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

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Coronary artery bypass grafting is pivotal in the contemporary management of complex coronary artery disease. Interpatient variability to antiplatelet agents, however, harbors the 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, nonfatal myocardial infarction, stroke, or cardiovascular hospitalization assessed at 6 months postoperatively. The primary end point occurred in 6% of patients assigned to dAPT and 10% of patients randomized to aspirin-monotherapy (relative risk 0.61, 95% confidence interval 0.25 to 1.51, p = 0.33). No significant treatment effect was noted in the occurrence of the safety end point. The total incidence of bleeding events was 25% and 19% in the dAPT and aspirin-monotherapy groups, respectively (relative risk 1.34, 95% confidence interval 0.80 to 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 <65 years (0% vs 10%, p = 0.02). In conclusion, the addition of clopidogrel in patients found to be aspirin resistant after coronary artery bypass grafting did not reduce the incidence of adverse events, nor did it increase the number of recorded bleeding events. dAPT did, however, lower the incidence of the primary end point in obese patients and those <65 years. **(Am J Cardiol 2014;113:1660−1667)**

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 on technical refinements of the procedure and optimization of medical management. The long-term benefits of CABG depend upon the durability of nonobstructed 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 antiplatelet therapy (dAPT) may improve the 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 the cumulation of their individual antiaggregatory effects, because their individual mechanisms of antiplatelet activity differ.[5] Dual platelet inhibition may be of particular importance in patients exhibiting single antiplatelet drug resistance.[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] Although 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 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 enrollment 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 enrollment. Exclusion criteria included valvular pathology warranting

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This trial is registered at *www.clinicaltrials.gov* (NCT01159639).

See page 1666 for disclosure information.

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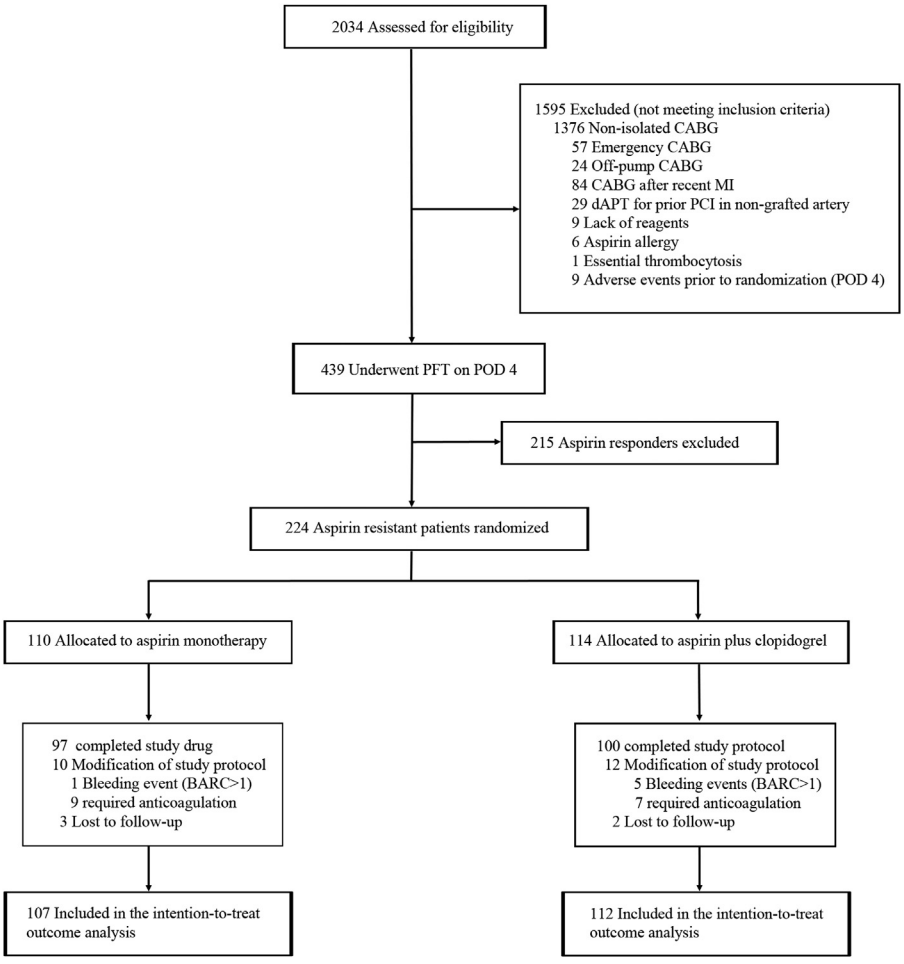

Figure 1. Patient eligibility, randomization, and follow-up. BARC = Bleeding Academic Research Consortium; PCI = percutaneous coronary intervention; PFT = platelet function testing.

surgical correction, off-pump CABG, requirement for dual antiplatelet management, anticoagulation, and critical condition before randomization. Patients who underwent CABG following a recent acute coronary syndrome were excluded, as there are 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, whereas 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 before enrollment.

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

The ASPI test evaluates cyclooxygenase-1-dependent platelet aggregation and is therefore a surrogate for aspirin responsiveness. Although aspirin response is better described as a continuous variable, dichotomizing patients into "responders" and "nonresponders" 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] $\geq$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