device to measure platelet aggregation in whole blood. Thromb Haemost. 2006; 96(6): 781-8.

19. Gasparovic H, Petricevic M, Kopjar T, Djuric Z, Svetina L, Biocina B. Impact of dual antiplatelet therapy on outcomes among aspirin-resistant patients following coronary artery bypass grafting. Am J Cardiol. 2014; 113(10): 1660-7.

20. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011; 123(23): 2736-47.

21. Petricevic M, Biocina B, Milicic D, Konosic S, Svetina L, Lekic A, et al. Bleeding risk assessment using whole blood impedance aggregometry and rotational thromboelastometry in patients following cardiac surgery. J Thromb Thrombolysis. 2013; 36(4): 514-26.

22. Petricevic M, Biocina B, Milicic D, Konosic S, Ivancan V, Milosevic M, et al. Bleeding risk assessment using multiple electrode aggregometry in patients following coronary artery bypass surgery. J Thromb Thrombolysis. 2013; 35(1): 31-40.

23. Petricevic M, Kopjar T, Biocina B, Milicic D, Kolic K, Boban M, et al. The Predictive Value of Platelet Function Point-of-Care Tests for Postoperative Blood Loss and Transfusion in Routine Cardiac Surgery: A Systematic Review. Thorac Cardiovasc Surg. 2014. DOI: 10.1055/s-0034-1378191.

24. Gasparovic H PM, Biocina B Impact and Diagnosis of Antiplatelet Therapy Resistance in Patients Undergoing Cardiac Surgery. Drug Development Research. 2013; 74: 492-504.

25. Weber AA, Przytulski B, Schanz A, Hohlfeld T, Schror K. Towards a definition of aspirin resistance: a typological approach. Platelets. 2002; 13(1): 37-40.

26. Nguyen TA, Diodati JG, Pharand C. Resistance to clopidogrel: a review of the evidence. J Am Coll Cardiol. 2005; 45(8): 1157-64.

27. Patrono C, Garcia Rodriguez LA, Landolfi R, Baigent C. Low-dose aspirin for the prevention of atherothrombosis. N Engl J Med. 2005; 353(22): 2373-83.

28. Wang X, Gong X, Zhu T, Zhang Q, Zhang Y, Wang X, et al. Clopidogrel improves aspirin response after off-pump coronary artery bypass surgery. Journal of biomedical research. 2014; 28(2): 108-13.

29. Neubauer H, Kaiser AF, Endres HG, Kruger JC, Engelhardt A, Lask S, et al. Tailored antiplatelet therapy can overcome clopidogrel and aspirin resistance--the BOchum CLopidogrel and Aspirin Plan (BOCLA-Plan) to improve antiplatelet therapy. BMC Med. 2011; 9: 3.

30. Furuno T, Yamasaki F, Yokoyama T, Sato K, Sato T, Doi Y, et al. Effects of various doses of aspirin on platelet activity and endothelial function. Heart Vessels. 2011; 26(3): 267-73.

31. Petricevic M, Biocina B, Safradin I, Milicic D. Modern antiplatelet management of coronary artery bypass patients: a role of platelet function testing in decision making. J Thromb Thrombolysis. 2014; 37(3): 249-50.

32. Samardzic J, Krpan M, Skoric B, Pasalic M, Petricevic M, Milicic D. Serial clopidogrel dose adjustment after platelet function testing improves outcome of acute coronary syndrome patients undergoing percutaneous coronary intervention with high on-treatment platelet reactivity. J Thromb Thrombolysis. 2014.

33. Gluckman TJ, McLean RC, Schulman SP, Kickler TS, Shapiro EP, Conte JV, et al. Effects of aspirin responsiveness and platelet reactivity on early vein graft thrombosis after coronary artery bypass graft surgery. J Am Coll Cardiol. 2011; 57(9): 1069-77.

34. Mannacio VA, Di Tommaso L, Antignan A, De Amicis V, Vosa C. Aspirin plus clopidogrel for optimal platelet inhibition following off-pump coronary artery bypass surgery: results from the CRYSSA (prevention of Coronary arteRY bypaSS occlusion After off-pump procedures) randomised study. Heart. 2012; 98(23): 1710-5.

35. Snoep JD, Hovens MM, Eikenboom JC, van der Bom JG, Huisman MV. Association of laboratory-defined aspirin resistance with a higher risk of recurrent cardiovascular events: a systematic review and meta-analysis. Arch Intern Med. 2007; 167(15): 1593-9.

Table 1.

Table 1. Baseline Demographic and Clinical Profiles (N=294)

Variable	Aspirin Monotherapy (n=107)	Responders (n=185)	p*
Age (years)	65±9	63±8	0.03
Male gender	82 (77%)	146 (79%)	0.66
Body mass index (kg/m^2)	30±4	29±4	0.05
EuroSCORE	3.6±3.7	2.9±2.4	0.17
LVEF (%)	55±10	55±11	0.90
Hyperlipidemia†	103 (96%)	172 (93%)	0.31
Diabetes mellitus	41 (38%)	65 (35%)	0.62
Smoker	41 (38%)	70 (38%)	1.00
Hypertension‡	103 (96%)	178 (96%)	1.00
Left main narrowing	57 (53%)	67 (36%)	0.01
Three-vessel coronary disease	80 (75%)	134 (72%)	0.68
Preoperative platelet reactivity			
ASPI test values, AUC	38±28	23±20	<0.01
ADP test values, AUC	80±25	68±28	<0.01
Preoperative medications			
Clopidogrel	27 (25%)	56 (30%)	0.42
Aspirin	94 (88%)	172 (93%)	0.14
B-blocker	83 (78%)	149 (81%)	0.55
Angiotensin-converting enzyme inhibitor	67 (63%)	159 (86%)	<0.01
Statin	104 (97%)	168 (91%)	0.05

* 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.

Table 2. Perioperative Details and Postoperative Medication Use

	Aspirin Monotherapy (n=107)	**Responders (n=185)**	**p***
Perioperative Data			
Left internal mammary use	101 (94%)	173 (94%)	1.00
Cross-clamp time (min)	57±22	55±21	0.35
CPB time (min)	86±25	82±27	0.16
Postoperative inotrope use	31 (29%)	51 (28%)	0.79
Postoperative Platelet Reactivity			
ASPI test values, AUC	53±22	20±6	<0.01
ADP test values, AUC	97±31	84±36	<0.01
Postoperative Medications			
Clopidogrel	0	0	1.00
Aspirin	107 (100%)	185 (100%)	1.00
Beta blocker	101 (94%)	178 (96%)	0.56
Angiotensin-converting enzyme inhibitor	12 (11%)	23 (12%)	0.85
Statin	100 (93%)	183 (99%)	0.01

*Two-tailed *p*

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

Table 3.

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

	Aspirin Monotherapy	**Responders**	**Relative Risk (95% CI)**	**p***
Efficacy End-points	**(n=107)**	**(n=185)**		
MACCE	11 (10%)	12 (6%)	0.81 (0.54-1.21)	0.27
All-cause death	4 (4%)	4 (2%)	0.79 (0.39-1.58)	0.47
Cardiovascular death	1 (1%)	2 (1%)	1.05 (0.47-2.36)	1.00
Stroke	4 (4%)	1 (1%)	0.31 (0.05-1.81)	0.06
Non-fatal MI	1 (1%)	1 (1%)	0.79 (0.20-3.16)	1.00
Composite MI or stroke or cardiovascular death	5 (5%)	4 (2%)	0.70 (0.33-1.45)	0.30
Cardiovascular hospitalization	3 (3%)	6 (3%)	1.05 (0.66-1.69)	1.00
Safety End-points				
Total bleeding events	20 (19%)	26 (14%)	0.87 (0.67-1.15)	0.32
BARC 1	19 (18%)	25 (14%)	0.88 (0.67-1.16)	0.40
BARC 2	0	1 (1%)	1.58 (1.45-1.73)	1.00
BARC 3	1 (1%)	0	N/A	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.

Table 4. Subgroup Analyses of the Primary End-Point

	***Aspirin* Monotherapy**	**Responders**	***Relative Risk (95% CI)***	**p***
Age, y				
≥65	6/58 (10%)	7/82 (9%)	0.91 (0.54-1.54)	0.77
<65	5/49 (10%)	5/103 (5%)	0.72 (0.39-1.36)	0.29
Sex				
Male	7/82 (9%)	10/146 (7%)	0.91 (0.61-1.38)	0.79
Female	4/25 (16%)	2/39 (5%)	0.52 (0.17-1.65)	0.20
Body mass index, kg/m^2				
>30	8/45 (18%)	3/65 (5%)	0.44 (0.16-1.16)	0.05
≤30	3/62 (5%)	9/120 (8%)	1.15 (0.81-1.62)	0.75
EuroSCORE				
≥3	6/48 (13%)	7/62 (11%)	0.95 (0.56-1.62)	1.00
<3	5/59 (8%)	5/123 (4%)	0.73 (0.39-1.37)	0.30
LVEF				
>50%	5/66 (8%)	5/117 (4%)	0.77 (0.41-1.45)	0.50
≤50%	6/41 (15%)	7/68 (10%)	0.85 (0.50-1.43)	0.55
Diabetes mellitus				
Yes	7/41 (17%)	4/65 (6%)	0.57 (0.26-1.26)	0.10
No	4/66 (6%)	8/120 (7%)	1.04 (0.68-1.57)	1.00
Three vessel disease				
Yes	8/80 (10%)	10/133 (8%)	0.88 (0.58-1.35)	0.61
No	3/27 (11%)	2/51 (4%)	0.60 (0.20-1.76)	0.33
Left main disease				
Yes	8/57 (14%)	3/67 (4%)	0.48 (0.18-1.28)	0.11
No	3/50 (6%)	9/118 (8%)	1.07 (0.76-1.51)	1.00

*Two-tailed *p*

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

Figures:

Figure 1.

Exploratory analysis flowchart. Patient eligibility, group for analysis selection and follow up. BARC = Bleeding Academic Research Consortium; CABG = Coronary Artery Bypass Grafting; dAPT = dual antiplatelet therapy; MI = Myocardial Infarction; PCI = percutaneous coronary intervention ; PFT = Platelet Function Testing ; POD 4 = Postoperative day 4

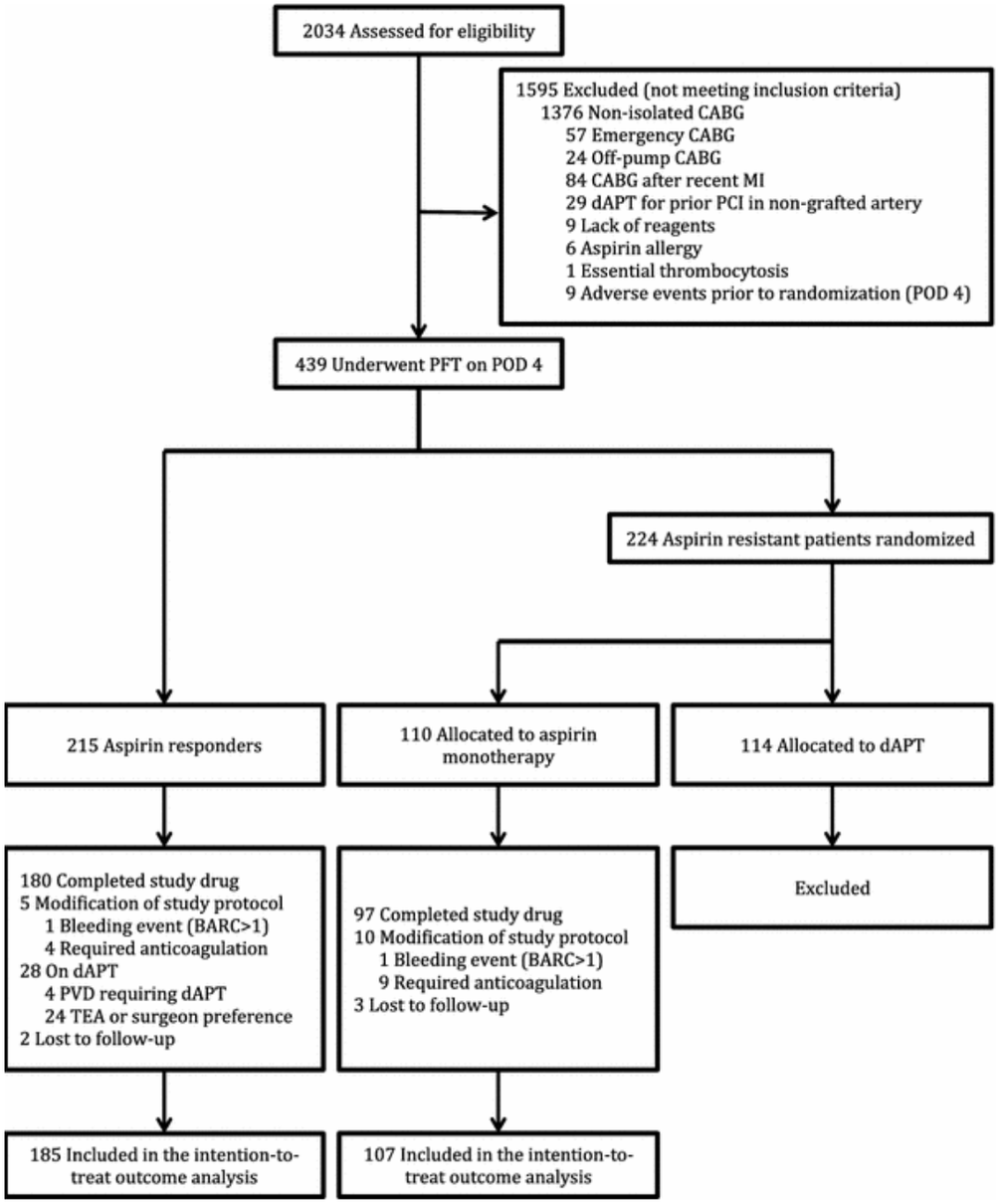

Figure 2.

Perioperative changes in platelet function test values in response to surgery. Increases in ASPI test values in aspirin-monotherapy group (A) and aspirin "responders" group (B) in response to surgery. Changes in ADP test values in the aspirin-monotherapy group (C) and aspirin "responders" group (D) in response to surgery.* Wilcoxon matched-pairs test. ASPI = cyclooxygenase-dependent platelet aggregation ; ADP = adenosine di-phosphate dependent plateet aggregation