Management of antiplatelet therapy resistance in cardiac surgery

Gašparović, Hrvoje; Petričević, Mate; Biočina, Bojan

Source / Izvornik: **Journal of Thoracic and Cardiovascular Surgery, 2014, 147, 855 - 862**

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

https://doi.org/10.1016/j.jtcvs.2013.10.008

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:105:646729

Gašparović H., Petričević M., Biočina B. (2014) ***Management of antiplatelet therapy resistance in cardiac surgery.*** **Journal of Thoracic and Cardiovascular Surgery, 147 (3). pp. 855-62. ISSN 0022-5223**

http://www.elsevier.com/locate/issn/00225223

http://www.sciencedirect.com/science/journal/00225223

http://dx.doi.org/10.1016/j.jtcvs.2013.10.008

Management of Antiplatelet Therapy Resistance in Cardiac Surgery

Hrvoje Gasparovic, MD, PhD*, Mate Petricevic, MD*, Bojan Biocina, MD, PhD

Department of Cardiac Surgery, Clinical Hospital Center Zagreb, University of Zagreb, Zagreb, Croatia

Running title: Antiplatelet Therapy Resistance in Cardiac Surgery

Correspondence:

Hrvoje Gasparovic, M.D., PhD, FETCS

Department of Cardiac Surgery

Clinical Hospital Center Zagreb

Kispaticeva 12

10 000 Zagreb

Croatia

Tel: +385-1-236-7517

Fax: +385-1-236-7531

E-mail: HGASPAROVIC@GMAIL.COM

Word count: 3087

Key words: antiplatelet therapy resistance; coronary artery bypass surgery; aspirin; clopidogrel; platelet function testing

*Dr. Gasparovic and Dr. Petricevic contributed equally to the manuscript

Ultramini abstract

The management of antiplatelet therapy resistance currently lacks clear outlines. This review summarizes the treatment options for patients found to have high residual platelet reactivity despite receiving the recommended anti-platelet agents. It also provides the cut-off points for platelet function tests differentiating anti-platelet therapy "responders" from "non-responders".

The role of coronary artery bypass grafting (CABG) in the management of complex coronary artery disease has been validated through an unparalleled level of scrutiny. Improvement in patient outcomes nowadays relies on continued refinements of the surgical technique and modulation of adjuvant pharmacotherapy. Postoperative antiplatelet therapy (APT) is paramount in maintaining the revascularization benefit. Individual variability to APT, however, results in unpredictable platelet inhibition. Currently available platelet function tests (PFT) dichotomize patients into "responders" and "non-responders" based upon arbitrarily defined cut-off points. Not surprisingly, the incidence of APT resistance across the spectrum of PFTs is widely discrepant, underscoring the fact that single pathway descriptors of platelet aggregation fail to portray the complexity of the process. Thrombosis is the principal mode of failure of saphenous vein grafts (SVG) in the early postoperative period[1]. Reports on the increased incidence of SVG failure in patients experiencing antiplatelet agent resistance underscore the importance of recognizing this entity and intervening in a timely fashion. This review summarizes the various assay-dependent definitions of APT resistance, with their respective rates of occurrence. The clinical impact of on-therapy high residual platelet reactivity (hRPR) in the cardiac surgical arena is discussed. Finally, guidelines on individual tailoring of antiplatelet therapy in patients found to retain high on-therapy platelet reactivity are suggested herein.

Methods

The PUBMED database was searched using the following subject terms: "platelet function testing", "antiplatelet", "aspirin", "clopidogrel", "resistance" and "cardiac surgery". Reference lists of identified publications were analyzed for additional linking studies. Priority was given to cohort studies and reviews.

Definition of anti-platelet therapy resistance

Aspirin is the most commonly used anti-platelet agent after CABG. Its use is associated with a 40% reduction in bypass graft occlusions[2], with the benefit being most evident in saphenous vein grafts[3, 4]. The incidences of SVG graft occlusions within the first year, when the impact of thrombosis is greatest, range between 7.4% and 26%[5-7]. This angiographic outcome is accompanied by a 20%-30% reoccurrence of angina[8] and a 5.9% need for repeat revascularization within the first year[9]. The current guidelines on postoperative APT recommend the initiation of 100-325 mg of aspirin within 6 hours of surgery[10]. In patients unable to take aspirin, 75 mg of clopidogrel is the suggested alternative[10].

The importance of prompt postoperative institution of aspirin is underscored by the fact that starting aspirin on the third postoperative day or later is unlikely to reflect favorably on graft patency[11,12]. The one-size-fits all recommendation for perioperative APT in the current guidelines, however, disregards the individual response variability.

The term aspirin resistance denotes the drug's inability to effectively suppress cyclooxygenase 1 (COX-1) dependent thromboxane A2 (TxA2) production. Aspirin's failure to act on its pharmacological target originates from variable enteral absorption, COX-1 gene mutations, drug-drug interactions, patient non-compliance, accelerated post-cardiopulmonary bypass (CPB) platelet turnover and TxA2-independent platelet activation pathways[13, 14]. The prevalence of aspirin resistance varies widely in the literature, due to variable platelet agonists used in testing and different aspirin-related platelet function descriptors (Table 1).

Clopidogrel is an inactive prodrug that undergoes extensive conversion into its active metabolite by the hepatic cytochrome P450 3A4 (CYP3A4) enzyme[15]. It irreversibly inhibits the P_2Y_{12} adenosine diphosphate (ADP) receptor, which is one of the pivotal routes of platelet activation. Difficulties in elucidating the true incidence of clopidogrel resistance parallel those

for aspirin, as it is also assay-dependent. P_2Y_{12} receptor, *ABCB1* and *CYP2C19* genetic polymorphisms affect clopidogrel pharmacodynamics[15,16]. Strategies moving beyond phenotype-directed into genotype-directed tailoring of APT have become available, but currently lack validation in larger trials[16]. Clopidogrel's metabolic activation is also altered by medications acting as substrates for CYP3A4. Significant reductions in the clopidogrel-induced inhibition of platelet aggregation have been noted in patients using atorvastatin and proton pump inhibitors. Conflicting data on the clinical relevance of such interactions have been published[17-22]. Antiplatelet agent response is best perceived as a continuous variable. The efficacy of APT, however, may be assessed in relation to cut-off points discriminating between "resistance" and "response", or by measuring the on-therapy percent platelet inhibition and comparing it to values obtained prior to APT. The drawback of the latter strategy is that it is affected by variability in baseline platelet reactivity. In contrast, strict cut-off values are invariably arbitrarily defined, but do allow for comparing outcomes in a binary model. The definition of antiplatelet agent resistance remains a moving target. Lordkipanidze et al compared six different platelet function tests to determine the prevalence of aspirin resistance, and found a poor mutual correlation between individual tests[23]. A succinct overview of the cut-off points defining antiplatelet agent resistance using different PFTs is presented in Table 1. Distinguishing between cardiac surgical patients in whom APT resistance is permanent from those in whom it may be a temporary phenomenon may hold practical value. The distinction between the two can be made by comparing preoperative to postoperative PFT results. In patients found to have on-therapy hRPR preoperatively, the resistance is likely a permanent one. Conversely, adequate preoperative platelet inhibition followed by early postoperative hRPR may suggest that the phenomenon is transient in nature. Our group has shown a consistent increase in postoperative platelet reactivity

evaluated with aggregometry in comparison to preoperative values[24] , which is suggestive of heightened platelet reactivity induced by surgery.

Clinical impact of anti-platelet therapy resistance

Aspirin-resistant TxA2 synthesis has been found to elevate the risk of stroke, myocardial infarction and cardiovascular death in patients with cardiovascular disease[25]. A graded increase in the aforementioned risk was observed with each increasing quartile of urinary 11-dehydro thromboxane B2 (UTxB2), which is a metabolic surrogate of TxA2 activity[25].

Investigators in the CRYSSA (prevention of Coronary arteRY bypaSS occlusion After off-pump procedures) trial noted an alarming correlation between graft occlusion and antiplatelet therapy resistance (RR 3.6, 95% CI 2.5 to 6.9; P <0.001)[5]. Conversely, synergistic aspirin- and clopidogrel-induced platelet inhibition was found to predict SVG patency (RR 5.1, 95% CI 1.4 to 16.3; P <0.01)[5]. The link between SVG occlusion and platelet hyperreactivity on aspirin was reported as the secondary objective of the Reduction in Graft Occlusion Rates (RIGOR) study[13]. A higher incidence of early SVG occlusion was found in patients taking aspirin who had increased levels of UTxB2 and shear-dependent platelet activation[13].

Clopidogrel resistance has also been found to be clinically significant by several investigators. Adverse cardiovascular events adjudicated at 6-months were found to be more common in clopidogrel-resistant patients undergoing primary angioplasty for acute myocardial infarction[26]. High platelet reactivity to adenosine-diphosphate (ADP) on dual anti-platelet therapy (dAPT) increased cardiovascular mortality (HR 2.55, [95% CI 1.08 to 6.07], P<0.034) and nonfatal myocardial infarction (HR 3.36, [95% CI 1.49 to 7.58], P<0.004) at

12-month follow-up in a similar clinical setting[27]. A more comprehensive overview of the clinical impact of APT resistance is provided in Table 1. Clopidogrel cessation is advocated in anticipation of elective cardiac surgery in order to minimize perioperative blood loss[10]. One must recognize that this, however, is potentially hazardous as it may induce a rebound prothrombotic and proinflammatory state[28]. Mahla et colleagues proved that clopidogrel can safely be continued up to surgery provided that residual on-therapy platelet reactivity evaluated by thromboelastography remained high[29]. Analogously, Di Dedda et al recently documented that 32% of patients scheduled for cardiac surgery retained hRPR on clopidogrel [30]. These observations again add credence to APT monitoring, as it may directly influence the preoperative discontinuation of clopidogrel and possibly lead to a revision of current guidelines.

Management options for antiplatelet agent resistance

With the problem of antiplatelet agent resistance lacking a clear outline and definition, it is not surprising that guidelines for its management remain to be formed. While a large proportion of the evidence examining the impact of APT resistance is either observational in nature or comes from the non-surgical arena, there are two prospective randomized trials that will provide more data on the augmentation of antiplatelet therapy in drug-resistant CABG patients[31, 32]. The former[31] has reached the data analysis stage, while the latter[32] is still recruiting patients. Coronary bypass grafts may be especially vulnerable in the immediate postoperative period, and there is growing evidence that antiplatelet therapy resistance should not be ignored. The first step in individualized tailoring of platelet inhibition should be platelet function testing at approximately 7 days of APT initiation (Figure 1). Once hRPR is recognized, extrinsic factors such as patient non-compliance, drug interactions or suboptimal glucose and cholesterol regulation should be ruled out.

As antiplatelet drug resistance may be a temporary manifestation, one course of action is to re-evaluate the drug effect without changing the current platelet inhibition regime. Within seven days both aspirin and unbolused clopidogrel reach steady state drug levels. We, therefore, recommend repeating platelet function testing 7 days after any PFT result that is outside the desired therapeutic window.

A significant proportion of patients recognized as clopidogrel resistant 24 hours after its institution were found to respond to the drug when re-evaluated at 30 days[33, 34]. Likewise, the proportion of CABG patients found to be aspirin resistant is inversely proportional to the time elapsed between its assessment and the procedure itself[35, 36]. This point again brings into focus the importance of isolating patients with permanent from those with transient postoperative APT resistance. In the event that a follow-up evaluation of platelet function shows persistence of low-responsiveness, different lines of management should be explored.

An effective approach to antiplatelet therapy resistance is to increase the drug dose. In diabetic patients found to be hyporesponsive to 100 mg of aspirin, increasing the dose to 300 mg led to superior platelet inhibition (Platelet Function Analyzer closure time increased from 170±45 to 229±75 seconds, $P<0.001$)[37]. Increased loading and maintenance doses of clopidogrel have also been found to surmount the resistance to lower-dose therapy[15, 38]. Doubling the dose of clopidogrel in patients found to be non-responders to 75 mg, effectively inhibited platelets in 60% of patients[39]. Neubauer et al reduced the incidence of clopidogrel resistance from 23.6% to 5% by modification of the administered dose based on an aggregometer-guided algorithm[38]. The conversion of non-responders using this strategy, however, remains unpredictable, which emphasizes the need for re-evaluating the effectiveness of platelet inhibition after the implemented dose change[39]. The BOCLA-plan (Bochum Clopidogrel and Aspirin Plan) incorporating a “test and treat” strategy effectively eliminated aspirin resistance by dose modification and subsequent platelet function testing[40].

Of the 19.4% patients found to be low-responsive to 100 mg of aspirin, 94.6% were converted to responders by increasing the dose to 300 mg[40]. The remaining 5.4% received effective platelet inhibition by further increasing the dose to 500 mg of aspirin[40]. It is important, however, to acknowledge the potential of high-dose aspirin to worsen endothelial-mediated arterial dilatation[41]. A similar protocol was implemented for the 30.8% of patients found to be resistant to 75 mg of clopidogrel. Increasing the dose to 150 mg, in line with the predefined BOCLA-plan, induced effective platelet inhibition in 69% of previously resistant patients[40].

Finally, an attractive solution to the problem of hRPR on one platelet inhibitor is to either add a different agent in order to induce an additive effect, or to substitute the original drug altogether. The different mechanisms of platelet inhibition targeted by aspirin and thienopyridines allow for cumulation of their individual anti-aggregational effects. Mannacio et al showed that dAPT effectively overcame single drug resistances, with a subsequent reduction in SVG occlusion (7.4% vs. 13.1%; P=0.04)[5]. Patients randomized to dAPT in the CRYSSA trial experienced similar rates of both minor (2% vs. 1.3%, P=0.5) and major bleeding episodes (1.3% vs. 1.3%, P=1.0) in comparison to the aspirin-monotherapy group[5]. The safety of dAPT was corroborated by similar chest tube outputs in both treatment arms (115±80 ml in the aspirin group vs. 125±70 ml in the dAPT group (P=0.2))[5]. The administration of clopidogrel on the background of aspirin therapy in the early postoperative period did not increase the rate of re-exploration or transfusion in a study by Chan et al[42] . Commonly utilized protocols include starting dAPT when chest tube drainage has been ≤50 ml for 2 hours [5, 42]. We would recommend exercising caution in restarting clopidogrel, however, in patients on preoperative dAPT with documented profound ADP inhibition. Our group has documented that preoperative Multiplate ASPI test values <20 area under the curve units (AUC) and ADP test <73 AUC predicted higher postoperative chest tube output[43].

While clopidogrel and aspirin account for the most commonly used combination of antiplatelet drugs, the potential advantages of novel agents may lead to a future revision of that paradigm. New generation P_2Y_{12} inhibitors are less susceptible to genetic polymorphisms.

Clopidogrel requires two CYP-mediated oxidative steps to reach its active metabolite, while prasugrel requires only one. It initiates faster and more potent platelet inhibition, with less inter-patient response variability than its predecessor[44]. The TRITON-TIMI 38 study (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction 38) demonstrated prasugrel's superiority over clopidogrel in the reduction of major adverse cardiovascular events (MACE) in patients with acute coronary syndromes (ACS) (HR 0.81; [95% CI, 0.73 to 0.90]; $P<0.001$)[45]. The reduction in MACE was offset by an increased risk of bleeding[45]. The post hoc analysis of patients in the prasugrel treatment arm who underwent CABG, mirrored the general study population's increased bleeding risk[46]. Overall mortality, however, was significantly lower in the prasugrel than the clopidogrel CABG cohort despite comparable risk profiles (adjusted OR: 0.26 [95% CI, 0.08 to 0.85]; $P=0.025$)[46]. A potential problem in interpreting these results is that all-cause mortality was as high as 8.67% in the clopidogrel cohort, which had a mean EuroSCORE of only 3.6 ± 3.2[46]. This caveat is amplified by the fact that EuroSCORE may even overestimate CABG mortality[46,47]. Nevertheless, prasugrel's highly effective platelet inhibition and very low incidence of non-responsiveness make it a suitable candidate for patients found to be resistant to prior antiplatelet therapy. In the BOCLA study, patients found to be clopidogrel resistant to even an augmented dosing regime, benefited from the addition of prasugrel in achieving the targeted antiplatelet effect[40].

Ticagrelor is absorbed as an active agent, and is therefore unaffected by the idiosyncrasies of intrinsic biotransformation. Its prompt and reversible P_2Y_{12} inhibition was responsible for a significant reduction in adverse events in its direct comparison to clopidogrel

in the Study of Platelet Inhibition and Patient Outcomes (PLATO) (HR 0.84; [95% CI, 0.77 to 0.92]; $P<0.001$)[48]. The ticagrelor cohort had a 22% relative reduction in mortality[48]. The incidence of bleeding in the CABG subgroup was not affected by ticagrelor, presumably due to the reversible nature of its P_2Y_{12} inhibition[48]. It has already been shown to be useful in upgrading antiplatelet therapy in patients found to be clopidogrel hyporesponders[49]. In the Response to Ticagrelor in Clopidogrel Nonresponders and Responders and Effect of Switching Therapies (RESPOND) trial it has provided more uniform and enhanced platelet inhibition in comparison to clopidogrel, practically eliminating on-therapy hRPR[49].

Prompt induction of platelet inhibition can be achieved with cangrelor. It is a direct-acting P_2Y_{12} inhibitor that immediately suppresses platelet aggregation[50]. Its effect is quickly reversible upon the drug's discontinuation[50]. Cangrelor's intravenous mode of administration overcomes the variability in enteral absorption and bioavailability seen in patients with acute hemodynamic compromise[51]. Additionally, its very short half-life (3 to 5 minutes) allows for precise bridging of anti-platelet therapy in patients scheduled for elective cardiac surgery, without increasing the risk of major bleeding[52]. While the pharmacokinetic properties of cangrelor make it unsuitable for long-term management of APT resistance, its potential applicability in the acute perioperative setting warrants mentioning.

Redundancy and parallel activation pathways characterize clot formation. The role of thrombin in the process of thrombosis goes beyond the generation of fibrin, as it is a very potent platelet agonist. Its platelet activation effects are mediated by protease-activated receptor PAR-1[53]. Vorapaxar is a novel antiplatelet agent that inhibits platelet aggregability by targeting PAR-1. In the Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events (TRA 2P)–Thrombolysis in Myocardial Infarction (TIMI) 50 trial, voraxapar reduced the incidence of death or adverse ischemic events over placebo on the background of standard therapy (HR 0.87; [95% CI, 0.80 to 0.94]; $P<0.001$)[53]. It

increased the risk of bleeding, including intracranial hemorrhage[53]. Exploiting alternative routes of platelet inhibition may be reasonable in patients found to be resistant to the more commonly targeted platelet receptors.

Since the activation of clopidogrel is dependent upon CYP3A4, it stands to reason that pharmacologic induction of this enzyme's metabolic activity may convert clopidogrel non-responders into responders[54]. Co-administration of rifampin and clopidogrel has been used to explore and prove this concept in healthy volunteers[54]. Whether this approach is of any value in the cardiac surgical population is as of yet unknown.

Discussion

Despite the absence of an all-encompassing method for defining antiplatelet response, there is sufficient evidence to support wider dissemination of tools designed to quantify on-therapy platelet reactivity. Strategies utilizing platelet function tests in order to guide transfusion therapy, reduce bleeding and tailor antiplatelet therapy are gaining momentum in the modern cardiac surgical practice[55,56]. Platelet aggregability after cardiac surgery is inconsistent over the early postoperative period. Its unpredictable nature stems from the integration of several opposing influences. The effects of postoperative platelet depletion and iatrogenic platelet inhibition are counterbalanced by accelerated post-CPB platelet turnover. Longitudinal follow-up of platelet reactivity is, therefore, a useful adjunct to standard postoperative protocols aiming to achieve optimal patient outcomes.

Antiplatelet therapy resistance may offset the benefits of surgical myocardial revascularization. Point-of-care platelet function tests provide timely information regarding residual platelet reactivity. Unfortunately, individual PFTs provide data that is not always reciprocated by other tests. This brings into focus the need for standardization and clinical

validation of each test. It is unlikely that different PFTs will ever provide completely interchangeable results because of the large variability of platelet activation pathways that are being tested. Recognizing the impact of APT resistance, however, should serve as an impetus for the definition of its management algorithms. While APT resistance after cardiac surgery may be a transient phenomenon, it occurs during the period when graft patency is most vulnerable. Dual antiplatelet therapy or incremental drug increases in conjunction with regular platelet function testing are useful in overcoming this problem. The contemporary expansion of the antiplatelet drug armamentarium will likely translate into superior outcomes in the clinical domain. The benefits of enhanced platelet inhibition must be balanced against an increased risk of bleeding, which is bound to be its unwanted, yet inevitable, corollary.

In summary, we advocate the use of point-of-care platelet function testing, and tailoring of antiplatelet therapy. Prospective accumulation of data on the clinical impact of such strategies is sorely needed in order for them to become validated on a larger scale.

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;34:93-108.
2. Collaborative overview of randomised trials of antiplatelet therapy--II: Maintenance of vascular graft or arterial patency by antiplatelet therapy. Antiplatelet Trialists' Collaboration. *Bmj.* 1994;308:159-68.
3. Bourassa MG, Fisher LD, Campeau L, Gillespie MJ, McConney M, Lesperance J. Long-term fate of bypass grafts: the Coronary Artery Surgery Study (CASS) and Montreal Heart Institute experiences. *Circulation.* 1985;72:V71-8.
4. Chesebro JH, Fuster V, Elveback LR, Clements IP, Smith HC, Holmes DR, Jr., et al. Effect of dipyridamole and aspirin on late vein-graft patency after coronary bypass operations. *N Engl J Med.* 1984;310:209-14.
5. 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;98:1710-5.
6. Alexander JH, Hafley G, Harrington RA, Peterson ED, Ferguson TB, Jr., Lorenz TJ, et al. Efficacy and safety of edifoligide, an E2F transcription factor decoy, for prevention of vein graft failure following coronary artery bypass graft surgery: PREVENT IV: a randomized controlled trial. *Jama.* 2005;294:2446-54.
7. Motwani JG, Topol EJ. Aortocoronary saphenous vein graft disease: pathogenesis, predisposition, and prevention. *Circulation.* 1998;97:916-31.

8. Cameron AA, Davis KB, Rogers WJ. Recurrence of angina after coronary artery bypass surgery: predictors and prognosis (CASS Registry). Coronary Artery Surgery Study. *J Am Coll Cardiol.* 1995;26:895-9.

9. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med.* 2009;360:961-72.

10. 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;34:73-92.

11. Lorenz RL, Schacky CV, Weber M, Meister W, Kotzur J, Reichardt B, et al. Improved aortocoronary bypass patency by low-dose aspirin (100 mg daily). Effects on platelet aggregation and thromboxane formation. *Lancet.* 1984;1:1261-4.

12. Sharma GV, Khuri SF, Josa M, Folland ED, Parisi AF. The effect of antiplatelet therapy on saphenous vein coronary artery bypass graft patency. *Circulation.* 1983;68:II218-21.

13. 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;57:1069-77.

14. 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;121:982-4.

15. Gurbel PA, Tantry US. Drug insight: Clopidogrel nonresponsiveness. *Nat Clin Pract Cardiovasc Med.* 2006;3:387-95.

16. Ahn SG, Yoon J, Kim J, Uh Y, Kim KM, Lee JH, et al. Genotype- and Phenotype-Directed Personalization of Antiplatelet Treatment in Patients with Non-ST Elevation

Acute Coronary Syndromes Undergoing Coronary Stenting. *Korean Circ J.* 2013;43:541-9.

17. Clarke TA, Waskell LA. The metabolism of clopidogrel is catalyzed by human cytochrome P450 3A and is inhibited by atorvastatin. *Drug Metab Dispos.* 2003;31:53-9.

18. Lau WC, Waskell LA, Watkins PB, Neer CJ, Horowitz K, Hopp AS, et al. Atorvastatin reduces the ability of clopidogrel to inhibit platelet aggregation: a new drug-drug interaction. *Circulation.* 2003;107:32-7.

19. Serebruany VL, Malinin AI, Callahan KP, Gurbel PA, Steinhubl SR. Statins do not affect platelet inhibition with clopidogrel during coronary stenting. *Atherosclerosis.* 2001;159:239-41.

20. Saw J, Steinhubl SR, Berger PB, Kereiakes DJ, Serebruany VL, Brennan D, et al. Lack of adverse clopidogrel-atorvastatin clinical interaction from secondary analysis of a randomized, placebo-controlled clopidogrel trial. *Circulation.* 2003;108:921-4.

21. Dunn SP, Steinhubl SR, Bauer D, Charnigo RJ, Berger PB, Topol EJ. Impact of proton pump inhibitor therapy on the efficacy of clopidogrel in the CAPRIE and CREDO trials. *J Am Heart Assoc.* 2013;2:e004564.

22. O'Donoghue ML, Braunwald E, Antman EM, Murphy SA, Bates ER, Rozenman Y, et al. Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two randomised trials. *Lancet.* 2009;374:989-97.

23. 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;28:1702-8.

24. 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;28:57-65.

25. Eikelboom JW, Hirsh J, Weitz JI, Johnston M, Yi Q, Yusuf S. Aspirin-resistant thromboxane biosynthesis and the risk of myocardial infarction, stroke, or cardiovascular death in patients at high risk for cardiovascular events. *Circulation.* 2002;105:1650-5.

26. Matetzky S, Shenkman B, Guetta V, Shechter M, Beinart R, Goldenberg I, et al. Clopidogrel resistance is associated with increased risk of recurrent atherothrombotic events in patients with acute myocardial infarction. *Circulation.* 2004;109:3171-5.

27. Marcucci R, Gori AM, Paniccia R, Giusti B, Valente S, Giglioli C, et al. Cardiovascular death and nonfatal myocardial infarction in acute coronary syndrome patients receiving coronary stenting are predicted by residual platelet reactivity to ADP detected by a point-of-care assay: a 12-month follow-up. *Circulation.* 2009;119:237-42.

28. Sambu N, Warner T, Curzen N. Clopidogrel withdrawal: is there a "rebound" phenomenon? *Thromb Haemost.* 2011;105:211-20.

29. Mahla E, Suarez TA, Bliden KP, Rehak P, Metzler H, Sequeira AJ, et al. Platelet function measurement-based strategy to reduce bleeding and waiting time in clopidogrel-treated patients undergoing coronary artery bypass graft surgery: the timing based on platelet function strategy to reduce clopidogrel-associated bleeding related to CABG (TARGET-CABG) study. *Circ Cardiovasc Interv.* 2012;5:261-9.

30. Di Dedda U, Ranucci M, Baryshnikova E, Castelvecchio S. Thienopyridines resistance and recovery of platelet function after discontinuation of thienopyridines in cardiac surgery patients. *Eur J Cardiothorac Surg.* 2013.

31. 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;13:148.

32. Rafiq S, Johansson PI, Zacho M, Stissing T, Kofoed K, Lilleor NB, et al. Thrombelastographic haemostatic status and antiplatelet therapy after coronary artery bypass surgery (TEG-CABG trial): assessing and monitoring the antithrombotic effect of clopidogrel and aspirin versus aspirin alone in hypercoagulable patients: study protocol for a randomized controlled trial. *Trials.* 2012;13:48.

33. Gurbel PA, Bliden KP. Durability of platelet inhibition by clopidogrel. *Am J Cardiol.* 2003;91:1123-5.

34. Gurbel PA, Bliden KP, Hiatt BL, O'Connor CM. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. *Circulation.* 2003;107:2908-13.

35. Golanski J, Chlopicki S, Golanski R, Gresner P, Iwaszkiewicz A, Watala C. Resistance to aspirin in patients after coronary artery bypass grafting is transient: impact on the monitoring of aspirin antiplatelet therapy. *Ther Drug Monit.* 2005;27:484-90.

36. 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;135:947-8.

37. Abaci A, Yilmaz Y, Caliskan M, Bayram F, Cetin M, Unal A, et al. Effect of increasing doses of aspirin on platelet function as measured by PFA-100 in patients with diabetes. *Thromb Res.* 2005;116:465-70.

38. Neubauer H, Lask S, Engelhardt A, Mugge A. How to optimise clopidogrel therapy? Reducing the low-response incidence by aggregometry-guided therapy modification. *Thromb Haemost.* 2008;99:357-62.

39. Stellbaum C, Ayral Y, Morguet A, Schultheiss HP, Rauch U. Doubling the clopidogrel dose in patients with reduced responsiveness to the standard dose is associated with a limited effectiveness as evaluated by impedance aggregometry. *Cardiovasc Revasc Med.* 2012;13:159-66.

40. 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.

41. 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;26:267-73.

42. Chan V, Kulik A, Bourke ME, Ressler L, Mesana TG, Ruel M. Clopidogrel is safe early after on- and off-pump coronary artery bypass surgery. *J Card Surg.* 2007;22:493-7.

43. 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;35:31-40.

44. Yousuf O, Bhatt DL. The evolution of antiplatelet therapy in cardiovascular disease. *Nat Rev Cardiol.* 2011;8:547-59.

45. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2007;357:2001-15.

46. Smith PK, Goodnough LT, Levy JH, Poston RS, Short MA, Weerakkody GJ, et al. Mortality benefit with prasugrel in the TRITON-TIMI 38 coronary artery bypass grafting cohort: risk-adjusted retrospective data analysis. *J Am Coll Cardiol.* 2012;60:388-96.

47. Mohr FW, Morice MC, Kappetein AP, Feldman TE, Stahle E, Colombo A, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet.* 2013;381:629-38.

48. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2009;361:1045-57.

49. Gurbel PA, Bliden KP, Butler K, Antonino MJ, Wei C, Teng R, et al. Response to ticagrelor in clopidogrel nonresponders and responders and effect of switching therapies: the RESPOND study. *Circulation.* 2010;121:1188-99.

50. Bhatt DL, Stone GW, Mahaffey KW, Gibson CM, Steg PG, Hamm CW, et al. Effect of platelet inhibition with cangrelor during PCI on ischemic events. *N Engl J Med.* 2013;368:1303-13.

51. Souckova L, Opatrilova R, Suk P, Cundrle I, Jr., Pavlik M, Zvonicek V, et al. Impaired bioavailability and antiplatelet effect of high-dose clopidogrel in patients after cardiopulmonary resuscitation (CPR). *Eur J Clin Pharmacol.* 2013;69:309-17.

52. Angiolillo DJ, Firstenberg MS, Price MJ, Tummala PE, Hutyra M, Welsby IJ, et al. Bridging antiplatelet therapy with cangrelor in patients undergoing cardiac surgery: a randomized controlled trial. *Jama.* 2012;307:265-74.

53. Morrow DA, Braunwald E, Bonaca MP, Ameriso SF, Dalby AJ, Fish MP, et al. Vorapaxar in the secondary prevention of atherothrombotic events. *N Engl J Med.* 2012;366:1404-13.

54. Lau WC, Gurbel PA, Watkins PB, Neer CJ, Hopp AS, Carville DG, et al. Contribution of hepatic cytochrome P450 3A4 metabolic activity to the phenomenon of clopidogrel resistance. *Circulation.* 2004;109:166-71.

55. Ferraris VA, Brown JR, Despotis GJ, Hammon JW, Reece TB, Saha SP, et al. 2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. *Ann Thorac Surg.* 2011;91:944-82.

56. Ranucci M, Baryshnikova E, Soro G, Ballotta A, De Benedetti D, Conti D. Multiple electrode whole-blood aggregometry and bleeding in cardiac surgery patients receiving thienopyridines. *Ann Thorac Surg.* 2011;91:123-9.

57. Sambu N, Radhakrishnan A, Dent H, Calver AL, Corbett S, Gray H, et al. Personalised antiplatelet therapy in stent thrombosis: observations from the Clopidogrel Resistance in Stent Thrombosis (CREST) registry. *Heart.* 2012;98:706-11.

58. Preisman S, Kogan A, Itzkovsky K, Leikin G, Raanani E. Modified thromboelastography evaluation of platelet dysfunction in patients undergoing coronary artery surgery. *Eur J Cardiothorac Surg.* 2010;37:1367-74.

59. 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;39:769-74.

60. Bednar F, Osmancik P, Vanek T, Mocikova H, Jares M, Straka Z, et al. Platelet activity and aspirin efficacy after off-pump compared with on-pump coronary artery bypass surgery: results from the prospective randomized trial PRAGUE 11-Coronary Artery Bypass and REactivity of Thrombocytes (CABARET). *J Thorac Cardiovasc Surg.* 2008;136:1054-60.

61. Poston R, Gu J, Manchio J, Lee A, Brown J, Gammie J, et al. Platelet function tests predict bleeding and thrombotic events after off-pump coronary bypass grafting. *Eur J Cardiothorac Surg.* 2005;27:584-91.

62. 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;96:781-8.

63. Petricevic M BB, Konosic S, Kopjar T, Milosevic M, Gasparovic H. Definition of acetylsalicylic acid resistance using multiple electrode aggregometry in patients following coronary artery bypass grafting. In: Forum THS, ed. *21st World Congress World Society of Cardio-Thoracic Surgeons*. Vol 14. Berlin, Germany: Abstract book; 2011.70-1.

64. Skoric B, Milicic D, Lovric D, Gornik I, Skoric KN, Sertic J. Initial patency of the infarct-related artery in patients with acute ST elevation myocardial infarction is related to platelet response to aspirin. *Int J Cardiol.* 2010;140:356-8.

65. Jambor C, Weber CF, Gerhardt K, Dietrich W, Spannagl M, Heindl B, et al. Whole blood multiple electrode aggregometry is a reliable point-of-care test of aspirin-induced platelet dysfunction. *Anesth Analg.* 2009;109:25-31.

66. Gurbel PA, Bliden KP, Navickas IA, Mahla E, Dichiara J, Suarez TA, et al. Adenosine diphosphate-induced platelet-fibrin clot strength: a new thrombelastographic indicator of long-term poststenting ischemic events. Am Heart J. 2010;160:346-54.

Table 1. Antiplatelet therapy resistance: assay-specific definitions, prevalence and clinical impact

Study	Patient population	Aspirin resistance			Clopidogrel resistance			Cut-off value for APT resistance		Outcome
		Incidence	Platelet function test	POC turn-around time	Incidence	Platelet function test	POC turn-around time	Aspirin	Clopidogrel	
Mannacio et al[5]	OPCAB pts (n=300)	32.6% (5 days after treatment inititation)	VerifyNow Aspirin (Accumetrics Inc, San Diego, CA)	<10 min	22%* (5 days after treatment initiation)	VerifyNow P2Y12	<10 min	Aspirin reaction units >550	P2Y12 resistance units >230 and platelet inhibition >30%	APT resistance predicted graft occlusion (RR 3.6, 95% CI 2.5 to 6.9; p<0.001).
Sambu et al[57]	Stent thrombosis pts (n=39)	28% (at inclusion)	Short TEG (Haemonetics Corp, Massachusetts, USA)	15 min	67%† (at inclusion)	Short TEG (Haemonetics Corp, Massachusetts, USA)	15 min	<50% TEG percent platelet inhibition	<30% TEG per cent platelet inhibition	Inclusion criterion was stent thrombosis
Gluckman et al[13]	CABG pts (n=229)	5% (at 3 days postoperatively); 0.9% (at 6 mo postoperatively)	AA induced platelet aggregometry (Chrono-Log, Havertown, PA)	7 min	Not reported	Not reported	N/A	>1 Ohm	Not reported	No correlation between APT resistance and SVG patency
		16% (at 3 days postoperatively); 10% (at 6 mo postoperatively)	VerifyNow Aspirin (Accumetrics Inc, San Diego, CA)	<10 min				Aspirin reaction units ≥550	Not reported	No correlation between APT resistance and SVG patency
		64% (at 3 days postoperatively); 12% (at 6 mo postoperatively)	PFA-100 CEPI	5-8 min				CEPI clotting time (CT) ≤193 s	Not reported	SVG occlusion was more prevalent in subjects with CADP CT≤88s (at 6 months); no correlation with CEPI
		73% (at 3 days postoperatively); 31% (at 6 mo postoperatively)	$UTxB_2$	N/A				$UTxB_2$ ≥400 pg/mg creatinine	Not reported	ASA-insensitive TXA_2 generation, measured by $UTxB_2$, predicted SVG thrombosis

Petricevic et al[24]	CABG pts (n=99)	31.3% (preoperatively); 46.5% (at 4 days postoperatively)	ASPI test Multiplate (Dynabyte Gmbh , Munich , Germany)	9 min	Not reported	Not reported	N/A	≥30 AUC‡	Not reported	Not reported
Preisman et al[58]	CABG pts (n=59)	44% (preoperatively)	TEG platelet mapping (Haemoscope Corporation, Niles, IL, USA)	up to 1 hour	85% (preoperatively)	TEG platelet mapping (Haemoscope Corporation, Niles, IL, USA)	up to 1 hour	AA induced platelet activation >50%	ADP induced platelet activation >50%	MAadp <42.5 mm predicted increased postoperative bleeding
Lordkipanidze et al[23]	Stable coronary disease (n=201)	4%	LTA (AA)	N/A	Not reported	Not reported	N/A	residual platelet aggregation >20%	Not reported	Not reported
		10.3-51.7%	LTA (ADP)	N/A				residual ADP-induced platelet aggregation >70%		
		18%	Whole blood aggregometry (Chronolog)	7 min				>3 Ohms		
		59,50%	PFA 100	5-8 min				Aperture closure time <193 sec		
		6,70%	VerifyNow Aspirin (Accumetrics Inc, San Diego, CA)	<10 min				Aspirin reaction units ≥550		
		22,90%	urinary 11-dehydro-thromboxane B2 concentration (dTxB2)	N/A				≥67.9 ng/mmol of creatinine		
Kempfert et al[59]	CABG/OPCAB pts, (n=59)	28.8% (preoperatively); 49.2% (at 5 days postoperatively)	Turbidimetric aggregometry (PAP-4, Berlin, Germany)	N/A	Not reported	Not reported	N/A	platelet aggregation >30% despite in vitro addition of 25µM ASA to exclude non-compliance	Not reported	3 deaths occured after 12 months follow up. All were perioperatively found to be aspirin resistant

Bednar et al[60]	CABG/OPCAB pts, (n=80)	Not reported	PAP-4 Platelet Aggregation Profiler (BioBata Corp)	N/A	Not reported	Not reported	N/A	Platelet aggregation was assessed as continuous variable without cut off for clopidogrel resistance	Not reported	Non significant relationship between platelet aggregation studies and chest tube discharge in 24 hours was noted
Poston et al[61]	OPCAB pts (n=76)	3% preoperatively; 13.2% postoperatively (at 3 days postoperatively)	TEG platelet mapping (Haemoscope, Niles, IL)	up to 1 hour	Not reported	Not reported	N/A	>1 SD above the normal value	Not reported [II]	$\%MA_{ASA}$ (TEG) higher in pts with occluded grafts (55±22 vs. 22±17, *P*=0.05); WBA %Ohm 6 min-low vs. high dose (69±25 vs. 35±20, *P*=0.05) higher in pts with occluded grafts
			Whole blood aggregometry (Chronolog , Havertown, PA	7 min	Not reported	Not reported	N/A	>1 SD above the normal value	Not reported	
Di Dedda et al[30]	Cardiac surgery pts (n=344)	Not reported	Not reported	N/A	32% preoperatively	ADP test Multiplate (Dynabyte Gmbh, Munich , Germany)	9 min	Not reported	[§]> 60% of lower limit of normal range (last clopidogrel dose within 1 day); ADP test >32 U.	The last ADP test result before the operation was significantly associated (p=0.002) with postoperative bleeding and the need for postoperative platelet concentrate transfusions; Thrombotic events not reported
									[§]>70% of lower limit of normal range (last clopidogrel dose 2 days); ADP test >37 U.	
									[§]>80% of lower limit of normal range (last clopidogrel dose 3 days prior to the test); ADP test >43 U.	
									[§]platelet aggregation within normal range (>53 U); last dose of clopidogrel >4 days	

Abbreviations: AA – arachidonic acid; ADP – adenosine diphosphate; CABG – coronary artery bypass grafting; CEPI – collagen/epinephrine agnosts; LTA – light transmittance aggregometry; OPCAB – off pump coronary artery bypass; POC – point-of-care; PFA – platelet function analyzer; TEG – thromboelastography

*in CRYSSA 12.6% of patients were resistant to both aspirin and clopidogrel

†In CREST 26% of patients were resistant to both aspirin and clopidogrel

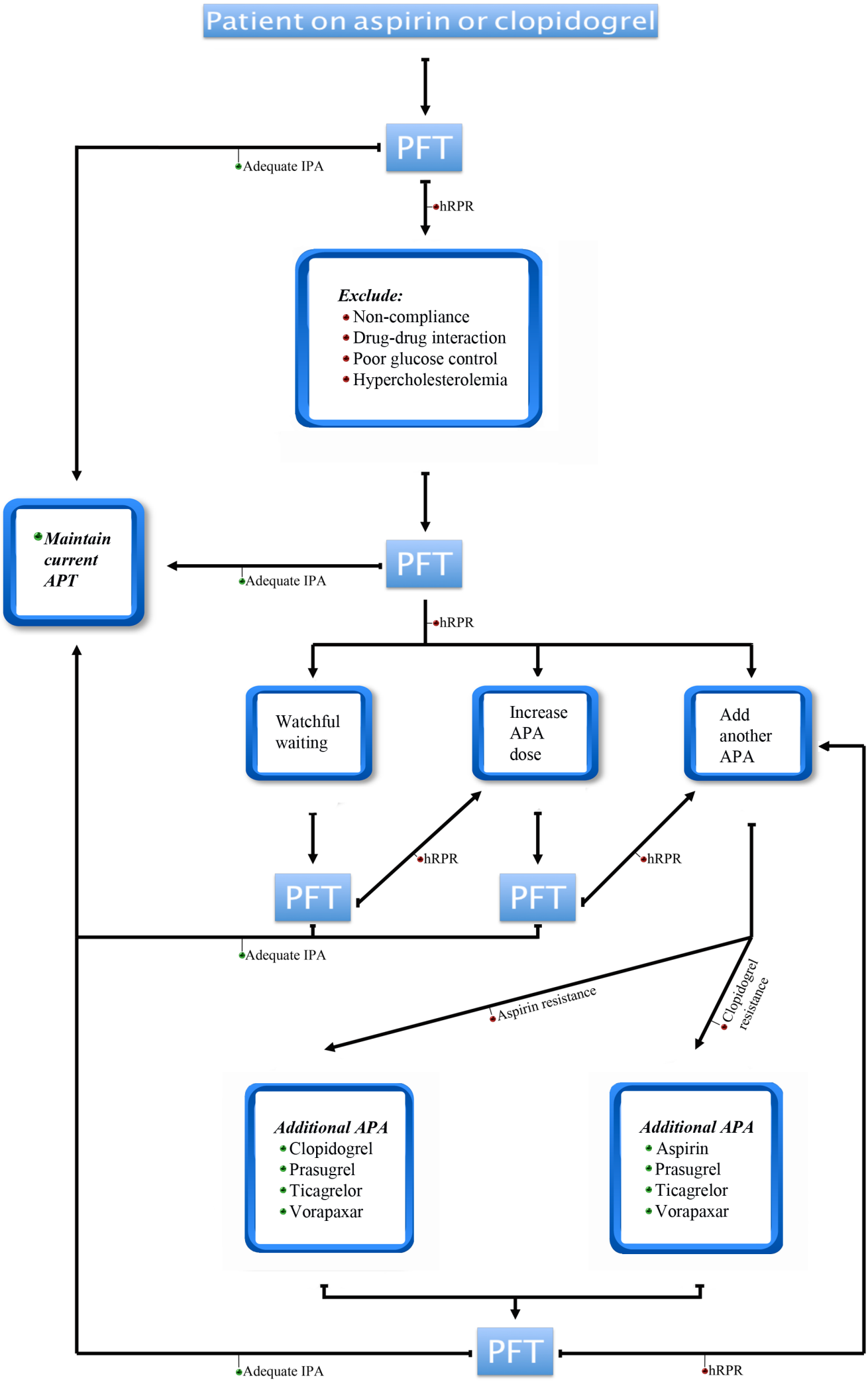
‡Multiple WBA provides 3 parameters: velocity, area under the curve (AUC) and percent platelet inhibition. AUC provides the greatest diagnostic yield[62]. Several studies report cutoff values delineating aspirin resistance using Multiplate[63-65]

§ Cut-off values were adjusted for number of days following preoperative clopidogrel discontinuation and expressed as percentage of the normal range value of ADP test as indicated by manufacturer (53-122 U (AUC))

[II]Gurbel et al investigated the prognostic value of thromboelastography (MAadp) in assessment of ischemic events among patients undergoing PCI. MAadp >47 mm was found to be the best predictor of ischemic events (receiver operating curve, AUC=0.84 [95% CI 0.78 – 0.89, $p < 0.0001$])[66].

Figure 1. Algorithm summarizing management options for patients with documented antiplatelet therapy resistance.

PFT, platelet function testing; IPA, inhibition of platelet aggregation; hRPR, high residual platelet reactivity; APA, antiplatelet agent; APT, antiplatelet therapy


Patient on aspirin or clopidogrel
PFT
Adequate IPA
hRPR
Exclude:
Non-compliance
Drug-drug interaction
Poor glucose control
Hypercholesterolemia
Maintain current APT
PFT
Adequate IPA
hRPR
Watchful waiting
Increase APA dose
Add another APA
PFT
hRPR
PFT
hRPR
Adequate IPA
Aspirin resistance
Clopidogrel resistance
Additional APA
Clopidogrel
Prasugrel
Ticagrelor
Vorapaxar
Additional APA
Aspirin
Prasugrel
Ticagrelor
Vorapaxar
PFT
Adequate IPA
hRPR