Investigating the Mechanisms of Hyporesponse to Antiplatelet Approaches

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ABSTRACT

Hyporesponsiveness, or resistance, to antiplatelet therapy may be a major contributor to poorer outcomes among cardiac patients and may be attributed to an array of mechanisms — both modifiable and unmodifiable. Recent evidence has uncovered clinical, cellular, and genetic factors associated with hyporesponsiveness. Patients with severe acute coronary syndromes (ACS), type 2 diabetes, and increased body mass index appear to be the most at risk for hyporesponsiveness. Addressing modifiable mechanisms may offset hyporesponsiveness, while recognizing unmodifiable mechanisms, such as genetic polymorphisms and diseases that affect response to antiplatelet therapy, may help identify patients who are more likely to be hyporesponsive. Hyporesponsive patients might benefit from different dosing strategies or additional antiplatelet therapies. Trials correlating platelet function test results to clinical outcomes are required. Results from these studies could cause a paradigm shift toward individualized antiplatelet therapy, improving predictability of platelet inhibition, and diminishing the likelihood for hyporesponsiveness.

Key words: catheterization/diagnostic interventional<cardiac, platelets, acute coronary syndromes<ischemic heart disease, myocardial infarction<ischemic heart disease, thrombosis/hypercoagulable states

Introduction

Hyporesponse (or resistance) to antiplatelet therapies has been increasingly recognized in recent years; suboptimal response to aspirin (ASA) and other antiplatelet therapies involves multiple underlying clinical, cellular, and genetic mechanisms, some of which are modifiable and others which are not. Effective intervention against modifiable mechanisms offers an obvious strategy to counteract hyporesponsiveness. Alternatively, better understanding of unmodifiable mechanisms of hyporesponse, such as genetic polymorphisms and diseases that affect response to antiplatelet therapy, can proactively identify patients who are more likely to respond suboptimally to platelet inhibitors, and thus, those who might benefit from different dosing strategies or additional antiplatelet therapies. Recognition of the multifactorial causes of hyporesponse can guide clinicians toward antiplatelet strategies that offer patients with acute coronary syndrome (ACS) the best chance for better outcomes. In this article, hyporesponsiveness to ASA and clopidogrel is assessed by exploring its causes and patient characteristics that are predictive of suboptimal response to platelet inhibition.

Investigations of Hyporesponse with Platelet Inhibitors

As pointed out earlier in this supplement, antiplatelet therapies have been shown to reduce ischemic events.[1–5] Also, as has been discussed, hyporesponse to antiplatelet therapy, regardless of the reason, may increase the likelihood of poor clinical outcome. In this section, we review various etiologies underlying hyporesponsiveness to antiplatelet therapy.

Aspirin

Several recent studies now support the association between ASA resistance and poorer clinical outcomes, including the aforementioned findings by Eikelboom and colleagues of increased risk of adverse outcomes in patients with relatively elevated baseline urinary 11-dehydro-thromboxane B_2 (UDTB) levels[6] and Chen and colleagues of increased markers of myonecrosis in ASA hyporesponsive patients.[7]

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However, a number of issues have hampered the speed and precision by which mechanisms of ASA hyporesponse have been identified. For example, there is an absence of consensus definitions for ASA hyporesponse. Furthermore, categorization of ASA resistance as a dichotomous response (rather than a continuous variable) has resulted in wide ranges of resistance incidence reported in the literature. Lastly, there is uncertainty concerning the stability of ASA response in a single patient over time.[8]

Proposed mechanisms of hyporesponse: In many patients, platelet activation occurs despite administration of therapeutic doses of ASA. In order to differentiate mechanisms of ASA hyporesponse, measurements of serum thromboxane B_2 and arachidonic acid-induced platelet activation were assessed in 700 ASA-treated patients undergoing cardiac catheterization.[9] The ASA reduced thromboxane B_2 levels in all but two evaluable patients compared with untreated controls; these patients were deemed noncompliant and not included in analyses. The major finding was that there is residual arachidonic acid-induced platelet activation in patients who receive ASA. Underdosing or noncompliance was attributed to this residual activation in only 2% of patients. The underlying mechanism in the vast majority of patients was a cyclooxygenase (COX)-1 and COX-2 independent pathway for platelet activation. Multivariate analysis showed that treatment with clopidogrel was associated with decreased arachidonic acid-induced platelet activation, indicating that this COX-independent mechanism was mediated in part via adenosine diphosphate (ADP)-induced platelet activation.

Evidence to support dose-dependent platelet inhibition by ASA independent of COX-1 effects comes from the recent Aspirin Induced Platelet Effects (ASPECT) study.[10] In this double-blind, double-crossover investigation of 3 commonly used ASA doses (81, 162, and 325 mg/d), arachidonic acid-induced aggregation was suppressed in a dose-independent fashion whereas collagen-induced platelet aggregation and shear-induced platelet aggregation were significantly affected by dose. Moreover, the prevalence of resistance measured by COX-1 nonspecific methods such as ADP-, collagen- and shear-induced aggregation, was also significantly affected by dose. The observation of dose-related effects despite near complete inhibition of arachidonic acid-induced aggregation may be explained by non-COX-1 mediated antiplatelet properties in ASA. Finally, the urinary levels of under-dehydrated hydrogen bonds (UDHB) were also significantly reduced by ASA doses higher than 81 mg/day. The latter findings may be related to the inhibitory effects of higher dose ASA on COX-2. An important message of the ASPECT study is that the prevalence of ASA resistance is highly assay-dependent.

The ASA hyporesponsiveness is unlikely to result solely from variabilities in COX pathways. Its etiology is likely multifactorial; multiple mechanisms of ASA hyporesponse have been proposed, and may be grouped as cellular, clinical, and genetic (Figure 1).[8] Obvious clinical factors include a failure to prescribe antiplatelet therapies and patient noncompliance with prescribed therapy, but also suboptimal absorption and drug interactions. In particular, when given concomitantly with ASA, ibuprofen has been shown to antagonize ASA-induced irreversible platelet inhibition by binding to the COX-1 binding site of ASA.[11] Several genetic polymorphisms have been proposed to explain varying degrees of ASA hyporesponse. They include polymorphisms affecting COX-1 receptors, platelet membrane proteins, collagen receptors, and von Willebrand factor (vWF).[8]

Hypotheses on overcoming aspirin hyporesponse: The Antithrombotic Trialists' Collaboration did not recommend daily ASA doses higher than 75–150 mg for long-term prevention of thrombotic events in high-risk patients because it found that that dosage range was as effective as

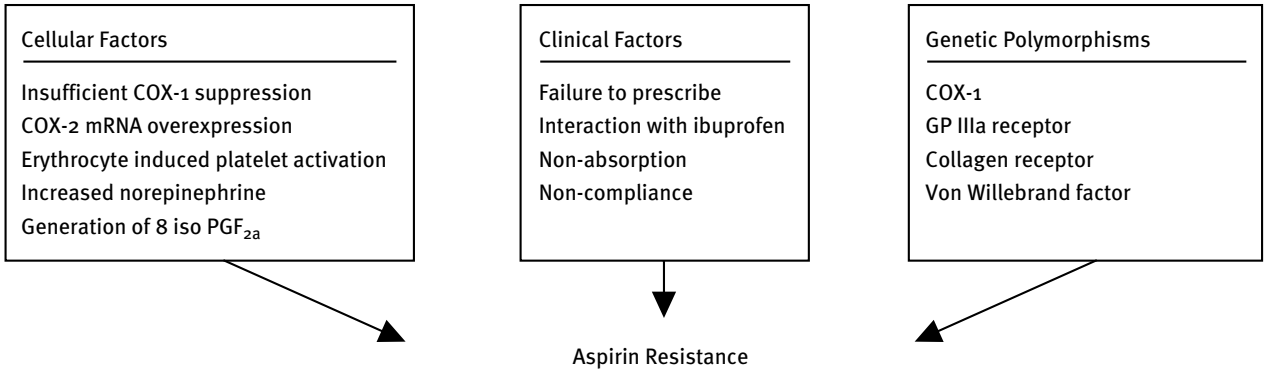

Figure 1: Potential mechanisms to explain aspirin hyporesponsiveness. Adapted with permission from Bhatt DL.[8]

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higher doses and had less risk of bleeding.[1] Although dose-related failure may be a cause of ASA hyporesponsiveness in some patients, multiple factors confound direct causation of dose and response with ASA (such as worsening thrombosis and variability of ASA response, which can change patients' categorization over time from hyporesponsive to responsive or vice versa). In the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) trial population of patients with ACS, it was found that bleeding risks were increased with increasing ASA dose when given alone or with clopidogrel. Higher ASA doses were not associated with lower clinical event rates, and reductions in major ischemic events did not vary significantly by ASA dose.[12] Also, the Blockade of the Glycoprotein IIb/IIIa Receptor to Avoid Vascular Occlusion (BRAVO) trial found that serious bleeding was more common among patients with vascular disease who received ASA doses of >162 mg/day.[13]

Substitution of another antiplatelet agent has been proposed as a possible strategy to avoid ASA hyporesponse. Given its different mechanism of action of inhibiting platelet activation, clopidogrel would be the logical choice for substitution. In vitro data have shown that platelets from patients who are hyporesponsive to ASA exhibit greater sensitivity to ADP.[14] Also, the aforementioned findings by Frelinger and colleagues suggest that clopidogrel may attenuate ASA hyporesponsiveness.[9] However, clinical studies are necessary to substantiate this hypothesis and there is clearly a clinical need to characterize further the problem of ASA hyporesponse and provide evidence-based solutions for patients with cardiovascular disease (CVD).

Clopidogrel

Clopidogrel response variability was first described using flow cytometry to detect ADP-induced fibrinogen binding in treated patients,[15] with subsequent confirmation in a study of percutaneous coronary intervention (PCI) patients using both turbidimetric aggregometry and flow cytometry.[16] Clopidogrel hyporesponsiveness appears to increase the risk for thrombotic events, particularly in patients undergoing PCI.[17] For instance, the previously mentioned study by Matetzky and colleagues found an increased likelihood of recurrent cardiovascular events among patients with ST-segment elevation myocardial infarction (STEMI) who were hyporesponsive to clopidogrel and underwent PCI.[18] In a different population of patients regarded as nonresponders with stable angina who underwent PCI, a higher rate of subacute stent thrombosis was identified.[19] Variability in ADP-induced aggregation is well known in patients with coronary artery disease treated with ASA therapy.[20]

Patients currently taking ASA therapy with low ADP-induced platelet aggregation who exhibit poor inhibition by clopidogrel may therefore remain at low ischemic risk. Thus, it was suggested that on-treatment platelet reactivity to ADP may be a better marker of ischemic risk than platelet inhibition.[21] Most recently, increased risk for postprocedural ischemic events was correlated with platelet reactivity in patients who underwent PCI and who were receiving ongoing clopidogrel therapy.[22] These studies confirm the interindividual variability of clopidogrel-induced platelet inhibition. The clinical challenge has been to definitively relate response variability to therapeutic failure and determine thresholds of platelet inhibition and posttreatment platelet reactivity necessary to prevent ischemic outcomes.

One of the major limitations in characterizing hyporesponse to clopidogrel therapy has been the lack of conformity among definitions of suboptimal response in trials. Multiple definitions have led to various estimates of the prevalence for this real clinical problem whose occurrence is associated with excessive thrombotic events in patients with ACS and post-PCI. Unfortunately, to date, a lack of a standard diagnostic modality and definition has hampered the identification and thus, the treatment, of clopidogrel hyporesponsiveness.[23] Multiple factors have been proposed to cause variability/hyporesponse to clopidogrel, including preinterventional platelet reactivity, genetic polymorphisms, and acute/chronic patient characteristics correlated with hyporesponse.

Preinterventional platelet reactivity as a predictor of hyporesponse: The use of platelet inhibition during PCI is important to reduce the risk for thrombus formation and events during the peri- and postprocedural intervals. Although 600 mg loading doses of clopidogrel may obviate the need for glycoprotein (GP) IIb/IIIa inhibition in lower-risk patients, platelet responses to clopidogrel loading doses vary widely. Patients who are hyporesponsive therefore might be at increased risk for post-PCI events. Until recently, the impact of variability in platelet reactivity on clinical outcome during PCI had not been thoroughly investigated in clopidogrel-treated patients. Two recent clinical studies support the extent of platelet aggregation at the time of PCI as a predictor of adverse postintervention outcomes.[24,25]

The Excelsior study involved 802 consecutive patients who received a 600 mg loading dose of clopidogrel prior to undergoing elective coronary stent placement.[24] Platelet aggregation was determined immediately before PCI via optical aggregometry and stratified into quartiles ranging from <4% to >32%. A composite 30-day endpoint of (major adverse cardiac event [MACE] death, MI, and need for target lesion revascularization) was determined. Fifteen patients (1.9%) had a MACE within 30 days of coronary intervention. A MACE at 30 days was 0.5% in the first two quartiles, but increased to 3.1% in the third quartile

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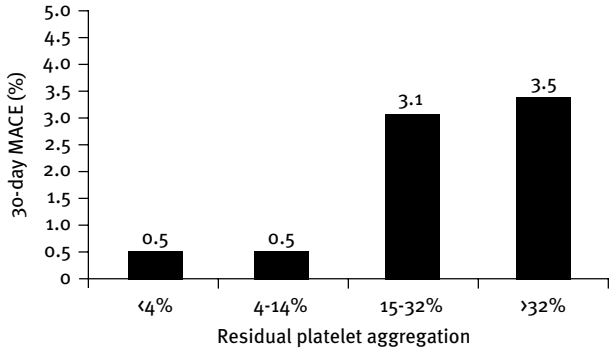

Figure 2: Thirty day composite of major cardiac events (MACE) according to quartiles of platelet aggregation. Adapted with permission from Hochholzer W et al.[24]

and 3.5% in the fourth quartile ($p = 0.034$) (Figure 2).[24] Platelet aggregation exceeding the median value conferred a 6.7 times greater risk of MACE (95% CI, 1.52–29.41; $p = 0.003$). Multivariate analysis revealed platelet aggregation immediately before PCI as an independent predictor of 30-day MACE occurrence (10% increase in ADP-induced aggregation prior to PCI was associated with an adjusted odds ratio for 30-day MACE of 1.32 (95% CI, 1.04–1.61; $p = 0.026$).

Cuisset and colleagues randomized 292 consecutive patients with NSTEMI to determine the effect of a 600 mg clopidogrel loading dose (versus 300 mg) given at least 12 hours prior to PCI with stenting on platelet reactivity and outcomes.[25] An ADP-induced platelet aggregation and expression of the adhesion molecule P-selectin were assessed at least 12 hours after clopidogrel administration but before PCI. Platelet aggregation and P-selectin expression were both significantly lower in the 600 mg clopidogrel group compared with the 300 mg group ($p<0.0001$ for both values). By 1-month follow up, 18 (12%) cardiovascular events occurred in patients who received 300 mg of clopidogrel versus 7 (5%) in the 600 mg group ($p = 0.02$); the difference remained significant when adjusted for potential confounding variables. The study confirmed the value of high posttreatment platelet reactivity (HPPR) on outcomes; in fact, HPPR was a better predictor of clinical outcomes than the loading dose. Thus, HPPR may be useful in identifying patients at high risk of experiencing post-PCI events.

Together, these two studies along with the previous study by Bliden demonstrated the clinical significance of preprocedural residual platelet function after administration of antiplatelet therapy. The Excelsior study showed variability in platelet reactivity in response to clopidogrel, and an association of greater residual platelet function with increased risk for cardiovascular events. Cuisset and colleagues demonstrated that a higher loading dose of clopidogrel achieved more complete inhibition of platelet activity (IPA), can possibly overcome hyporesponsiveness, and was associated with greater protection against clinical events during the first month after PCI.

Genetic/metabolic influences on clopidogrel activity: Clopidogrel is metabolized via hepatic cytochrome P450 3A4 (CYP3A4), suggesting that variations in CYP3A4 activity may mediate platelet response variability.[26,27] Lau and colleagues sought to determine whether variations in CYP3A4 activity contribute to clopidogrel variability in platelet inhibition by measuring platelet aggregation in 32 patients undergoing PCI with stenting and 35 healthy volunteers.[28] According to the degree of ADP-induced platelet aggregation, 22% and 16% were classified as clopidogrel nonresponders, 32% and 12% as low responders, and 47% and 72% as responders among patients and healthy volunteers, respectively; an inverse correlation was found between platelet activation and CYP3A4 activity ($p = 0.003$). Coadministration with the CYP3A4 inducer rifampin was found to significantly enhance clopidogrel's inhibition of platelet aggregation versus clopidogrel alone ($p = 0.001$); in fact, 3 clopidogrel nonresponders subsequently became clopidogrel responders after rifampin administration. This study reaffirms the existence of interindividual variability with platelet inhibition; in this case, due to variations in intrinsic CYP3A4 activity. Importantly, it also suggests a strategy for improving clopidogrel response in patients documented to be hyporesponsive using a point-of-care platelet function testing device.

Polymorphisms of the CYP3A4 gene have been proposed to result in variable clopidogrel-mediated platelet response.[29] Five different single nucleotide polymorphisms of CYP3A4 were examined in 82 patients receiving clopidogrel maintenance therapy who were at the steady-state phase (>1 month) of clopidogrel therapy. Carriers of the CYP3A4 polymorphism IVS10+12A allele had reduced GP IIb/IIIa receptor activation and increased responsiveness to clopidogrel ($p = 0.025$ and $p = 0.02$, respectively); clopidogrel-naïve patients with the IVS10+12A allele also had reduced GP IIb/IIIa activation during the 24 h following a loading dose ($p = 0.025$), increased platelet inhibition ($p = 0.006$), and better drug response ($p = 0.003$). Noncarriers of IVS10+12A were predominant in this study, consistent with the high prevalence of patients who are thought to be hyporesponsive to standard dosing of clopidogrel.

The CYP2C19 genetic variation was also associated with clopidogrel responsiveness in a prospective study of healthy men treated for 7 days with clopidogrel 75 mg/day.[30] Of the 28 participants, 20 were wild-type CYP2C19 homozygotes and 8 were heterozygous for the loss-of-function polymorphism CYP2C19. ADP-mediated platelet aggregation decreased gradually in homozygous participants during treatment with clopidogrel (48.9% of baseline by day 7; $p<0.001$). However, no significant change from baseline was observed in heterozygotes, and their platelet aggregation was significantly different from that of the homozygous group ($p = 0.003$). The results suggest the importance of the CYP2C19*2 mutant allele as a contributor

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to clopidogrel response in healthy individuals, but further study is needed to substantiate the influence of CYP2C19 genetic polymorphisms on clopidogrel response in clinical settings.

Although the pharmacogenetic and metabolic studies reviewed here were small and the results require confirmation in larger populations, they represent the early stages of a paradigm shift in the field. Ultimately, it is hoped that the identification of genetic markers will allow for individualized approaches to antiplatelet therapy.

Conditions Associated with Decreased Antiplatelet Efficacy

Several subsets of patients have been shown to have suboptimal responses to antiplatelet therapy, among them patients with severe ACS, type 2 diabetes, increased body mass index (BMI), and high pre-treatment platelet reactivity to ADP.[31]

The ability of clopidogrel to inhibit platelet aggregation is affected by the severity of ACS. In a study of 72 patients undergoing PCI (33 patients had stable angina or Braunwald class 1 unstable angina, 39 patients had Braunwald class 2 or 3 unstable angina), all patients received 450 mg of clopidogrel at least 3 h prior to interventions and 235 mg of ASA before PCI. The inhibition of platelet aggregation (IPA) was assessed prior to PCI via a point-of-care platelet analyzer. Mean IPA was significantly lower in patients with class 2 or 3 unstable angina (19% versus 32%, $p = 0.004$). In multivariate analysis, higher angina class independently predicted lower IPA ($p = 0.018$). Importantly, Soffer and colleagues also demonstrated significant interpatient variability in response to clopidogrel loading.[32]

Insulin normally inhibits platelet aggregation via inhibition of the $P2Y_{12}$ pathway. However, patients with type 2 diabetes have reduced responsiveness to insulin, leading to upregulation of the $P2Y_{12}$ pathway and increased platelet reactivity, with resultant reductions in responsiveness to antiplatelet agents.[33–35] The impact of insulin therapy on platelet dysfunction was evaluated in patients with CAD who were taking ASA and clopidogrel (201 patients with type 2 diabetes and 65 nondiabetic patients).[36] Platelet aggregation was assessed using ADP (specific) and nonspecific agonists for the $P2Y_{12}$ pathway. High shear-induced platelet reactivity also was assessed. Diabetic patients demonstrated significant increases in platelet aggregation compared with nondiabetic patients ($p<0.0001$). Insulin treatment emerged as the strongest predictor of ADP-induced platelet aggregation; in response to $P2Y_{12}$-specific stimuli with ADP, insulin-treated diabetic patients had increased platelet aggregation compared with diabetic patients not treated with insulin (Figure 3).[36] Collectively, the results showed that $P2Y_{12}$-specific and nonspecific pathways of platelet reactivity are altered in type 2 diabetes, and patients who receive insulin therapy demonstrate greater ADP-induced platelet aggregation compared to non-insulin treated patients.

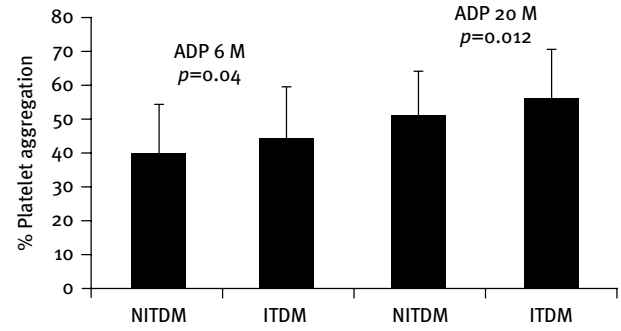

Figure 3: Adenosine diphosphate -stimulated platelet aggregation in noninsulin-treated type 2 diabetes (NITDM) and insulin-treated type 2 diabetes mellitus (ITDM). Reproduced with permission from Angiolillo DJ et al.[36]

Clopidogrel hyporesponsiveness is associated with significant increases in cardiovascular events and death in patients who undergo PCI with coronary stenting.[37] Given the alteration in antiplatelet response demonstrated in type 2 diabetics, Geisler and colleagues assessed response to a 600 mg clopidogrel loading dose in 485 patients (161 had type 2 diabetes). Following administration of a 600 mg dose of clopidogrel, platelet response was significantly lower in the diabetic patients compared with nondiabetic patients ($p = 0.01$). For the subgroup of patients with ACS who received coronary stenting for stable angina, diabetic patients had significantly greater posttreatment platelet aggregation, including ADP-induced ($p = 0.002$) and collagen-induced ($p = 0.005$) aggregation, compared with nondiabetic patients.[38] The decreased responsiveness to a 600 mg loading dose of clopidogrel observed in diabetic patients with ACS suggests that diabetes impacts residual platelet activity and places patients at increased risk for recurrent thrombotic events.

The BMI is another factor that may cause interpatient variability with response to clopidogrel, whose dose—unlike heparin and GP IIb/IIIa inhibitors—is not weight-adjusted. The effect of BMI on response to clopidogrel was examined in 48 patients undergoing coronary stent implantation who received a 300 mg loading dose of clopidogrel prior to intervention. On the basis of BMI, 60% of patients were overweight (BMI $\geqslant 25$) and 40% were normal weight (BMI <25). The ADP-induced platelet aggregation was significantly greater in overweight patients at baseline, at 24 h, and during the overall time period. Platelet inhibition at 24 hours was suboptimal ($<40\%$) in 59% of overweight patients compared with 26% of normal-weight patients ($p = 0.04$); elevated BMI was the only independent predictor of suboptimal platelet response. The data suggest that there is higher platelet function in overweight patients and that these patients might require a higher loading dose of clopidogrel or other adjunctive therapies to achieve adequate inhibition of platelet aggregation early after coronary stenting.[39] Similar findings were reported in a recent study of 402 patients.[40]

Hyporesponsiveness to Dual Antiplatelet Therapy

The dual antiplatelet therapy with ASA and clopidogrel has become part of standard care for patients undergoing PCI. The variability in platelet response has been observed with each drug, but variability in the response to their combination has not been studied extensively. In a study of 50 patients pretreated with ASA and clopidogrel prior to PCI, five (10%) exhibited hyporesponse to both agents.[41] The small size notwithstanding, the study offered a suggestion of hyporesponsiveness to dual agents in a subset of patients.

The concept of hyporesponsiveness to dual agents was further evaluated in 150 elective PCI patients who had received ASA for $\geqslant 1$ week and bivalirudin at the time of intervention.[42] Immediately after PCI, patients received 300 mg clopidogrel and 325 mg ASA, followed by 75 mg clopidogrel and 325 mg ASA daily. Hyporesponse ASA was defined as having 2 or 3 of the following criteria: rapid platelet function analyzer-ASA score $\geqslant 500$, 5μmol/L ADP-induced aggregation $\geqslant 70\%$, and 0.5 mg/mL arachidonic acid-induced aggregation $\geqslant 20\%$. Hyporesponse to clopidogrel was defined as baseline minus posttreatment aggregation $\leqslant 10\%$ in response to 5 and 20μmol/L ADP. By those criteria, 12.7% of patients were hyporesponsive to ASA and 24% to clopidogrel. Forty-seven percent of ASA-hyporesponsive patients were also hyporesponsive to clopidogrel. Possible mechanisms for this dual hyporesponse proposed by the authors included the following:

- Broad increases in platelet reactivity to all platelet agonists
- Diabetes: More than 50% of patients in the ASA-resistant group were diabetic
- Increased platelet turnover in ASA-hyporesponsive patients may lead to the formation of young platelets that are able to form thromboxane A_2 and are ADP-hyporesponsive

Hyporesponsiveness to dual agents might identify patients who have an even greater risk of thrombotic complications compared with patients having hyporesponse to only one platelet inhibitor. The CK-MB elevation following PCI is a marker of increased risk for death, MI, and repeat revascularization; indeed, patients in this study who were hyporesponsive to either antiplatelet agent were more likely to have elevated CK-MB levels following stent implantation. Patients who were hyporesponsive to dual agents had a 2-fold increase in the rate of myonecrosis versus dual drug-sensitive patients.[42]

Conclusion

Suboptimal response to antiplatelet therapies likely has a multifactorial etiology, which has yet to be fully elucidated. As the field progresses, more options may become available to address this real clinical problem, whether they be novel approaches with currently available platelet inhibitors or new antiplatelet compounds. There is a clear need for larger trials whose objective is to definitively correlate results from tests of platelet function to clinical outcomes. In the future, results from these investigations could potentially cause a shift in paradigm toward individualized antiplatelet therapy, which confers more predictable platelet inhibition and less chance for hyporesponsiveness.

References

1. Antithrombotic Trialists Collaboration: Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71–86
2. The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators: Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-elevation. *N Engl J Med* 2001;345:494–502
3. Chen ZM, Jiang LX, Chen YP, Xie JX, Pan HC, for the COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group: Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomized placebo controlled trial. *Lancet* 2005;366:1607–1621
4. Steinhubl SR, Berger PB, Mann JT III, Fry ETA, DeLago A, et al.: Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002;288:2411–2420
5. Sabatine MS, Cannon CP, Gibson CM, López-Sendón JL, Montalescot G, et al.: Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005;352:1179–1189
6. Eikelboom JW, Hirsh J, Weitz JI, Johnston M, Yi Q, et al.: Aspirin-resistant thromboxane biosynthesis and the risk of myocardial infarction, stroke, of cardiovascular death in patients at high risk for cardiovascular events. *Circulation* 2002;105:1650–1655
7. Chen WH, Lee PY, Ng W, Tse HF, Lau CP: Aspirin resistance is associated with a high incidence of myonecrosis after non-urgent percutaneous coronary intervention despite clopidogrel pretreatment. *J Am Coll Cardiol* 2004;43:1122–1126
8. Bhatt DL: Aspirin resistance: more than just a laboratory curiosity. *J Am Coll Cardiol* 2004;43:1127–1129
9. Frelinger AL 3rd, Furman MI, Linden MD, Li Y, Fox ML, et al.: Residual arachidonic acid-induced platelet activation via an adenosine diphosphate-dependent but cyclooxygenase-1- and cyclooxygenase-2-independent pathway: a 700-patient study of aspirin resistance. *Circulation* 2006;113:2888–2896
10. Gurbel PA, Bliden KP, DiChiara J, Newcomer J, Weng W, et al.: Evaluation of dose-related effects of aspirin on platelet function: results from the Aspirin-Induced Platelet Effect study. *Circulation* 2007;115:3156–3164
11. Catella-Lawson F, Reilly MP, Kapoor SC, Cucchiara AJ, DeMarco S, et al.: Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N Engl J Med* 2001;345:1809–1817
12. Peters RJG, Mehta SR, Fox KAA, Zhao F, Lewis BS, For the Clopidogrel in Unstable Angina to Prevent Recurrent Events

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20360

(CURE) trial: Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: observations from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. *Circulation* 2003;108:1682–1687
13. Topol EJ, Easton D, Harrington RA, Amarenco P, Califf RM, et al.: Randomized, double-blind, placebo-controlled, international trial of the oral IIb/IIIa antagonist lotrafiban in coronary and cerebrovascular disease. *Circulation* 2003;108:399–406
14. Macchi L, Christiaens L, Brabant S, Sorel N, Allal J, et al.: Resistance to aspirin in vitro is associated with increased platelet sensitivity to adenosine diphosphate. *Thromb Res* 2002;107:45–49
15. Järemo P, Lindahl TL, Fransson SG, Richter A: Individual variations of platelet inhibition after loading doses of clopidogrel. *J Intern Med* 2002;252:233–238
16. Gurbel PA, Bliden KP, Hiatt BL, O'Connor CM: Clopidogrel for coronary stenting: response variability, drug resistances, and the effect of pretreatment platelet reactivity. *Circulation* 2003;107:2908–2913
17. Gurbel PA: The relationship of platelet reactivity to the occurrence of post-stenting ischemic events: emergence of a new cardiovascular risk factor. *Rev Cardiovasc Med* 2006;7:S20–S28
18. Matetzky S, Shenkman B, Guetta V, Shecter M, Bienart R, et al.: Clopidogrel resistance is associated with increased risk of recurrent atherothrombotic events in patients with acute myocardial infarction. *Circulation* 2004;109:3171–3175
19. Müller I, Besta F, Schulz C, Massberg S, Schönig A, et al.: Prevalence of clopidogrel non-responders among patients with stable angina pectoris scheduled for elective coronary stent placement. *Thromb Haemost* 2003;89:783–787
20. Gurbel PA, Bliden KP: The stratification of platelet reactivity and activation in patients with stable coronary artery disease on aspirin therapy. *Thromb Res* 2003;112:9–12
21. Samara WM, Bliden KP, Tantry US, Gurbel PA: The difference between clopidogrel responsiveness and posttreatment platelet reactivity. *Thromb Res* 2005;115:89–94
22. Bliden KP, DiChiara J, Tantry US, Bassi AK, Chaganti SK, et al.: Increased risk in patients with high platelet aggregation receiving chronic clopidogrel therapy undergoing percutaneous coronary intervention: Is the current antiplatelet therapy adequate? *J Am Coll Cardiol* 2007;49:657–666
23. Wang TH, Bhatt DL, Topol EJ: Aspirin and clopidogrel resistance: an emerging clinical entity. *Eur Heart J* 2006;27:647–654
24. Hochholzer W, Trenk D, Bestehorn HP, Fischer B, Valina CM, et al.: Impact of the degree of peri-interventional platelet inhibition after loading with clopidogrel on early clinical outcome of elective coronary stent placement. *J Am Coll Cardiol* 2006;48: 1742–1750
25. Cuisset T, Frere C, Quilici J, Morange P-E, Nait-Saidi L, et al.: Benefit of a 600-mg loading dose of clopidogrel on platelet reactivity and clinical outcomes in patients with non-ST-segment elevation acute coronary syndrome undergoing coronary stenting. *J Am Coll Cardiol* 2006;48:1339–1345
26. Lau WC, Waskell LA, Watkins PB, Neer CJ, Horowitz K, et al.: Atorvastatin reduces the ability of clopidogrel to inhibit platelet aggregation: a new drug-drug interaction. *Circulation* 2003;107:32–37
27. Clarke TA, Waskell LA: The metabolism of clopidogrel is catalyzed by human cytochrome P45 3A and is inhibited by atorvastatin. *Drug Metab Dispos* 2003;31:53–59
28. Lau WC, Gurbel PA, Watkins PB, Neer CJ, Hopp AS, et al.: Contribution of hepatic cytochrome P450 3A4 metabolic activity to the phenomenon of clopidogrel resistance. *Circulation* 2004;109:166–171
29. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, Ramírez C, Cavallari U, et al.: Contribution of gene sequence variations of the hepatic cytochrome P450 3A4 enzyme to variability in individual responsiveness to clopidogrel. *Arterioscler Thromb Vasc Biol* 2006;26:1895–1900
30. Hulot JS, Bura A, Billard E, Azizi M, Remones V, et al.: Cytochrome P450 2C19 loss-of-function polymorphism is a major determinant of clopidogrel responsiveness in healthy subjects. *Blood* 2006;108:2244–2247
31. 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;107:2908–2913
32. Soffer D, Moussa I, Harjai KJ, Boura JA, Dixon SR, et al.: Impact of angina class on inhibition of platelet aggregation following clopidogrel loading in patients undergoing coronary intervention: do we need more aggressive dosing regimens in unstable angina? *Catheter Cardiovasc Interv* 2003;59:21–25
33. Ferreira IA, Mocking AIM, Feijge MAH, Gorter G, van Haeften TW, et al.: Platelet inhibition by insulin is absent in type 2 diabetes mellitus. *Arterioscler Thromb Vasc Biol* 2006;26:417–422
34. Ferroni P, Basili S, Falco A, Davi G: Platelet activation in type 2 diabetes mellitus. *J Thromb Haemost* 2004;2:1282–1291
35. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, Ramírez C, Sabaté M, et al.: Platelet function profiles in patients with type 2 diabetes and coronary artery disease on combined aspirin and clopidogrel treatment. *Diabetes* 2005;54:2430–2435
36. Angiolillo DJ, Bernardo E, Ramírez C, Costa MA, Sabaté M, et al.: Insulin therapy is associated with platelet dysfunction in patients with type 2 diabetes mellitus on dual oral antiplatelet treatment. *J Am Coll Cardiol* 2006;48:298–304
37. Geisler T, Langer H, Wydymus M, Gohring K, Zurn C, et al.: Low response to clopidogrel is associated with cardiovascular outcome after coronary stent implantation. *Eur Heart J* 2006;27: 2420–2425
38. Geisler T, Anders N, Paterok M, Langer H, Stellos K, et al.: Platelet response to clopidogrel is attenuated in diabetic patients undergoing coronary stent implantation. *Diabetes Care* 2007;30:372–374
39. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, Ramírez C, Sabaté M, et al.: Platelet aggregation according to body mass index in patients undergoing coronary stenting: should clopidogrel loading-dose be weight adjusted? *J Invasive Cardiol* 2004;16:169–174
40. Sibbing D, von Beckerath O, Schömig A, Kastrati A, von Beckerath N: Impact of body mass index on platelet aggregation after administration of a high loading dose of 600 mg of clopidogrel before percutaneous coronary intervention. *Am J Cardiol* 2007;100:203–205
41. Lepäntalo A, Virtanen KS, Heikkilä J, Wartiovaara U, Lassila R: Limited early antiplatelet effect of 300 mg clopidogrel in patients with aspirin therapy undergoing percutaneous coronary interventions. *Eur Heart J* 2004;25:467–483
42. Lev EI, Patel RT, Maresh KJ, Guthikonda S, Granada J, et al.: Aspirin and clopidogrel drug response in patients undergoing percutaneous coronary intervention: the role of dual drug resistance. *J Am Coll Cardiol* 2006;47:27–33

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