Review Article

Clopidogrel Resistance: Current Aspects and Future Directions

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Dual antiplatelet therapy combining aspirin and clopidogrel is the standard care for patients who have acute coronary syndromes (ACS) or are undergoing percutaneous coronary intervention (PCI), according to the current ACC/AHA and ESC guidelines.[1-5] However, despite the administration of dual antiplatelet therapy, some patients do develop recurrent cardiovascular ischemic events, with stent thrombosis being the most catastrophic.[6] It is well established that the antiplatelet response to clopidogrel varies widely among patients.[7,8] Patients who display little attenuation of platelet reactivity under clopidogrel therapy are recognized as low- or non-responders, or clopidogrel-resistant.[9] This review focuses on the methods used to identify patients with low clopidogrel responsiveness, the underlying mechanisms, clinical significance and current therapeutic strategies to overcome clopidogrel resistance.

Clopidogrel resistance - definition

Clopidogrel resistance is a phenomenon that has recently emerged in everyday medical practice. However, the term 'non-responsiveness' would seem more appropriate, given that patients appear to retain a degree of response to medical treatment. Although there is currently no clear definition for this phenomenon, a widely accepted description is "the persistent activity of clopidogrel target (i.e. P2Y12 receptors of the platelet) despite an adequate antiplatelet regime".[8,10] Clopidogrel non-responsiveness is reported to vary between 4% and 44% among different populations.[7,8]

In laboratory terms, the definition of clopidogrel resistance varies depending on the different tests used for quantifying residual platelet reactivity and the selection of cut-off values. More specifically, when light transmittance aggregometry is used, the optimal threshold for defining high residual platelet reactivity is set as a percentage of platelet inhibition lower than 20%, or induced maximal platelet aggregation greater than 50%.[11-13] On the other hand, the point-of-care assay VerifyNow© P2Y12 (Accumetrics, San Diego, CA, USA) is most commonly used with a cut-off value that ranges in different research groups from 230-240 platelet reactivity units (PRU). It has been demonstrated that this PRU range has a high correlation with adverse clinical events.[14-18]

From the clinical point of view, clopidogrel resistance manifestation may be less frequent. However, when it appears it involves a series of clinical ischemic and/or thromboembolic complications, with stent thrombosis being one of the most dramatic among them.

Laboratory methods for platelet function

A patient's response to clopidogrel therapy can be monitored by measuring plate-

let aggregation in blood samples. A variety of methods are available for quantifying platelet aggregation, among which the most widely used are light transmittance aggregometry (LTA), the vasodilator-stimulated phosphoprotein phosphorylation assay, whole blood aggregometry, PFA-100 and the VerifyNow assay. A synopsis of these tests is given in Table 1.

Until now LTA is widely considered as the gold standard of platelet function tests, as it was introduced and utilized in the field of platelet monitoring approximately 50 years ago. Despite the automation of the assay, it remains time- and labor-intensive and requires technical expertise; it is therefore restricted to specialized laboratories. In addition, the results of different research groups cannot be compared due to a lack of standardization.[19]

The VerifyNow© P2Y12 assay is a point-of-care device that uses an automated analyzer with single-use, disposable assays. This assay is simple, accurate and fast in measuring individual response to antiplatelet agents. Therefore, it is possible to determine the platelet response from the patient's whole blood samples in less than 5 minutes. Based on studies that compared the use of different platelet function tests, the strongest correlation with LTA was observed when using the point-of-care "VerifyNow P2Y12" assay.[20-22] The recently presented POPULAR study compared the findings of 6 different platelet tests (LTA, VerifyNow P2Y12, Plateletworks, Impact-R, PFA-100 and Innovance PAF P2Y). With regard to clinical outcomes, the VerifyNow assay demonstrated the highest correlation and a similar "area under curve" with LTA.[23] Furthermore, a high correlation between the VerifyNow assay and, to a lesser extent, LTA with the plasma level of the active metabolite of clopidogrel was described, suggesting that these may be the preferred laboratory tests for evaluating patient response to clopidogrel.[24] From a clinical point of view, point-of-care devices, such as VerifyNow, can identify patients undergoing PCI who are at risk for cardiovascular events.[15,16,18]

Mechanisms of clopidogrel resistance

Genetic polymorphisms

Different mechanisms responsible for the phenomenon of clopidogrel resistance have been suggested, with genetic polymorphisms being one of the most widely studied. Clopidogrel is a prodrug, the formation of its active metabolite being a two-step process performed by P450 (CYP) enzymes.[25] The genes encoding these enzymes appear to be polymorphic, with specific alleles being associated with decreased enzymatic activity and, consequently, reduced production of clopidogrel active metabolite.[26] One of the

Table 1. Overview of platelet function assays.

Test	Function	Positive aspects	Limitations
LTA	Measures luminosity as aggregation occurs in ADP-stimulated platelet-rich plasma	Considered gold standard, widely studied	Time and labor-consuming, requires expertise, lack of standardization
VASP	Measures the inhibition of VASP phosphorylation by ADP, which is mediated by P2Y12 through the inhibition of adenylyl cyclase	Stable, specific for P2Y12	Expensive, time-consuming, flow cytometer is required
PFA-100	Calculates platelet aggregation under high shear, mimicking platelet-rich thrombus formation after injury to a small vessel wall	Simple, rapid	Von Willebrand and platelet count dependent, poor correlation with LTA
WBA	Measures electrical impedance (maximal amplitude) between two electrodes immersed in whole blood 5 min after the addition of ADP	More sensitive to the antiplatelet effect, sample requires less preparation	Not specific (aspirin dependent), poor correlation with LTA
VerifyNow	Measures platelet-induced aggregation in a system containing fibrinogen-coated beads, contains ADP as platelet agonist and PGE1 as a suppressor of intracellular free calcium levels	Rapid, automated, easy to use, standardized, no expertise needed, best correlation with LTA	No instrument adjustment

LTA – light transmittance aggregometry; ADP – adenosine diphosphate; VASP – vasodilator-stimulated phosphoprotein; WBA – whole blood assay.

key enzymes in clopidogrel metabolism is CYP2C19, which is involved in both stages of clopidogrel biotransformation.[27,28] It has been suggested that common polymorphisms of the CYP2C19 enzyme, whose frequency varies from 30% to 55% of the population depending on ethnic group and genetic background,[29] affect the individual response to clopidogrel both pharmacokinetically and pharmacodynamically.[30-32] It has been described that carriers of at least one low-function CYP2C19 allele experience a reduction of the active metabolite in plasma up to 32.4% in comparison to healthy gene carriers.[31] This is especially the case for the CYP2C19*2 allele, which is the most common type among the reduced-function genes being showcased as a prime indicator of low response to clopidogrel in many studies.[33-37] Recent data have indicated that CYP2C19*3 and *4 alleles may also affect clopidogrel metabolism in the same way as CYP2C19*2.[38,39] Polymorphisms in enzymes other than CYP2C19 may also be involved in reduced clopidogrel metabolism, e.g. in carriers of a reduced-function CYP2C9 gene[30] and the CYP2B6 gene.[31]

Drug-drug interactions

A major issue in the field of clopidogrel resistance has been the interaction with other concomitant medication. Proton pump inhibitors (PPI) were among the first drugs to be put under the microscope for possible interferences with clopidogrel metabolism. Gilard et al first showed that subjects being treated with omeprazole exhibited a diminished biological action to clopidogrel using the VASP method.[40] Furthermore, Cuisset et al described patients who underwent coronary stenting for non-ST-elevation acute coronary syndromes as having more clopidogrel non-responders in the omeprazole than in the pantoprazole group (44% vs. 23%, p=0.04).[41] Since PPIs are metabolized by the same CYP metabolic pathway as clopidogrel,[42] a possible explanation for the poor responsiveness to clopidogrel was the competitive effect of PPI on the CYP2C19 enzyme. In contrast to the reported possible interaction of omeprazole and clopidogrel, the use of pantoprazole or esomeprazole has not been linked to a reduced clopidogrel response.[43] However, platelet aggregation was significantly higher in patients undergoing omeprazole treatment compared to those not receiving PPI treatment, though it was similar in patients treated with pantoprazole or esomeprazole.[44] Increased residual platelet reactivity under PPI treatment was also documented using the VerifyNow assay.[45] On May 2009, the European Medicines Agency issued a statement concerning the possible negative interaction between clopidogrel and omeprazole. This was followed by an online announcement on 17 November 2009 by the US Food and Drug Administration discouraging the concomitant use of these drugs. However, contrary to the above mentioned findings, the COGENT trial randomized 3627 patients with ACS and/or stent placement on clopidogrel. Each patient received additionally either omeprazole or placebo and was monitored over a mean period of almost 4 months. Findings revealed 136 adjudicated cardiovascular events and 105 adjudicated gastrointestinal events. No difference in the incidence of cardiovascular events between the two groups was found, but there were significantly fewer gastrointestinal events in the omeprazole group than in the placebo group.[46]

Early studies suggested a possible negative effect on clopidogrel's efficacy from the use of statins,[47-49] possibly due to the shared CYP3A4 enzymatic pathway between statins and clopidogrel. However, ample research data, taking advantage of new point-of-care methods for examining platelet aggregation, have clearly ruled out a significant interaction between statins and clopidogrel, concluding that the concomitant use of the above mentioned drugs is safe.[50-54]

Clinical significance of *in vitro* clopidogrel low responsiveness

Several studies have shown that inadequate platelet-inhibition leads to adverse clinical outcomes, including recurrent ischemic cardiovascular events, stent thrombosis and periprocedural myocardial infarction. These studies have been performed in different subgroups of patients undergoing PCI for ST-elevation myocardial infarction (STEMI) or non-STEMI, as well as elective PCI procedures; a synopsis is shown in Table 2. Particular attention has been given to the most dramatic complication of stent implantation, stent thrombosis. Studies of reduced platelet responsiveness regarding stent thrombosis are given in Table 3.

Management of patients with poor clopidogrel response

There is a clear and disturbing relationship between a low response to clopidogrel and cardiovascular events. Clinical approaches to overcome the low response to clopidogrel have not been established; however, different methods have been applied in an at-

Table 2. Overview of studies analyzing clinical outcome associated with clopidogrel resistance.

Reference	Year	n	Population	Clopidogrel dose (mg) LD/MD	Clopidogrel resistance assay	Follow up, months	Clinical outcome associated with clopidogrel resistance*
Matetzky et al[77]	2004	60	Primary PCI for STEMI	300 / 75	LTA (ADP 5 μmol/L)	6	Recurrent cardiovascular events: 40% of the upper, 6.7% of the 2nd and none of the 3rd and 4th quartile
Gurbel et al[78]	2005	192	Non-emergent PCI	300 or 600 / 75	LTA (ADP 20 μmol/L)	6	CV death, MI, UA, stroke: 38 patients reached primary endpoint with significantly higher platelet aggregation reaction (63 ± 12% vs. 56 ± 15%, p=0.02)
Cuisset et al[79]	2006	106	PCI for NSTEMI	300 / 75	LTA (ADP 10 μmol/L) or (arachidonic acid 0.5 mg/ml)	1	CV death, stent thrombosis, stroke or recurrent ACS: Upper quartile vs. quartiles 1,2,3: OR 22.4; 95% CI, 4.6-109
Hochholzer et al[80]	2006	802	Elective PCI	600 / 75	LTA (ADP 5 μmol/L)	1	MACE distribution in the quartiles: 4th 3.5%, 3rd 3.1%, 2nd 0.5% and 1st 0.5%; platelet aggregation above the median carried a 6.7-fold risk of MACE (p=0.003)
Geisler et al[81]	2006	379	PCI in stable angina or ACS	600 / 75	LTA (ADP 20 μmol/L)	3	CV death, MI, stroke: HR 3.71; 95% CI, 1.08-12.69; p=0.037
Bliden et al[82]	2007	100	Non-emergent PCI	– / 75 for at least one month before PCI	LTA (ADP 5 μmol/L) or (arachidonic acid 1 mg/ml)	12	ischemic events in 70% vs. 8% patients with vs. without on-clopidogrel high platelet reactivity (p=0.001)
Patti et al[16]	2008	160	PCI (STEMI excluded)	600 / 75	VerifyNow P2Y12	1	Cardiac death, MI, TVR: Upper quartile vs. quartile 1,2,3: OR 6.1; 95% CI, 1.1-18.3; p=0.033
Price et al[18]	2008	380	PCI with DES	600 / 75	VerifyNow P2Y12	6	CV death, MI: Higher rates of CV deaths (2.8 vs. 0%, p=0.04), combined endpoint (6.5 vs. 1.0%, p=0.008)
Marcucci et al[15]	2009	683	PCI for ACS	600 / 75	VerifyNow P2Y12	12	CV death: HR 2.55; 95% CI, 1.08-6.07; p=0.034 Nonfatal MI: HR 3.36; 95% CI, 1.49-7.58; p=0.004

*Levels of clopidogrel resistance are often scaled into quartiles, the upper or 4th quartile representing the group with the highest residual platelet reactivity. ADP – adenosine diphosphate; CI – confidence interval; CV – cardiovascular; DES – drug eluting stent; HR – hazard ratio; LD – loading dose; LTA – light transmittance aggregometry; MACE – major adverse cardiac events; MD – maintenance dose; MI – myocardial infarction; NSTEMI – non-STEMI; OR – odds ratio; PCI – percutaneous coronary intervention; STEMI – ST-elevation MI; TLR – target lesion revascularization; UA – unstable angina; VASP– vasodilator-stimulated phosphoprotein.

tempt to overcome clopidogrel resistance; these include higher loading and/or maintenance doses or switching to other antiplatelet agents.

Adjusting clopidogrel dose

An adapted approach to overcoming clopidogrel resistance is to adjust the dosage. In patients undergoing PCI a loading dose of 600 mg clopidogrel was associated with a higher level of platelet inhibition, lower mean post-treatment reactivity to adenosine diphosphate (ADP), and a lower incidence of non-responsiveness when compared to a 300 mg dose.[55-57] In the ISAR-CHOICE study, however, there was no additional effect regarding clopidogrel metabolite levels and platelet inhibition between the 600 mg and the

Table 3. Overview of studies focusing on stent thrombosis related to clopidogrel resistance.

Reference	Year	n	Population	Clopidogrel dose (mg) LD/MD	Clopidogrel resistance assay	Follow up, months	Stent thrombosis associated with clopidogrel resistance
Barragan et al[83]	2003	1684	Patients with coronary stents	/150	VASP	1	Higher % platelet reactivity in patients with SAT (63.3% versus 39.8%, p<0.0001)
Ajzenberg et al[84]	2005	10 with SAT and 22 controls	Patients with coronary stents	300 / 75	Shear-induced platelet aggregation (SIPA)	-	Higher platelet reactivity in patients with SAT (p=0.0008)
Gurbel et al[85]	2005	20 with SAT and 100 controls	Patients with coronary stents	300	LTA (ADP 5 and 20 μmol/L)	-	Higher platelet reactivity in patients with SAT (65.3% versus 51.2%; p=0.001)
Buonamici et al[86]	2007	804	PCI for any cause with DES	600 / 75	LTA (ADP 10 μmol/L)	6	Stent thrombosis in 8.6% of non-responders vs. 2.3% in responders (p<0.001). HR: 3.08; 95% CI, 1.32-7.16; p=0.009
Price et al[18]	2008	380	PCI for any cause with DES	600 / 75	VerifyNow P2Y12	6	Higher rates of stent thrombosis in non-responders compared to responders (4.6% vs. 0%, p=0.004)
Geisler et al[87]	2010	1019	PCI for any cause	600 / 75	LTA (ADP 20 μmol/L)	3	Patients with stent thrombosis showed a higher residual platelet aggregation (p=0.03)

SAT – subacute stent thrombosis. Other abbreviations as in Table 2.

900 mg loading dose.[58] The authors concluded that a single dose of clopidogrel higher than 600 mg was not associated with additional significant suppression of platelet function; this was probably due, after analyzing the pharmacokinetic profile and metabolites, to limited clopidogrel absorption. The 600 mg dose appears to achieve maximum inhibition more rapidly than the 300 mg dose.[56]

The OASIS-7 trial randomized 25,087 patients with unstable angina or acute MI to a high dose regimen (600 mg loading dose of clopidogrel, followed by 150 mg per day for 1 week) or the standard regimen (300 mg on the first day followed by 75 mg/day). At 30 days, the primary endpoint, the combined rate of cardiovascular death, MI, and stroke, occurred similarly in 4.4% of patients on the standard-dose clopidogrel and in 4.2% of patients on the high dose. However, among the two-thirds of the study patients undergoing PCI, the risk of stent thrombosis was reduced by 30% and the risk of MI was reduced by 22% in the group that received the high dose, compared to the group that received the standard dose. The high-dose group had more major bleeding, but there was no increase in intracerebral or fatal bleeds. No benefit was found in the group on a higher dose who did not have PCI.[59]

Although higher loading and maintenance doses of clopidogrel lead to improved responsiveness, there

is still a broad variability in the degree of antiplatelet effects achieved. Importantly, Bonello et al described, in a small group of patients undergoing PCI, the concept of adjusting the clopidogrel loading dose according to platelet monitoring as measured by vasodilator-stimulated phosphoprotein (VASP).[60] This adjustment is safe and may significantly improve the clinical outcome after PCI in patients with clopidogrel resistance, despite a first 600 mg loading dose. Tailoring antiplatelet therapy according to *in vitro* measurements of platelet function seems a promising approach to achieving optimal patient care. However, the GRAVITAS trial, the first large-scale clinical trial, designed to examine whether adjustment of clopidogrel therapy, on the basis of platelet function testing using a point-of-care assay, safely improves outcome after PCI with drug-eluting stents in clopidogrel resistant patients, did not show any superiority of 150 mg vs. 75 mg of clopidogrel.[13] A substudy of GRAVITAS, the Genotype Information and Functional Testing Study (GIFT), will assess which genes influence residual platelet reactivity on standard dose clopidogrel therapy. It will also seek to determine whether certain genes influence incremental change in platelet reactivity with a high-dose clopidogrel maintenance dose in patients who have high residual platelet reactivity on standard dosage.

Prasugrel

Prasugrel is a novel thienopyridine introduced for the treatment of acute coronary syndromes. As with clopidogrel, it is a *per os* administrated prodrug that, after absorption, is converted to its active metabolite, which targets the P2Y12 ADP platelet receptors. In contrast to clopidogrel, it is mainly metabolized by cytochrome isoenzymes CYP3A and CYP2B6, though there is a lesser contribution from CYP2C9 and CYP2C19. On the other hand, the latter cytochrome isoenzymes are the two key enzymes in the formation of clopidogrel's active metabolite; this would explain why common loss-of-function mutations in these alleles affect clopidogrel, while having minimal influence on the formation of prasugrel's active metabolite.[31,32]

Prasugrel quickly demonstrated that it achieves higher and more rapid inhibition of platelet aggregation and a greater reduction of pharmacodynamic non-responders, compared with the standard clopidogrel dose of 75 mg.[30,32,61] Studies have also demonstrated that prasugrel exerts a greater effect on the inhibition of platelet aggregation, even compared to higher doses of clopidogrel. Wiviott et al showed, in a randomized crossover study of 201 post-PCI patients, that prasugrel in a loading dose (LD) of 60 mg and 10 mg maintenance dose (MD) achieved higher and more consistent levels of platelet inhibition than clopidogrel at 600 mg LD and 150 mg MD.[13] The recent ACAPULCO study reinforced this observation by proving prasugrel's superiority in platelet inhibition compared to high-dose clopidogrel MD 150 mg or 900 mg LD.[62] Similar results have been described in clopidogrel resistant patients, with the superiority of prasugrel being more apparent in patients carrying the CYP2C19*2 loss-of-function allele.[63] In a small though challenging study, Pena et al described clopidogrel responsiveness in 7 patients who presented with stent thrombosis. The sequential increase of clopidogrel maintenance dose up to 300 mg could not achieve the levels of inhibition achieved by prasugrel. All 7 patients, 6 of whom had at least one poor-metabolizing allele of CYP2C19, did not respond to 150 mg clopidogrel and 2 of them remained resistant even to a 300 mg clopidogrel maintenance dose, whereas prasugrel achieved adequate platelet inhibition in all of them.[64]

Novel drugs

Cilostazol is a potent inhibitor of phosphodiesterase, targeting both platelets and vascular smooth muscle cells, and is considered effective in preventing subacute stent thrombosis.[65] Triple antiplatelet therapy with the addition of cilostazol has been proved in several large-scale studies to be more efficient in preventing adverse clinical events, especially stent thrombosis, without an increase in side effects compared to standard dual antiplatelet therapy.[66-68] By laboratory means, cilostazol has also been reported to increase platelet inhibition compared to standard dose clopidogrel in studies using the VerifyNow assay.[69] Adding cilostazol to standard clopidogrel also appears to be more effective in platelet inhibition, even compared to a high maintenance dose of clopidogrel (150 mg/d), as has been demonstrated by the ACCEL-RESISTANCE study.[70] Cilostazol is undoubtedly a tool that could prove to be helpful in tackling clopidogrel resistance.

Ticagrelor is an oral, direct-acting drug which, like the thienopyridines, targets the ADP receptor P2Y12. However, unlike clopidogrel and prasugrel, the receptor inhibition is reversible.[71] The PLATO trial compared ticagrelor (180 mg loading dose, 90

mg twice daily thereafter) and clopidogrel (300-600 mg loading dose, 75 mg daily thereafter) in 18,624 patients admitted to hospital with an acute coronary syndrome.[72] The ticagrelor group had a significantly lower occurrence of cardiovascular events, but was associated with a higher rate of major bleeding that was not related to coronary artery bypass grafting. Recently, the RESPOND Study suggested that ticagrelor therapy might be an appropriate approach to overcome non-responsiveness to clopidogrel in patients with stable coronary artery disease. Under ticagrelor treatment, platelet reactivity was below the cut-off points previously associated with ischemic risk – measured by LTA, VerifyNow P2Y12 assay, and VASP – in 98% to 100% of patients versus 44% to 76% of patients after clopidogrel therapy. Furthermore, the antiplatelet effect of ticagrelor was the same in responders and nonresponders.[73]

Cangrelor, another reversible non-thienopyridine ADP receptor P2Y12 inhibitor, administered intravenously, was assessed in the CHAMPION-PLATFORM[74] and the CHAMPION-PCI trials.[75] Both failed to show superiority compared to clopidogrel. *In vitro*, however, the addition of even a sub-therapeutic dose of cangrelor to the platelet-rich plasma of clopidogrel-pretreated patients resulted in an additional reduction of ADP-induced platelet aggregation as measured with the LTA. Moreover, cangrelor treatment was able to reduce the inter-individual variation observed in clopidogrel-inhibited platelet aggregation.[76] Cangrelor is a potent intravenous ADP-receptor antagonist with a rapid onset and offset of action. Such valuable qualities certainly warrant further study aimed at identifying suitable niches for cangrelor in order to override clopidogrel resistance.

Conclusion

The use of clopidogrel has increased tremendously over recent years. This is due to its unchallenged beneficial effects, when combined with aspirin, on reducing clinical adverse events in patients who have acute coronary syndromes or are undergoing PCI.

Both laboratory and clinical entities concerning clopidogrel resistance have emerged concurrently. Given that assays for the measurement of platelet reactivity have become easy to use, along with affordability and good prognostic value, it is most likely that measurements of platelet reactivity might become a routine laboratory test in the near future. This could mark the beginning of an era of individualized antiplatelet therapy, depending on platelet reactivity tests. Indeed, higher loading and maintenance doses will be an option in patients with a low on-clopidogrel response. Possible alternative strategies will be the use of more potent antiplatelet agents, though potential beneficial effects have to be balanced with an increased risk of bleeding. Consideration of the patient's characteristics, for example genetic polymorphisms and an individual risk profile, will, in addition to defining further the mechanisms leading to clopidogrel resistance, offer additional diagnostic tools and the tailoring of appropriate antiplatelet therapy.

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