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Cardiovascular Therapeutics

Clopidogrel "Resistance": Where are We Now?

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SUMMARY

Antiplatelet therapy with aspirin and clopidogrel in PCI patients, though effective, is still associated with thrombotic complications. These are multifactorial in origin, but partially attributable to "clopidogrel resistance." However, how best to identify and manage "clopidogrel resistance" remains unclear. Targeting therapeutic changes specifically at those individuals with poor response to clopidogrel is likely to be a solution. A "one size fits all" approach to clopidogrel dosing is probably flawed. This review will explore (1) the definition and mechanisms of clopidogrel resistance, (2) assessment of clopidogrel resistance by (i) platelet function testing and (ii) genetic testing, (3) the management of "clopidogrel resistance," and (4) newer antiplatelet agents, and evolving stent technology. A pubmed literature review was performed using the keywords "clopidogrel", "resistance", "poor response", "adverse events", "platelet function tests", and "genetic tests". In looking at new agents, keywords "prasugrel", "cangrelor", "ticagrelor" "Elinogrel", and "P2Y12 receptor antagonists" were used. Third, a search was performed looking at "stent design", "IVUS", "bioabsorbable stents", and "stent apposition". Whilst new P2Y12 receptor antagonists and improved stent technology may reduce thrombotic events in the future, there is still a need for clopidogrel. There is good evidence that poor response to clopidogrel is associated with adverse outcome. Platelet function tests probably provide more clinically useful data than genetic tests, but the question of how best to identify and manage variability in response to clopidogrel demands further research.

Introduction

Dual antiplatelet therapy with aspirin and clopidogrel has become routine practise in Percutaneous Coronary Intervention (PCI). Although thrombotic complications have reduced significantly with this combination, major adverse cardiac events still occur [1,2]. Whilst complications such as stent thrombosis (ST) have a multifactorial aetiology, it occurs more commonly in individuals demonstrating a poor response to clopidogrel [3–5]. How to address this issue in clinical practise remains unclear. Genetic and platelet function assays have the potential to identify individuals at risk of, or with, poor response to clopidogrel, and to facilitate treatment changes. However how, or if, these assays should be utilized remains controversial.

In 2010, the FDA approved a label for clopidogrel with a "boxed warning", describing a diminished effectiveness of clopidogrel in patients with an impaired ability to convert it to the active form [6]. An ACCF/AHA statement did not recommend routine genetic or platelet function testing in PCI patients, due to insufficient evidence [7]. However, it suggested genetic testing may be considered before starting clopidogrel therapy in high-risk patients, and that platelet function testing may be considered in those who suffer adverse events, whilst already established on clopidogrel, in both cases with a view to guiding treatment modulation.

Mechanism of Action

Clopidogrel is a second-generation thienopyridine. It is an intestinally absorbed prodrug, converted to its active thiol metabolite (R130964) by hepatic cytochrome (CYP) P450 enzymes, including CYP3A4, CYP3A5, and CYP2C19. The active metabolite irreversibly forms a disulfide bridge with two cysteine residues (cys17 and cys270) present in the extracellular domain of the (ADP) P2Y12 receptor, thus inhibiting it. P2Y12 receptor blockade also reduces platelet dense granule secretion. This may be responsible for reduction of arachidonic acid (AA), collagen, and thrombin induced platelet activation observed with clopidogrel, since dense granule secretions are associated with amplification of such pathways. Clopidogrel is unlikely to have a direct effect on collagen and thrombin agonism, since increased concentrations of these agonists overcome the inhibitory effect.

The net effect of the above processes is activation of intracellular pathways, and inhibition of the conformational change of platelet Glycoprotein (GP) IIb/IIIa receptors required for fibrinogen cross-linking and platelet activation [7–11]. Clopidogrel has also been reported to have an antiinflammatory effect, reducing CRP, platelet leukocyte aggregation, p-selectin and CD40L levels. It may also have an effect on the enzymatic components of coagulation, decreasing the rate of thrombin formation [8].

Clopidogrel has superseded the first generation thienopyridine ticlopidine because of both better tolerability and safety. In addition, there is no requirement for routine monitoring [12], and it has at least an equivalent efficacy [13].

Variability in response to clopidogrel, which follows an almost normal distribution, has been demonstrated, with "resistance" reported in up to 44% of PCI patients [14–16].

The Use of Clopidogrel in Current Clinical Practice

The CAPRIE trial suggested 75 mg clopidogrel was marginally more effective than aspirin as secondary prevention in patients with stroke, myocardial infarction, or peripheral arterial disease [12]. The evidence also supports the use of clopidogrel in addition to aspirin in (1) patients with acute coronary syndromes and (2) in PCI patients [17–20]. Clopidogrel may also have a role in the management of atrial fibrillation, particularly in individuals unsuitable for warfarin therapy [21].

Clopidogrel In PCI

Current guidelines suggest using clopidogrel loading doses (LD) in non-ST elevation ACS (NST-ACS), ST elevation-ACS (ST-ACS) and in elective PCI. Seventy five milligrams clopidogrel daily maintenance therapy is recommended postprocedure [22]. With this approach the clinical course of the majority of patients treated with clopidogrel is excellent [7]. The latest ESC/EACTS guidelines consider the newer P2Y12 receptor antagonists prasugrel and ticagrelor an alternative to clopidogrel in NST-ACS and first line over clopidogrel, unless contraindicated or unavailable, in ST-ACS [22].

There is still controversy over the optimum (1) LD; (2) maintenance dose; and (3) duration of treatment for clopidogrel. In addition, those "resistant" to clopidogrel are at increased risk of complications, including periprocedural myocardial infarction and ST [23–25].

Loading Doses

Clopidogrel LDs facilitate a more intense and rapid build up of platelet inhibition, with 300 mg originally being recommended. ESC/EACTS guidelines consider 300 mg LDs reasonable in the context of early loading for elective PCI [22]. However, 600 mg LD have now been shown to (1) have a faster onset of action, (2) generate greater platelet inhibition, and (3) be associated with reduced response variability when compared to 300 mg. This correlates with a clinical benefit [26–28]. The latest ESC/EACTS guidelines suggest using 600 mg in NST-ACS and in ST-ACS. Six hundred milligrams is also recommended for elective PCI when clopidogrel cannot be given greater than 6 h preprocedure.

Although the ALBION study suggested an increased platelet inhibition with 900 mg clopidogrel LD over 600 mg [29], this is disputed by another study using the same test (optical aggregation), and two studies using other platelet function tests [30–32]. However, 900 mg clopidogrel doses administered to "poor responders" results in increased platelet inhibition [32]. This implies "poor responders" may have a different pharmacological profile, and therefore may benefit from tailored LDs.

Twelve hundred milligrams LDs, when administered as two 600 mg LDs 2 h apart, resulted in more rapid platelet inhibition in a general PCI population [33]. Intestinal absorption may be the limiting factor to increasing LDs above 600 mg in the general population. Repeated 600 mg LDs have also been shown to be effective when targeted to a 'poor responder' population [34].

Maintenance Duration and Dose

Whilst the standard and licensed maintenance dose of clopidogrel is 75 mg, doses of 150 mg have been associated with greater platelet inhibition [35]. The optimum duration of clopidogrel maintenance therapy, particularly in patients with drug eluting stents (DES), is unclear. However, it is known that (1) premature discontinuation of antiplatelet therapy is a risk factor for ST, (2) ST still occurs beyond 6 months from stent insertion, and (3) there is a clustering of adverse events in the 90 days after clopidogrel cessation [36]. ST has been reported to increase by a factor of more than 30 when clopidogrel is discontinued within 6 month of DES insertion, and by a factor of approximately six when discontinued beyond 6 months [37,38].

Adherence to Drug Treatment

Poor compliance with clopidogrel therapy is associated with adverse outcome. It is the strongest predictor of ST at 1 month and 6 months, with one large cohort (2898 patients) reporting 12% of those noncompliant 6 months post-DES insertion suffering ST [39]. More research is needed assessing how to (1) predict who might not adhere to treatment and (2) how adherence to treatment might be improved.

However, this is not enough to explain thrombotic complications with, in the same study, 73.8% of those suffering ST clopidogrel compliant. Similar results have been reported in other large registries [40].

Clopidogrel Resistance

Definition

Definitions of clopidogrel resistance are numerous, discrepant, and both test and operator specific. With multiple definitions in current usage, some with a limited evidence base, it is often difficult to establish a consensus from data in the literature.

Defining 'resistance' as thrombotic complications whilst on clopidogrel is often used clinically. However, these events are

undoubtedly multifactorial, and this definition is therefore not specific to insufficient blockade of clopidogrel related pathways.

There are two broad ways to define clopidogrel resistance on platelet function testing. First, a poor response to clopidogrel therapy, assessed by the change in ADP induced platelet reactivity compared to baseline. Second, as high "on treatment" platelet reactivity. The later is consistent with how other drug "responses" (e.g. the use of the international normalized ratio for warfarin) are assessed. It is also a practical definition for those on maintenance therapy, where no baseline test is available. There is some evidence to suggest clopidogrel resistance by this definition may also correlate more closely with adverse outcome than a poor response to therapy, and this is our favored definition [41].

The definition of resistance also varies with the nature of the platelet function test, for example, modified thrombelastography (TEG) looks at the effect of clopidogrel on blood viscoelasticity, whereas VASP specifically measures P2Y12 receptor activation. Similarly genetic tests define clopidogrel resistance as the presence of specific genetic polymorphisms.

Mechanisms of Clopidogrel Resistance

Pharmacokinetic Factors

First, intestinal absorption may be impaired. This may be related to genetic variation in ABCB1, which encodes a P-glycoprotein efflux transporter [42]. The ABCB1 C3435T single nucleotide polymorphism significantly reduces absorption of clopidogrel 300 mg or 600 mg LD, in both homozygous and heterozygous form. Importantly in one study those suffering adverse events (death, nonfatal MI, stroke) 1 year post-MI were significantly more likely to have the homozygous form [43].

Second, there is marked interindividual variability in the hepatic CYP P450 enzymes necessary for the conversion of clopidogrel to its active metabolite [44]. Pharmacogenetic factors are emerging in this area, with CYP3A4, CYP3A5, and CYP2C19 all associated with clopidogrel activation [45–48]. Variation in CYP3A4 activity has been shown to strongly correlate with platelet aggregation whilst on Clopidogrel therapy [46]. Suh J et al. demonstrated that in patients with the nonexpressor genotype for CYP3A5, there was both lower clopidogrel responsiveness and worse outcomes in patients undergoing stent implantation, although contradictory studies exist [45,49]. CYP2C19 may be particularly important, responsible for 45% of the first step, and 10% of the last step of clopidogrel activation. A study of 2208 patients receiving clopidogrel therapy demonstrated those carrying CYP2C19 loss-of-function alleles had a higher rate of cardiovascular events, particularly PCI patients [43]. One such allele, CYP2C19*2, has been associated with an increased risk of major adverse cardiovascular events in 5 of 7 studies [7].

Pharmacodynamic Factors

Patients with a raised Body Mass Index or diabetes, have an increased incidence of "resistance" and a corresponding increased sensitivity to ADP, with regard to both platelet adhesion and aggregation [44,50]. Genes associated with clopidogrel's biological activity include P2RY12 and ITGB3 [51,52], but studies assessing the association between genes encoding the P2Y12 receptor and clopidogrel responsiveness have found no relationship [53,54]. Some small studies have associated genetic polymorphisms of the GPIIb/IIIa receptor with clopidogrel response variability, but other studies found no association [52,54–56]. Polymorphisms have also been reported in platelet membrane receptors, such as GP1a, which play an important role in the aggregatory response [57]. Intracellular P2Y12 dependant and independant pathways may also be upregulated in poor responders, for example, through the P2Y1 pathway, or through pathways dependant on other platelet agonists such as AA, thrombin, and collagen [58,59].

Assessing Response to Clopidogrel in Clinical Practice

Assays for assessing responses to clopidogrel, platelet reactivity whilst on clopidogrel, and more recently for measuring genetic markers, are available.

The ideal characteristics of a test for clopidogrel response depends to some extent on the setting. In the context of research studies, tests like light transmittance optical aggregation can afford to be expensive, require expertise, be labor intensive, and only be available in specialist centers. However, for use in day-to-day clinical practise, a simple bedside test is required. The test should be (1) easy to operate, (2) cost effective, (3) able to generate rapid results, (4) able to identify poor response to clopidogrel, in a manner that correlates with clinical outcome, and (5) able to facilitate the modification of therapy to improve clinical outcome.

Platelet Function Testing

The current gold standard of assessing responses to clopidogrel is light transmission aggregometry using 20 μM ADP stimulation [60]. Residual platelet aggregation greater than 50% relative to baseline is defined as poor response after clopidogrel. However it is unsuitable for bedside usage [61]. In addition, it is highly specific for one aspect of platelet function (aggregation in response to ADP), rather than assessing the overall effect of antiplatelet agents on tendency to thrombosis.

Point-of-care platelet function tests are potentially more attractive. The VerifyNow system measures agglutination of fibrinogen-coated beads mixed with whole blood, in response to ADP stimulation. In the setting of PCI, clopidogrel resistance measured by this method has been correlated with an increased incidence of periprocedural MI [62]. The POPULAR study suggested VerifyNow may be the best point of care assay in predicting clinical outcome, though it still has a low positive predictive value [63].

The VASP platelet reactivity index is a specific assay of P2Y12 receptor blockade. VASP levels, a protein which is phosphorylated in the presence of P2Y12 stimulation, are measured using flow cytometry. Response to clopidogrel measured by VASP has been shown to correlate with optical aggregation [64]. Significant differences in VASP index between patients with previous ST and PCI controls [24,65] have been noted. VASP has been used to guide treatment modification in clopidogrel poor responders, and

importantly, in one small study, this was associated with an improved clinical outcome [34].

TEG is a whole blood assay, which can be modified (mTEG) to assess the effect of antiplatelet agents on blood clotting. A good correlation between TEG and optical aggregation was found in detecting the effects of clopidogrel in the context of PCI [66]. Responses can be calculated in 15 min, based on one "on treatment" sample making it suitable for widespread clinical use [9]. In addition, it can provide a more global assessment of clopidogrel activity with parameters assessing (1) the enzymatic component of coagulation, (2) overall clotting tendency, and (3) AA induced platelet activation [10,67].

The more commonly utilized platelet function tests are summarised in Table 1.

Genetic Testing

Pharmocogenetic testing identifies a specific cause for "poor response". This can guide therapeutic manipulation. In individuals with CYP2C19 loss of function mutations, drugs such as prasugrel and ticagrelor, which are not affected by them, can potentially be utilized.

However, the clinical utility of such tests is unclear. Given the multiple genetic determinates of clopidogrel pharmacokinetics, which gene should be tested? Information about the predictive value for clinical events of individual genetic variants is limited, but the positive predictive value of CYP2C19 loss of function mutations is low, estimated at 12–20% for patients with ACS undergoing PCI [7].

There is no point-of-care genetic assay, limiting usage in the acute setting. However the Verigene system (Nanosphere, Northbrook, IL, USA) gives results in a few hours [68].

Genetic testing gives incomplete information, as it does not incorporate the nongenetic determinates of platelet reactivity. This may be misleading. A recent study of NSTEMI PCI patients using VASP showed that 20% of CYP2C19 polymorphism carriers had a good response to 600 mg clopidogrel LD, whilst 50% of patients with functional CYP2C19 genes had a "poor response" to clopidogrel [69]. Therefore directly measuring response may be more accurate.

Other Potentially Important Effects of Clopidogrel

There may be clinically important effects of clopidogrel that cannot be assessed looking at ADP. There are disparities between apparent rates of clopidogrel resistance as assessed by ADP-induced platelet aggregation and the occurrence of adverse clinical outcomes. Some studies show far higher numbers of poor responders than clinical treatment failure would suggest [70] and others, in which the vast majority of participants would be "resistant" using current criteria, show benefits of clopidogrel on outcome [71].

The mechanism of action for clopidogrel is probably multifactorial with (1) antiinflammatory effects [72], (2) actions on the enzymatic components of coagulation [67], and (3) actions on AA induced platelet activation being reported [10]. The relative clinical importance of these additional mechanisms of action, the potential to modulate them, and the benefits of incorporating them into one overall assessment of clopidogrel response remains to be proven.

Managing Poor Response and Risk of Poor Response

Altering the Dose of Clopidogrel

Higher LD or repeated LD of clopidogrel is associated with a significant reduction in poor responders [32,34]. Bonello et al. used VASP Index to guide clopidogrel LD to individual response in elective PCI patients. Poor responders were reloaded 24 h later with 600 mg. This was repeated up to 2.4 g total clopidogrel in persistent poor responders. Not only did this approach improve biochemical response, it also resulted in a significant reduction in 30 day MACE rate, with no associated increased risk in bleeding [34].

Maintenance doses can also be adjusted. An observational study of 52 Clopidogrel resistant patients undergoing PCI supported a reduction in stent thrombosis and MACE rates with 150 mg maintenance doses of clopidogrel (with no associated increase in bleeding risk) [73]. However, GRAVITAS showed that although doubling clopidogrel maintenance dose in poor responders may improve the measured response, it does not necessarily improve outcome [74].

Changing to Alternative Agents

A meta-analysis suggested new P2Y12 receptor antagonist may significantly reduce mortality and ST in PCI patients [71]. The third generation thienopyridine prasugrel is associated with higher levels of active metabolite, reduced response variability, and reduced numbers of poor responders. The TRITON-TIMI 38 trial showed prasugrel was associated with a lower incidence of ST in the context of PCI. Although TRITON-TIMI 38 used suboptimal Clopidogrel LD, a recent study demonstrated that prasugrel also generates faster and greater platelet inhibition than 600 mg clopidogrel [75,76].

Ticagrelor, an oral reversible P2Y12 inhibitor, generates faster and more pronounced platelet inhibition than clopidogrel, with a rapid onset and offset of action. The PLATO trial suggested ticagrelor significantly reduced the adverse event rate in ACS, without an increase in bleeding risk when compared to clopidogrel. There also appeared to be a benefit on overall mortality, although ongoing concerns about geographical differences in outcome mean it has yet to be approved by the FDA [77].

Cangrelor is a reversible intravenous P2Y12 inhibitor. The CHAMPION trial, comparing clopidogrel and cangrelor in the setting of PCI, showed no benefit in the primary endpoint (a composite of death, myocardial infarction, or ischemia-driven revascularization at 48 h), and indeed stopped recruiting prematurely as a result of interim analysis. It is therefore no longer considered a viable alternative to clopidogrel, except perhaps in the context of patients that cannot tolerate oral therapy [78]. The BRIDGE study assessing cangrelor usage in patients undergoing bypass surgery is on-going [79].

Table 1 Comparison of the clinical utility of common platelet function tests

Assay	Methodology	Pros	Cons	Time to obtain result	Correlation between "poor response" and adverse clinical outcome?	Evidence that it can guide therapeutic manipulation?	Evidence that therapeutic manipulation with this assay correlates with improved clinical outcome?
Multiplate Analyser (Multiplate Group, Germany)	Whole blood assay. Platelets, with ADP stimulation, aggregate on electrode wires, increasing the electrical impedance between them.	Whole blood assay. Ease of use.	Further data required on optimal cut off values.	10 min	Yes	Yes	No
VASP Platelet Reactivity Index (Biocytex, France)	VASP levels can be measured using flow cytometric techniques. It is a biomarker of P2Y12 stimulation.	Specific for P2Y12 receptor activation.	Expensive, and complex assay. Highly specific for platelet function.	30 min	Yes	Yes	Yes
VerifyNow (Accumetrics, USA)	Whole blood assay measuring agglutination of fibrinogen coated beads in response to ADP stimulation.	Whole blood assay. Ease of use. Evidence base.	Not recommended within two weeks of abciximab usage.	12 min	Yes	Yes	No
Plateletworks (Helena Laboratories, USA)	Compares platelet count in EDTA tubes with citrate tubes (using collagen and ADP stimulation).	Whole blood assay. Ease of use.	Requires cell counter. Minimal evidence for use.	2 min	Yes	No	No
Thrombelastograph Platelet Mapping (Haemoscope Corporation, USA)	ADP stimulated blood is placed in an oscillating cup. As blood clots, fibrin strands link it to a torsion wire. The resulting torque is converted to an electrical signal, which is plotted as a function of time.	Whole blood assay. Ease of use. Wide range of information derived from assay.	Sample preparation.	15 min	Yes	Yes	No
PFA-100 (Siemens Healthcare Diagnostics, USA)	Whole blood assay measuring the occlusion time of an aperture in a membrane under high stress conditions.	Ease of use. Mimics blood flow dynamics. Whole blood assay.	Poor evidence base for use in clopidogrel. Very non specific: Varies for example with levels of Von Willibrand factor.	5 min	No	No	No

Elinogrel is another agent in early testing. It is reversible, available in intravenous and oral forms with a half-life of 12 h [80]. In addition, cilostazol a phosphodiesterase type 3 inhibitor, acting via a different pathway to the above agents, has been shown to intensify platelet inhibition in clopidogrel poor responders, although the clinical benefit is unclear [7,81].

Stent Technology and Stent Optimization

Incomplete stent apposition, which has been associated with stent thrombosis [82], may be reduced by intravascular ultrasound and high pressure balloon postdilatation [83] The MUSIC study suggested that routine intravascular ultrasound to optimize bare metal stent deployment, was associated with acceptable stent thrombosis rates on aspirin monotherapy (2 cases in 161 patients) [84]. Bioabsorbable coronary stents are attractive since once the stent is absorbed, the stimuli for ST is no longer present. Coating stents with antibodies which capture endothelial progenitor cell may enhance stent reendothelialization [85], and coating stents with antiplatelet agents may increase local drug concentration. Overall improvements in stent technology and delivery do appear to be reducing event rates. Event rates in the recent GRAVITAS trial were very low, and even lower in TRIGGER-PCI, leading to its premature discontinuation [68,74,86].

However, if patients could be identified as at very high risk of ST before potential stent insertion they may be better treated without DES.

Practical Application

Current tests of clopidogrel "resistance" have a low positive predictive value for thrombotic complications, in part due to their multifactorial aetiology [87]. However further refinement of "cut offs" for poor response, and incorporation of ADP-independent actions of clopidogrel into assessment of response may make testing more clinically relevant. The clinical scenarios should, in part, determine the degree of platelet inhibition desired. Those with low bleeding risk, but high thrombotic risk may benefit from more powerful platelet inhibition. This would give an individualized definition of "poor response".

There are practical limitations to therapeutic manipulation. Even with point of care assays, measuring response to clopidogrel involves administering a LD, waiting 6 h for maximal drug concentrations, and performing platelet function tests. In the acute setting, such as a patient being admitted for primary angioplasty for acute ST elevation MI, this is not practical.

An alternative might be using baseline platelet reactivity to predict poor response. Some studies have associated high baseline platelet reactivity with poor response to clopidogrel [88], but the observation that some poor responders have low baseline platelet reactivity and some responders have high baseline platelet reactivity suggests this method may be limited [41].

It may also be possible, and easier in clinical practice, to identify cohorts at high risk of poor response based on clinical characteristics and modify their therapy without testing. Diabetic and obese individuals have been shown to respond poorly to clopidogrel. The OPTIMUS study showed that in diabetics, increased clopidogrel maintenance doses were associated with enhanced platelet inhibition [89]. Subgroup analysis of TRITON-TIMI 38 suggested a particular benefit for diabetic patients treated with Prasugrel [75]. An empirical approach of utilizing higher doses of clopidogrel or prasugrel (as suggested by UK NICE guidelines) may be sensible in these groups [90].

The Risks of Bleeding

Although improving response to clopidogrel or using newer more potent agents may decrease thrombotic complications, this must be balanced against a potential increased bleeding risk. Bleeding complications are increasing, and even minor bleeding by the GUSTO criteria increases 30-day mortality by 60% post-PCI [91]. Bleeding in both elective and emergency PCI is an independent predictor of 1-year mortality [92].

The TRITON study demonstrated that prasugrel was most efficacious (compared to clopidogrel) in those with the most hyperactive platelets (diabetics and ST-ACS). This group had a significantly reduced ischemic event rate, with minimal bleeding complications compared to clopidogrel, whereas those with unstable angina had the opposite: much more significant bleeding rates, with a minimal reduction in ischemic events. Individual risk factors for bleeding must be considered as well: prasugrel is associated with greater bleeding risks in those with previous cerebrovascular events [75].

Key Ongoing Trials

Ongoing large clinical outcome trials will yield much needed evidence. TARGET PCI will measure baseline CYP2C19 status (Verigene CYP2C19 assay), and serial platelet function tests (VerifyNow) to modulate maintenance therapy [93]. TRILOGY-ACS is a comparison of clopidogrel and prasugrel in ACS patients being treated medically [94]. PEGASUS-TIMI 54 is a study investigating the use of ticagrelor, in addition to aspirin, more than 12 months after MI [95].

Conclusions

Although new P2Y12 receptor antagonists and improved stent technology may reduce thrombotic events in the future, clopidogrel is still the mainstay of thienopyridine use in PCI patients. Newer agents are more expensive, and may be unsuitable for certain patients groups. The need for clopidogrel will continue.

Response to clopidogrel is variable, but as yet there is no evidence-based consensus on utilizing assays of platelet function to successfully guide treatment modification. Genetic testing, though identifying a specific mechanism of poor response, is clinically less relevant than platelet functions tests, which incorporate both genetic and nongenetic determinates of clopidogrel resistance.

Currently, the need for platelet inhibition is to some extent individually assessed for both bleeding and thrombotic risk. The use of assays of platelet reactivity while on clopidogrel to guide treatment modulation is reasonable in high-risk patients. Alternative

agents or dosing regimens can be used in those at high thrombotic risk (like individuals with previous ST on clopidogrel) but also at low bleeding risk. GRAVITAS suggested that simply doubling the clopidogrel maintenance dose in poor responders is not enough to improve outcome, and ongoing trials will help determine whether other approaches might be used routinely. As we await the results of such important studies, the challenge of introducing into clinical practise a simple bed side test not only to improve platelet reactivity in poor responders to clopidogrel, but also clinical outcome, remains.

Conflict of Interest

The authors declare no conflict of interest.

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