

Review Article

Antithrombotic therapy in patients with acute coronary syndromes: a balance between protection from ischemic events and risk of bleeding

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Abstract: Platelet activation plays a primary role in the pathogenesis of acute coronary syndromes (ACS); thus, anti-thrombotic therapy with aspirin and clopidogrel represents the mainstay of treatment in those patients. However, low clopidogrel response has become a contemporary issue in interventional cardiology, increasing the risk of ischemic events and significantly worsening short- and long-term prognosis after coronary stenting. Alternative approaches to overcome this phenomenon have been investigated as well as increase in the loading and maintenance clopidogrel doses, reloading patients already on chronic therapy, use of newer and more effective antiplatelet agents. Otherwise a more aggressive antiplatelet treatment may lead to possible increase in bleeding complications. A strategy of an individualized antiplatelet therapy according to point-of-care platelet function tests may represent the optimal approach to balance both ischemic and hemorrhagic risk.

Keywords: Antithrombotic therapy, acute coronary syndromes, platelet reactivity, bleeding risk

Introduction

The pathophysiology of acute coronary syndromes (ACS) is characterized by atherosclerotic plaque rupture or erosion, leading to acute thrombosis in a coronary vessel. Platelet activation plays a primary role in the pathogenesis of ACS, as well as in the recurrence of events both in medically-treated and in invasively-managed patients with ACS [1]; thus, in those patients dual antiplatelet therapy with aspirin and clopidogrel represents an evidence-based, guideline-recommended, standard of care.

Current status of antiplatelet therapy in ACS

Clopidogrel is a second generation thienopyridine; it is a prodrug metabolized in the liver by the cytochrome P450 (CYP) system to a short-lived thiol that selectively and irreversibly binds to the P2Y₁₂ receptor. By blocking the ADP-dependent mechanisms, clopidogrel causes inhibition of platelet activation and aggregation; maximal inhibition by this drug ranges from 40% to 60%, and this is reached 3-7 days after a

standard dose of 75 mg, 6-12 hours after a 300 mg load and 2 hours after a 600 mg load [2].

Several randomized studies have shown the clinical benefit of adding clopidogrel to aspirin in patients with ACS; in the CURE [3] (Clopidogrel in Unstable angina to prevent Recurrent Events) trial, use of clopidogrel (300 mg loading dose, then 75 mg/day for an average duration of 9 months) plus aspirin was associated with 20% risk reduction of cardiovascular death, non fatal myocardial infarction (MI) or stroke compared to aspirin alone, with the greatest reduction observed in the rates of re-infarction (5.2% vs 6.7%). Although incidence of bleeding events was significantly higher in patients receiving clopidogrel (3.7% vs 2.7%, RR 1.38; P=0.001), there were no significant difference in the occurrence of life-threatening bleeding or hemorrhagic stroke. Those results were confirmed in the PCI-CURE study [4], in which therapy with clopidogrel (initiated before the procedure and continued on average for 8 months after angioplasty) significantly reduced the risk of cardiovascular death or MI even in

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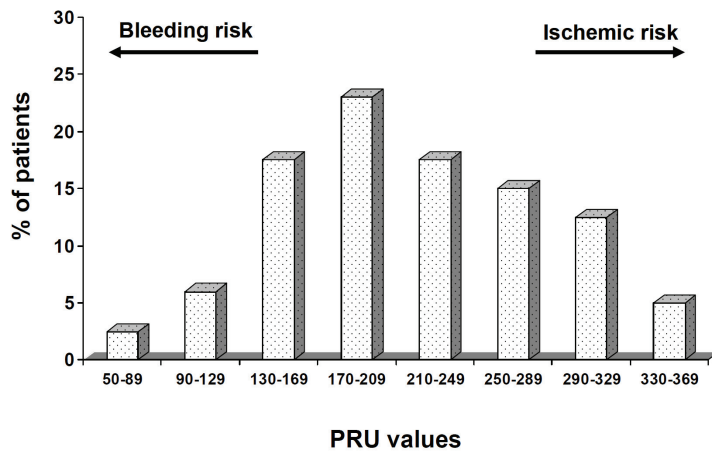


Figure 1. Distribution of residual platelet reactivity after clopidogrel administration in patients undergoing PCI (ARMYDA database). PCI= Percutaneous coronary intervention; PRU= P2Y₁₂ reaction units.

ACS patients receiving an invasive strategy.

However, despite those favorable findings, up to 15% of patients with ACS continue to suffer from ischemic events during long-term follow-up, and this may be at least in part related to the inter-individual variability in clopidogrel responsiveness [5,6]. This phenomenon is surely multifactorial and largely influenced by environmental, clinical and genetic factors: in particular, age, body mass index, smoking, presence of diabetes, ACS at presentation, drug-drug interactions and patient compliance have to be considered [7], as well as genetic polymorphisms affecting drug absorption, variations in biotransformation rate into active metabolite and linkage to P2Y₁₂ receptor. Pharmacokinetic studies indicated that clopidogrel is converted into the active metabolite in two steps oxidative process, catalyzed by different CYP enzymes [8]. Genes encoding for those enzymes are polymorphic, and there is evidence that some allelic variants of such enzymes greatly influence individual response to clopidogrel and are linked to an increased risk of adverse cardiovascular events; in particular, this has been demonstrated for the CYP2C19 variants, an enzyme that extensively contributes to both oxidative steps generating the active clopidogrel metabolite. The CYP2C19 gene is located on chromosome 10 and at least 25 genetic variants have been described; among those, two loss-of-function variant alleles, CYP2C19*2 and *3, represent the majority of the defective genotypes [8]. In a

large observational cohort on 1,477 ACS patients treated with clopidogrel and enrolled in the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction) trial, carriers of CYP2C19 loss-of-function alleles had a higher risk of the combined end-point including cardiovascular death, MI or stroke (12.1% vs 8.0% in non carriers; HR 1.53, 95% CI 1.07-2.19, P=0.01) [9].

Evaluation of individual clopidogrel response has become a contemporary issue in interventional cardiology. With regard to results of platelet function assays in patients receiving clopidogrel therapy and undergoing percutaneous coronary intervention (PCI) [10], impairment of clopidogrel response should be considered as a continuum, rather than an “on/off” phenomenon (Figure 1), and the wide variability in the reported prevalence of low clopidogrel response may depend on different assays used, variable definitions empirically applied and action of potential confounders. Various studies have been performed with the aim to achieve a standardized definition of low clopidogrel response as the correlation between results of laboratory assays and clinical outcome, and to demonstrate the prognostic impact of high residual platelet reactivity (i.e. low clopidogrel response) on short- and long-term outcome after PCI. In the ARMYDA PRO [11] (Antiplatelet therapy for Reduction of Myocardial damage during Angioplasty-Platelet Reactivity Predicts Outcome) study, high platelet reactivity after clopidogrel administration, measured at the time of the procedure by the point-of-care VerifyNow® P2Y₁₂ assay, was associated with 6-fold higher risk of 30-day major cardiac adverse events (MACE) after PCI, and this was mainly due to an increased incidence of peri-procedural MI. The ROC curve analysis identified an optimal cut-off of P2Y₁₂ reaction units (PRU) ≥ 240 to discriminate patients at higher risk of events at 30 days, with a sensitivity of 81% and a specificity of 53%. This clinical threshold was similar to that observed by Price et al.[12] in 380 patients undergoing PCI, in whom a PRU ≥ 235 was predictive of poorer outcome at 6 months; a recent

study demonstrated that a PRU threshold ≥ 240 was also able to predict 12-month clinical recurrence in ACS patients receiving PCI [13].

Given the inter-individual variability in clopidogrel responsiveness, various studies have been designed to evaluate whether higher clopidogrel dosages can act more rapidly and more effectively, and may decrease the incidence of clopidogrel low responders. This has been investigated in the ARMYDA 2 trial [14], enrolling consecutive PCI patients with a variety of coronary syndromes and randomized to receive, meanly 6 hours before the intervention, the standard 300 mg clopidogrel loading dose vs a 600 mg loading strategy. The primary end point (incidence of death, MI and target vessel revascularization at one month) occurred in 4% of patients in the high-dose vs 12% of those in the standard-dose arm ($P=0.041$; 52% risk reduction at multivariate analysis in patients receiving the higher regimen). These results were confirmed in a subsequent meta-analysis of 10 studies [15], in which pre-treatment with 600 mg clopidogrel load prior to PCI was associated with 46% risk reduction of cardiac death or non fatal MI, without excess in major and minor bleeding. Accordingly, the current Guidelines suggest the use of 600 mg clopidogrel load when a rapid (within 2 hours) platelet inhibition is needed in patients candidates to PCI. However, against the general concept that increasing doses of clopidogrel are consistently associated with increasing degree of platelet suppression, no benefit of a loading dose >600 mg has been demonstrated in clinical and platelet function studies. The randomized trial ALBION [16] (Assessment of the Best Loading Dose of Clopidogrel to Blunt Platelet Activation, Inflammation and Ongoing Necrosis) compared three different clopidogrel loading strategies (300 mg vs 600 mg vs 900 mg) in patients with ACS; as compared with the 600 mg dose, the 900 mg loading regimen did not achieve a higher platelet inhibition by optical aggregometry. These results were expanded in the ISAR-CHOICE [17] (Intracoronary Stenting and Antithrombotic Regimen: Choose Between 3 High Oral Doses for Immediate Clopidogrel Effect) trial, in which the 900 mg clopidogrel loading dose, compared with the 600 mg regimen, did not increase plasma concentration of the active thiol metabolite, and this has been attributed to the limited intestinal absorption of the drug and to the variability in cytochrome P450 enzyme activity. In

the recent randomized ARMYDA 4 RELOAD [18], another relevant issue has been investigated, i.e. the possible benefit of high-dose clopidogrel reloading in patients already receiving chronic clopidogrel therapy and undergoing PCI. In the overall population of 503 patients, 30-day incidence of MACE did not differ between patients who had received a 600 mg clopidogrel reload prior to the intervention and those who did not (6.7% vs 8.8%; $P=0.5$); however, in the subgroup of patients with ACS, a significant reduction in the occurrence of MACE at one month was observed in the reload arm (6.4% vs 16.3%; OR 0.34, 95% CI 0.32-0.90; $P=0.033$).

An increased maintenance dose of clopidogrel might be associated with higher platelet suppression and reduced rates of non-responders, with possible improvement in clinical outcome. In the ISAR-CHOICE 2 [19] (Intracoronary Stenting and Antithrombotic Regimen: Choose a High Oral maintenance dose for Intensified Clopidogrel Effect) study, administration of 150 mg/day maintenance dose of clopidogrel resulted in increased inhibition of ADP platelet aggregation at 30 days after PCI vs the standard 75 mg daily regimen, and this more potent antiplatelet effect has been also demonstrated in patients with diabetes mellitus [20]. In a randomized study from the ARMYDA study group [21], use of 150 mg/day maintenance dose of clopidogrel in PCI patients for one month reduced the rates of non-responders (62% reduction), improved endothelial function and decreased the inflammatory status vs the 75 mg daily dose. However, all those studies did not evaluate clinical endpoints. The largest, prospective study investigating the efficacy and safety of higher clopidogrel loading and maintenance dose in ACS patients is the CURRENT-OASIS 7 [22] (Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events - Seventh Organization to Assess Strategies in Ischemic Symptoms) trial. Patients were randomly assigned to a double-dose regimen (600 mg load followed by a maintenance dose of 150 mg/day for 6 days and then 75 mg/day thereafter) or a standard-dose regimen of clopidogrel (300 mg load followed by 75 mg daily thereafter). The primary outcome at 30 days (cardiovascular death, MI or stroke at 30 days) occurred in 4.4% of patients in the standard dose vs 4.2% in the high-dose group, with a modest excess of bleeding in the latter (2.5% vs 2.0%; HR 1.24; 95% CI 1.05-1.46; $P=0.01$); of note, a pre-specified analysis in the subgroup of patients undergoing PCI [23] showed that the

higher regimen was associated with significant reduction of the composite clinical end-point at one month (14% risk reduction; $P=0.039$), as well as of stent thrombosis (46% reduction; $P=0.0001$).

New antiplatelet agents

Novel P2Y₁₂ receptors antagonists are characterized by more potent and rapid onset of antiplatelet action. Prasugrel, a third-generation thienopyridine, is a prodrug that requires hepatic conversion; however, this process needs only one cytochrome P450-dependent oxidative step to generate the active metabolite and this difference explains the faster onset of action than clopidogrel, the greater inhibition of platelet aggregation, the lower incidence of non responders and the lesser influence of genetic polymorphisms. The clinical efficacy of prasugrel was evaluated in the phase III TRITON-TIMI 38 [24] (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel – TIMI 38) trial. This study compared the efficacy and safety of prasugrel (60 mg loading dose, 10 mg daily maintenance dose) vs clopidogrel (300 mg loading dose, 75 mg daily maintenance dose) in ACS patients undergoing PCI. Over a median follow-up of 14.5 months, patients pre-treated with prasugrel showed significantly lower incidence of primary end point, including cardiovascular death, MI or stroke (9.9% vs 12.1% in the clopidogrel arm; $P<0.001$); this benefit was essentially due to prevention of non-fatal MI. However, a significant 32% excess in life-threatening and fatal bleedings was observed in the prasugrel group: thus, the greater platelet inhibition and the consequent more effective prevention of ischemic events by more potent antiplatelet agents need to be weighed against an increase in bleeding complications. Prasugrel was still associated with a significant net clinical benefit compared to clopidogrel (HR 0.87; 95% CI 0.79-0.95; $P=0.004$), and a further analysis suggested a marked benefit with this drug in patients with diabetes mellitus [25] and in those presenting with ST-segment elevation MI, whereas, the excess of bleeding was more evident in patients with previous history of stroke or transient ischemic attack, age ≥ 75 years or body weight < 60 kg.

Ticagrelor is an oral, reversible, short-acting non-thienopyridine P2Y₁₂ antagonist; it is not a

prodrug, it has a direct action, and in platelet aggregation studies the inhibition of platelet aggregation by ticagrelor was more pronounced than clopidogrel, with lower degree of inter-individual response variability [26]. The DISPERSE 2 [27] (Dose Confirmation Study Assessing AntiPlatelet Effects of Ticagrelor vs Clopidogrel in non ST Segment Elevation Acute Coronary Syndrome) phase II study showed that ticagrelor is more effective than clopidogrel in preventing thrombotic events, with similar rate of bleeding. The phase III PLATO [28] (PLATElet Inhibition and Patient Outcomes) trial was a double-blind, randomized study comparing ticagrelor (180 mg loading dose, 90 mg twice daily thereafter) and clopidogrel (300-to-600 mg loading dose, 75 mg daily thereafter) for the prevention of cardiovascular events in patients with ACS. At 12 month, the incidence of the composite end-point, including death from vascular causes, MI or stroke, was significantly reduced in the ticagrelor group (9.8% vs 11.7% in the clopidogrel arm; HR 0.84; 95% CI 0.77-0.92; $P<0.001$). Of note, all-cause mortality through 12 months was also reduced with ticagrelor (4.5% vs 5.9%; $P<0.001$), a finding that has not been observed with oral antiplatelet agents other than aspirin. However, ticagrelor was associated with increased rates of major bleeding not related to coronary-artery bypass graft (4.5% vs 3.8%; $P=0.03$), as well as more elevated incidence of intracranial fatal bleeding. It should be noted that only 19% of patients in this study received a 600 mg clopidogrel loading, and that patients treated with ticagrelor developed more frequently side effects such dyspnea and brady-arrhythmias.

Bleeding risk

In the past decades, bleeding was considered an inevitable and acceptable complication related to the antithrombotic therapies in patients with ACS; given the variability in the bleeding definition used, the variable management strategies (conservative vs invasive), the different types and doses of antiplatelet agents, the heterogeneous clinical pattern (i.e. different prevalence of advanced age or chronic renal failure), the reported incidence of major bleeding varies between 1% and 10% [29]. However, a growing body of data has documented that the risk of death in ACS patients is affected not only by recurrent ischemic events, but also by bleeding complications.

Eikelboom et al. [30] analyzed individual patient data from a large dataset involving >30,000 patients from 3 studies: the OASIS (Organization to Assess Ischemic Syndromes) registry, OASIS-2 and CURE. In this analysis, 2.3% of patients developed major bleeding during follow-up, and occurrence of major bleeding was associated with a 5-fold increase in mortality; furthermore, there was a close relationship between severity of bleeding and risk of death. Of note, incidence of MI and stroke was also significantly higher in patients who developed major bleeding vs those who did not. In the ACUITY [31] (Acute Catheterization and Urgent Intervention Triage Strategy) trial, mortality at 30 days was >6 fold higher in patients with vs those without major bleeding (7.3% vs 1.2%; $P < 0.0001$); again, patients with major bleeding had also a significant increase in the incidence of ischemic events (MI, unplanned revascularization and stent thrombosis). Moreover, at multivariable analysis, major bleeding was the strongest independent predictor of mortality, even more than MI. Pocock et al [32], utilizing the same ACUITY database, observed that both MI and major bleeding significantly affected subsequent mortality, but with a different temporal impact during follow-up: MI increased the likelihood of death 15.6 times within the first day after its occurrence, then its prognostic impact was progressively reduced; in contrast, the risk of death after a major bleeding was 4-fold higher within the first 30 days of the event, and the risk remained significantly elevated (2.2-fold increase) beyond 30 days.

Several mechanisms may explain the association between bleeding and mortality, as well as between bleeding and ischemic events after PCI [29,30]. Bleeding evidence often leads to the abrupt withdrawal and/or reversal of antithrombotic therapy, which may in turn result in more elevated risk of thrombosis, with subsequent MI, stroke, stent thrombosis and cardiovascular death. Bleeding may also cause platelet activation, and bleeding causing hypovolemia, hypoperfusion and anemia may impair oxygen carrying capacity and delivery to the myocardium, provoking myocardial ischemia. Moreover, patients with major bleeding frequently require invasive procedure, such as intra-aortic balloon counterpulsation, intubation, endoscopy, surgical procedures, that increase the likelihood of adverse outcomes. Finally, blood product transfusions have been associated with adverse events, as demonstrated in a previous meta-analysis [33] indicating a significant association

between transfusions and 30-day mortality (HR 3.94; 95% CI 3.26-4.75) among ACS patients. These results were also confirmed in an analysis of the CRUSADE [34] registry, in which a higher risk of in-hospital death or death/MI was found in patients receiving red blood cells transfusions during hospitalization; the reason is still unclear but it can be hypothesized that [29]: a) transfusions increase the inflammatory status; b) nitric oxide is depleted in stored red cells, which may act as a nitric oxide sink, resulting in vasoconstriction, reduced oxygen carriage of the blood and platelet aggregation; 3) stored blood red cells are also depleted of 2,3-diphosphoglycerate, thereby increasing the affinity of hemoglobin for oxygen and pulling oxygen out of tissue and away from normal red blood cells.

In consideration of the strong clinical impact of major bleeding on 30-day outcome in ACS patients, identifying patients at higher bleeding risk is an important goal in clinical practice, especially after the introduction of newer, more potent antiplatelet and antithrombin agents, which may further increase the occurrence of this complication. Mehran et al [35], developed a simple-to-use risk score for bleeding from a pooled analysis of the ACUITY and HORIZON-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trials, using 6 clinical independent predictors of major bleeding: female sex, advanced age, elevated serum creatinine and white blood cell count, anemia, ST segment elevation MI (STEMI) and non-STEMI at presentation. The individual risk for 30-day bleeding was calculated as the summation of the 6 integers (1 from each baseline variable), identifying 4 categories of increased bleeding risk: low, moderate, high and very high (calculated risk of 1.9%, 3.3%, 6.9% and 12.4%, respectively, in patients treated with heparin plus a Glycoprotein IIb/IIIa inhibitors; 0.7%, 2.0%, 3.7% and 8.4%, respectively, in patients receiving bivalirudin monotherapy).

Various studies demonstrated that high residual platelet reactivity on clopidogrel correlates with enhanced risk of adverse ischemic events after PCI, but two recent reports showed that a low residual platelet reactivity (i.e. increased clopidogrel response) is associated with higher risk of bleeding; this confirms the potential usefulness of point-of-care platelet function tests also for the stratification of patients according to their bleeding risk. Sibbing et al. [36] observed

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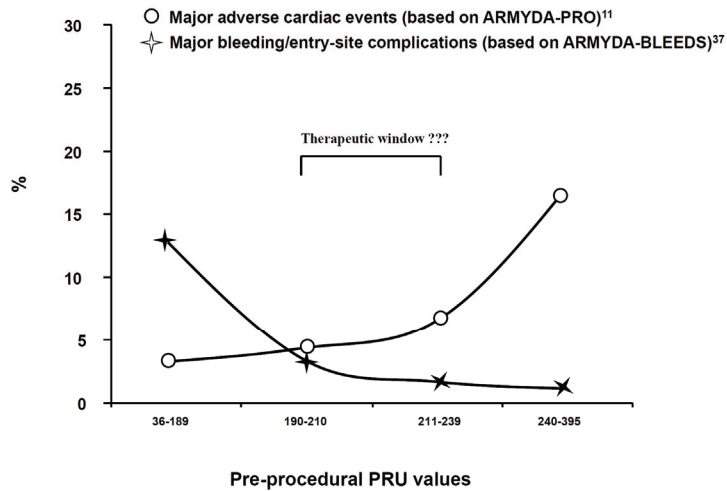


Figure 2. Incidence of ischemic/bleeding events according to pre-procedural platelet reactivity. PRU= P2Y₁₂ reaction units.

that the incidence of bleeding was increased in patients with high clopidogrel response by the Multiplate® system, and in turn, the incidence of stent thrombosis was elevated in those with low response to the drug. In the ARMYDA-BLEEDS [37] study, patients in the lowest PRU quartile by the VerifyNow® assay had 4.5-fold higher incidence of major bleeding at 1 month after PCI vs those in the highest quartile (10.1% vs 1.4%; $P=0.05$); ROC analysis identified a PRU value ≤ 189 as an optimal cut-off point to predict bleeding outcome, with sensitivity of 87% and specificity of 70%. ARMYDA-BLEEDS, by defining this lower threshold for bleeding, may represent the “pendant” of the previously mentioned ARMYDA-PRO study [11], in which a cut-off point of $PRU \geq 240$ was identified as a threshold for increased ischemic risk; thus, the PRU range between 190 and 240 might potentially represent the optimal therapeutic window during clopidogrel therapy, in which both ischemic and bleeding risks are low. Incidence of ischemic and bleeding events according to PRU values follows a curvilinear distribution (Figure 2), in which, below a certain safety threshold of PRU, ischemic events are not further reduced, to the expense of increasing bleeding, and above an efficacy threshold, bleeding is not reduced, but ischemic events may be significantly increased.

Balancing ischemic and bleeding risk

The ultimate goal of anti-thrombotic therapy in

ACS is to increase efficacy without losing safety. An emerging approach is to reduce the ischemic risk through an individualized, “tailored” therapy according to the measurement of platelet reactivity.

A platelet reactivity-guided therapy was evaluated by Bonello et al [38], who investigated the issue of clopidogrel loading dose adjustment according to platelet monitoring by the vasodilator-stimulated phosphoprotein (VASP) index. Despite the small sample size, VASP-guided clopidogrel dosing significantly improved clinical outcome after PCI in patients with low response to clopidogrel already treated with 600 mg loading dose, without increase in the bleeding risk. Recently, the GRAVITAS [39] (Gauging Responsiveness With a

VerifyNow Assay: Impact of Thrombosis and Safety) trial evaluated whether high-dose is superior to standard-dose clopidogrel therapy for the prevention of cardiovascular events after PCI in patients with high on-treatment reactivity by the point-of-care VerifyNow® assay. In this study, patients with $PRU > 230$ measured within 24 hours from the intervention, were randomly assigned to 600 mg clopidogrel load followed thereafter by 150 mg daily maintenance dose for 6 months vs no additional loading dose followed by 75 mg daily. Incidence of the primary end-point at 6-month (death from cardiovascular causes, non-fatal myocardial infarction or stent thrombosis) was similar in the two arms (HR 1.01, 95% CI 0.58-1.76; $P=0.97$), without bleeding excess in the high-dose group. However, in the hours after PCI there is a relevant elevation in platelet reactivity because of procedural platelet activation; thus, evaluation of platelet reactivity when performed early after PCI is characterized by a low signal-to-noise ratio, and results may not reflect the baseline individual degree of response to antiplatelet drugs [40].

Conclusions

Antithrombotic therapy is the mainstay of treatment in patients with ACS and low clopidogrel response may increase the risk of ischemic events in those patients when treated with coronary stenting. Alternative approaches to overcome this phenomenon are increase in the

loading and maintenance clopidogrel doses, reloading patients already on chronic therapy, use of newer and more effective antiplatelet agents. However, a “more aggressive” antiplatelet strategy reduces the ischemic risk in ACS patients, but at the prize of a possible increase in bleeding complications. Given the important prognostic role of both ischemic and hemorrhagic events in the follow-up of ACS patients undergoing percutaneous revascularization, the strategy of an individualized antiplatelet therapy according point-of-care platelet function tests may represent the optimal approach to balance both those risks, but it has to be corroborated by prospective, randomized, ad-hoc studies yet.

Stratification of patients according to their ischemic and bleeding risk by point-of-care platelet function tests could be, however, considered in the context of an individualized approach including a series of strategies globally aimed to improve clinical outcome: in patients with high ischemic risk (high on-treatment platelet reactivity), a more extensive use of Glycoprotein IIb/IIIa inhibitors and of newer P2Y₁₂ receptor antagonists (prasugrel, ticagrelor) would be advisable, as well as a possible increase in clopidogrel maintenance dose and utilization of unfractionated heparin rather than bivalirudin in ACS patients undergoing an early invasive strategy. Whereas, in patients with high bleeding risk (low on-treatment platelet reactivity), a restricted use of drug-eluting stents, no utilization of Glycoprotein IIb/IIIa inhibitors and of newer P2Y₁₂ receptor antagonists, use of standard clopidogrel maintenance dose, use of bivalirudin rather than unfractionated, PCI by a radial rather than a femoral approach and more liberal utilization of gastro-protective agents would be indicated.

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