Antiplatelet drugs represent the basis of treatment for cardiovascular atherothrombotic disease processes. Clopidogrel selectively inhibits the platelet adenosine diphosphate (ADP) P2Y₁₂ receptor and is accepted as the antiplatelet drug of choice in addition to aspirin for patients with unstable angina and non-ST-segment elevation myocardial infarction (NSTEMI) (1, 2) as well as for patients undergoing percutaneous coronary intervention (PCI) (3–5). Clopidogrel has also shown to improve outcomes in patients with ST-segment elevation myocardial infarction (STEMI) (6, 7). In spite of the clear clinical benefit of clopidogrel therapy as shown in numerous large-scale trials, a considerable number of cardiovascular events continue to occur. Recurrent events despite adjunctive clopidogrel therapy have been, in part, attributed to variability in interindividual response profiles to this antiplatelet agent (8). The present manuscript provides an overview of the current status of knowledge on clopidogrel response variability as well as the possible future strategies to overcome the clinical implications associated with this phenomenon.

Mechanism of action of clopidogrel

ADP plays an essential role in platelet activation and, consequently, aggregation processes through its binding to G-protein-coupled purinergic receptors, P2Y₁ and P2Y₁₂ (9, 10). In particular, P2Y₁ activation leads to a change in platelet shape and initiates a weak phase of platelet aggregation, while P2Y₁₂ activation leads to glycoprotein (GP) IIb/IIIa activation, granule release, amplification of platelet aggregation, and stabilisation of the platelet aggregate. The family of thienopyridines irreversibly inhibits the ADP P2Y₁₂ receptor. Clopidogrel (second generation thienopyridine) has largely replaced ticlopidine (first generation thienopyridine) due its more favorable safety profile (11). Clopidogrel, like all thienopyridines, is a pro-drug which is absorbed into the bloodstream from the intestine (absorption limited by an intestinal pump P-glycoprotein coded by the ABCB1 gene) (12). Approximately 85% of the pro-drug is inhibited by esterases and only ≈15% is metabolised by several cytochrome P450 (CYP) isofoms in the liver which, through a double oxidation process, give origin to its active metabolite (8). This metabolite irreversibly binds and blocks the ADP P2Y₁₂ receptor preventing the platelet activation process mediated by this signalling pathway described above.

Variability in response to clopidogrel: Current knowledge

The occurrence of an acute ischemic event despite antiplatelet therapy usage has introduced the concept of “resistance” to antiplatelet agents. Although previous studies have dichotomised the antiplatelet effects induced by clopidogrel using terms like clopidogrel “responders” versus “non-responders” or “resistant” (8, 13, 14), clopidogrel responsiveness should be considered as a continuous phenomenon that follows a normal distribution. The term “resistance” should be restricted to a laboratory finding consisting in failure of an antiplatelet agent to block its specific target (P2Y₁₂ platelet receptor for clopidogrel). Since thrombotic events involve multiple signalling pathways, it is premature to attribute these outcomes to drug “resistance” without actually testing the particular antiplatelet agent in the affected patient. Without such confirmation, this occurrence should be considered “treatment failure” rather than “resistance” to the antiplatelet agent.

Several platelet function tests may be used to assess clopidogrel-induced antiplatelet effects, many of which have shown a relationship between clopidogrel response and cardiovascular events (15). Turbidimetric light transmittance aggregometry (LTA) with ADP as an agonist has been the most widely used technique and by many considered the gold-standard method to mitted by an intestinal pump P-glycoprotein coded by the ABCB1 gene) (12). Approximately 85% of the pro-drug is inhibited by esterases and only ≈15% is metabolised by several cytochrome P450 (CYP) isofoms in the liver which, through a double oxidation process, give origin to its active metabolite (8). This metabolite irreversibly binds and blocks the ADP P2Y₁₂ receptor preventing the platelet activation process mediated by this signalling pathway described above.

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**Table 1: Clinical outcomes and inadequate clopidogrel response defined according to various platelet function assays.**

<table>
<thead>
<tr>
<th>N</th>
<th>Clinical setting</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LTA (light transmittance aggregometry)</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>STEMI undergoing PCI</td>
<td>Post-primary PCI ischaemic events (6 months)</td>
</tr>
<tr>
<td>192</td>
<td>Non-emergent PCI</td>
<td>Post-PCI ischaemic events (6 months)</td>
</tr>
<tr>
<td>120</td>
<td>Elective PCI</td>
<td>Post-PCI myonecrosis/inflammation</td>
</tr>
<tr>
<td>106</td>
<td>ACS undergoing PCI</td>
<td>Post-PCI ischaemic events (30 days)</td>
</tr>
<tr>
<td>120</td>
<td>Elective PCI</td>
<td>Post-PCI myonecrosis</td>
</tr>
<tr>
<td>150</td>
<td>Elective PCI</td>
<td>Post-PCI myonecrosis</td>
</tr>
<tr>
<td>802</td>
<td>Elective PCI</td>
<td>Post-PCI ischaemic events (30 days)</td>
</tr>
<tr>
<td>379</td>
<td>Stable and unstable angina undergoing PCI</td>
<td>Post-PCI major cardiovascular events (3 months)</td>
</tr>
<tr>
<td>100</td>
<td>Chronic clopidogrel therapy undergoing non-emergent PCI</td>
<td>Post-PCI ischaemic events (12 months)</td>
</tr>
<tr>
<td>190</td>
<td>NSTEACS undergoing PCI</td>
<td>Periprocedural myocardial infarction</td>
</tr>
<tr>
<td>173</td>
<td>Type 2 diabetes mellitus on chronic dual antiplatelet therapy</td>
<td>Ischaemic events (24 months)</td>
</tr>
<tr>
<td>367</td>
<td>MI undergoing PCI</td>
<td>Post-PCI myonecrosis</td>
</tr>
<tr>
<td>105</td>
<td>Elective PCI</td>
<td>Stent thrombosis</td>
</tr>
<tr>
<td>804</td>
<td>PCI with drug-eluting stent</td>
<td>Stent thrombosis</td>
</tr>
<tr>
<td></td>
<td>VASP-P (vasodilator-stimulated phosphoprotein phosphorilation) assay</td>
<td></td>
</tr>
<tr>
<td>144</td>
<td>Stable angina and low-risk NSTEACS undergoing PCI</td>
<td>Post-PCI major adverse cardiac events (6 months)</td>
</tr>
<tr>
<td>195</td>
<td>NSTEACS undergoing PCI</td>
<td>Post-PCI ischaemic events (30 days)</td>
</tr>
<tr>
<td>46</td>
<td>Subacute stent thrombosis</td>
<td>Stent thrombosis</td>
</tr>
<tr>
<td>120</td>
<td>Subacute stent thrombosis</td>
<td>Stent thrombosis</td>
</tr>
<tr>
<td>99</td>
<td>PCI with high risk for stent thrombosis</td>
<td>Stent thrombosis</td>
</tr>
<tr>
<td></td>
<td>VerifyNow P2Y&lt;sub&gt;12&lt;/sub&gt; assay</td>
<td></td>
</tr>
<tr>
<td>380</td>
<td>PCI with drug eluting stents</td>
<td>Major adverse cardiac events and stent thrombosis (6 months)</td>
</tr>
<tr>
<td>160</td>
<td>PCI</td>
<td>Major adverse cardiac events (30 days)</td>
</tr>
<tr>
<td>683</td>
<td>ACS undergoing PCI</td>
<td>Major adverse cardiac events (12 months)</td>
</tr>
<tr>
<td>179</td>
<td>NSTEACS undergoing coronary angiography</td>
<td>Major adverse cardiac events (12 months)</td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td></td>
</tr>
<tr>
<td>1608</td>
<td>Elective PCI with drug-eluting stent</td>
<td>Stent thrombosis</td>
</tr>
<tr>
<td>49</td>
<td>Subacute stent thrombosis</td>
<td>Stent thrombosis</td>
</tr>
</tbody>
</table>

STEMI, ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; ACS, acute coronary syndrome; NSTEACS, non-ST elevation acute coronary syndrome. *Platelet function test: multiple electrode platelet aggregometry (MEA). †Platelet function test: shear-induced platelet aggregation (SIVA).
assess antiplatelet drug response, including clopidogrel. Since ADP can induce activation and thus aggregation not only through P2Y$_{12}$ (specifically blocked by the active metabolite of clopidogrel), but also through P2Y$_{1}$. receptors, assays more specific to the P2Y$_{12}$ signalling pathway have been developed. Flow cytometric analysis of vasodilator-stimulated phosphoprotein (VASP) phosphorylation is a marker of P2Y$_{12}$ receptor reactivity and, thus, considered the more specific for assessing clopidogrel-induced inhibition (16). However, these two techniques are complex, time-consuming, need experienced technicians and are not available in most centers. The VerifyNow P2Y$_{12}$ assay is a user-friendly point-of-care system, based on a turbidimetric measurement of agglutination of platelets to fibrinogen-coated micro-beads, which may allow a more practical approach in the clinical setting, thanks to its easy-to-use characteristics and broad availability. Several other assays, including thromboelastography, impedance aggregometry, multiple electrode platelet aggregometry (MEA), have been used to assess for clopidogrel induced antiplatelet effects. Description of these platelet function assays goes beyond the scope of this manuscript and is provided elsewhere (15).

Since the best laboratory test to evaluate the antiplatelet effects of clopidogrel has not been established, criteria for a standard definition of clopidogrel responsiveness have not been achieved. Nevertheless, there have been overwhelming data over the course of the past years that various platelet function assays using different criteria/cut-off values to define clopidogrel responsiveness have been associated with adverse outcomes.

**Clinical Focus**

### Clopidogrel response variability and clinical outcomes

The clinical implications of clopidogrel response variability have been mostly evaluated in patients undergoing PCI, where clopidogrel usage is predominant. This has been tested in various clinical settings: stable coronary artery disease, non-ST elevation acute coronary syndromes (NSTEACS, including unstable angina and NSTEMI), and STEMI. Although clopidogrel-induced antiplatelet effects have been described in various ways (e.g. percentage inhibition, absolute change, etc.), most clinical outcome studies have identified that the degree of post-treatment platelet reactivity to be the best predictor of recurrent ischaemic events (8, 13, 14, 17). Table 1 summarises the results from reported studies in which clopidogrel response has been associated with an increase risk of adverse ischaemic events.

#### Mechanisms of clopidogrel response variability

Several mechanisms leading to variability in response to clopidogrel have been proposed and many of them still need to be fully elucidated. Clopidogrel response variability is likely a multifactorial process, which includes genetic, cellular, and clinical causes (Table 2) (8).

**Genetic factors**

Polymorphisms of genes codifying proteins involved in clopidogrel absorption (e.g. ABCB1), hepatic metabolism (e.g. cytochrome P450 isoenzymes) and platelet reactivity (e.g. platelet membrane receptors) have been suggested to have an impact on variations on interindividual response to clopidogrel.

ABCB1 codifies MDR1 (multidrug resistance transporter), an intestinal P-glycoprotein involved in clopidogrel absorption and its genetic variants have been associated with clopidogrel response (11, 43). In a recent study, allelic variations of genes modulating absorption, metabolism and biologic activity among 2,208 patients presenting with an acute myocardial infarction (MI) and receiving clopidogrel therapy were determined (44). The presence of two variant alleles of ABCB1 was associated with a higher rate of cardiovascular events (death from any cause, non-fatal stroke and MI) at one year of follow-up. Recent observations from our group suggest that genetic variations of MDR1 may modulate clopidogrel effects depending on the dose administered (45).

Several cytochrome P450 (CYP) isofoms are involved in the hepatic metabolism of clopidogrel into its active metabolite. Polymorphisms in CYP3A4, CYP3A5, CYP2C9 and CYP2C19 have been previously reported as possible determinants of variability in response to clopidogrel (44, 46–54). Several studies recently published have evaluated CYP polymorphisms and their relation with clinical outcomes. Of these, studies evaluating CYP2C19 have provided the most consistent findings. This may be attributed to the fact that CYP2C19 is involved in both metabolic steps in the liver and functional studies have shown that carriers of at least one CYP2C19 reduced-function allele had significantly lower levels of active metabolite and diminished platelet inhibition (54). In a study by Simon et al. (44), patients with an acute MI carrying any two CYP2C19 loss-of-function alleles had a higher rate of cardiovascular events at one year of follow-up, especially those undergoing PCI. In a sub-study of TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction), carriers of at least one CYP2C19 re-

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**Table 2: Mechanisms leading to clopidogrel response variability.**

<table>
<thead>
<tr>
<th>Clopidogrel response variability</th>
<th>Genetic factors</th>
<th>Cellular factors</th>
<th>Clinical factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Polymorphisms of MDR1</strong></td>
<td><strong>Polymorphisms of CYP isofoms</strong></td>
<td><strong>Accelerated platelet turnover</strong></td>
<td><strong>Failure to prescribe</strong></td>
</tr>
<tr>
<td><strong>Polymorphisms of P2Y$_{12}$</strong></td>
<td><strong>Polymorphisms of P2Y$_{1}$</strong></td>
<td><strong>Increased ADP exposure</strong></td>
<td><strong>Poor compliance</strong></td>
</tr>
<tr>
<td><strong>Polymorphisms GPIIb/IIIa</strong></td>
<td><strong>Up-regulation of P2Y$_{12}$ pathway</strong></td>
<td><strong>Reduced CYP activity</strong></td>
<td><strong>Under-dosing</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Up-regulation of P2Y$_{1}$ pathway</strong></td>
<td><strong>Drug-drug interactions</strong></td>
<td><strong>Drug-drug interactions</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Up-regulation of P2Y-independent pathways</strong></td>
<td><strong>Diabetes mellitus</strong></td>
<td><strong>Diabetes mellitus</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Acute coronary syndrome</strong></td>
<td><strong>Acute coronary syndrome</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Elevated body mass index</strong></td>
<td><strong>Elevated body mass index</strong></td>
</tr>
</tbody>
</table>

MDR, multidrug resistance transporter; CYP, cytochrome P450; ADP, adenosine diphosphate.
duced-function allele in clopidogrel-treated subjects (n=1,477) had a higher rate of cardiovascular events, including stent thrombosis (54). In a population of young patients (aged less than 45 years) who were chronically treated with clopidogrel after MI (n=378), Collet et al. observed that CYP2C19*2 genetic variant was an independent predictor of cardiovascular events in a long-term follow-up (53). Recently, Sibbing et al. found in patients who underwent coronary stent placement after pretreatment with 600 mg of clopidogrel (n=2,485) that CYP2C19*2 carrier status was significantly associated with an increased risk of stent thrombosis (52).

Several other small pharmacogenetic studies have suggested that polymorphisms of genes encoding for platelet membrane receptors may be involved in the downstream effects of clopidogrel. These include polymorphisms in P2YR12 (which codes P2Y12 receptor), ITGB3 (which codes the platelet-fibrinogen receptor GP Ib/IIa), ITGA2 (which codes the platelet-collagen receptor GP Ib), and in PAR-1 gene (which codes the protease-activated receptor –1, a platelet receptor for thrombin); however, study findings have not been consistent (55–66).

**Cellular factors**

Several cellular factors have been implied in reduced clopidogrel effects. Reticulated platelets (RP) are young platelets more active than the non-reticulated ones. Guthkonda et al. showed in 90 patients with stable coronary artery disease taking aspirin and clopidogrel that a higher proportion of circulating RP correlated with a higher ADP-induced aggregation by LTA (67). Therefore, an accelerated platelet turnover, indicated by high RP numbers, may result in impaired clopidogrel response (68). Upregulation of purinergic (P2Y1 and P2Y12) signalling pathways which may be a primary disorder of the platelet or secondary to increased ADP exposure (e.g. due to platelet-red blood cell interaction) have been proposed as other mechanisms implicated in variability in response to clopidogrel (69). Upregulation of P2Y-independent pathways has also been suggested to mitigate clopidogrel induced effects. Platelets from patients with diabetes mellitus are characterised by one or more of the above cellular abnormalities (69, 70). Finally, the baseline degree of metabolic activity of the CYP enzymatic system may condition the degree of transformation of clopidogrel into its active metabolite (71). This is further supported by the fact that drugs that are either potent inducers (e.g. St. John’s wort, rifampicin) or inhibitors (e.g. ketoconazole, eritromycin) of the CYP system can modify clopidogrel antiplatelet effects (71).

**Clinical factors**

Although multiple factors are associated with inadequate clopidogrel response, the most important factors for achieving adequate clopidogrel antiplatelet effects are compliance and dosing. A poor compliance with clopidogrel therapy is evidently a cause of reduced clopidogrel response and subsequently a risk factor for recurrent cardiovascular events (7, 13, 14). Currently, the approved loading and maintenance dose for clopidogrel by the US Food and Drug Administration are 300 mg and 75 mg/ daily, respectively. As will be discussed later, several studies have shown that an increase either in the loading or the maintenance dose results in better response profiles (72–78). This in turn has also been associated with improved clinical outcomes (23, 79).

Some clinical factors, such as diabetes mellitus (69, 70), obesity (80, 81) and the presence of an acute coronary syndrome (82, 83), have been reported to be associated with lower clopidogrel-induced antiplatelet effects and may, in part, contribute to their worse clinical outcomes.

Hepatic metabolism is a critical step to achieve the clopidogrel antiplatelet effects. Drugs that are substrates or inhibit the different CYP isoforms involved in clopidogrel conversion into its active metabolite can potentially interfere and lead to an impairment of antiplatelet effects. This potential interaction is of concern especially when dealing with drugs that are commonly used in patients with cardiovascular disease. To date the most commonly used agents in cardiovascular medicine that have raised concern are lipophilic statins, proton pump inhibitors (PPI), and calcium channel blockers. Functional studies have observed an interaction between lipophilic statins, which are metabolised by CYP (e.g. atorvastatin, simvastatin, lovastatin) and clopidogrel (84, 85). Hydrophilic statins (e.g. pravastatin, rosuvastatin) not metabolised by CYP have not shown to have any interaction. Despite some initial observations on a potential clopidogrel-statins interaction, numerous other pharmacodynamic studies failed to see this effect and most importantly clinical studies have not been affected by concomitant lipophilic statin therapy in clopidogrel treated patients (86–89). Decreased platelet inhibition of clopidogrel and worse clinical outcomes has been observed in patients receiving concomitantly clopidogrel and calcium-channel blockers, such as dihydropyridines (90). Recently, a new possible drug-drug interaction, between PPIs and clopidogrel has been described, raising a great concern in the scientific community (91, 92). Two large retrospective analyses have shown that concomitant use of PPIs and clopidogrel was associated with an increased risk of cardiovascular events after an acute coronary syndrome when compared with patients not taking PPIs (93, 94). In mechanistic studies, omeprazole (metabolised mainly by CYP2C19) has been reported to reduce clopidogrel-induced antiplatelet effects (95, 96). The available data with other PPIs does not allow drawing definitive conclusions about this interaction being a class effect. In functional studies, pantoprazole and esomeprazole were not associated with an impairment in clopidogrel response (96, 97), while lansoprazole affected the degree of inhibition of platelet aggregation (IPA) after a loading dose of clopidogrel, but not prasugrel, only in subjects with high IPA (upper tertile) after a dose of clopidogrel alone (98). Further functional and clinical studies are warranted to assess the real extent of this interaction.

**Future directions: Overcoming inadequate clopidogrel response**

Due to its potentially severe and even fatal consequences, variability in clopidogrel response has emerged a major clinical problem warranting measures to overcome this phenomenon. The first and foremost important approach is to ensure patient compliance. Although ongoing studies will better define possible drug-drug interactions and how to deal with this issue, which

may be a challenge in the polypharmacy patient, this needs to be considered as a potential cause of inadequate clopidogrel responsiveness. Currently, three strategies can be proposed to overcome inadequate clopidogrel responsiveness with goal to reduce the risk of recurrent ischaemic event: a) increase clopidogrel dosing; b) triple antiplatelet therapy; c) new P2Y$_{12}$ antiplatelet agent.

### a) Increase clopidogrel dosing

Several studies have shown that a high clopidogrel loading dose regimen (≥2600 mg) achieves a greater and faster degree of platelet inhibition when compared to a standard 300 mg loading dose (72, 73, 76, 78). The better response profiles associated with high clopidogrel loading regimens have been associated with better clinical outcomes, mainly driven by reduce periprocedural MI in patients undergoing PCI (23, 76, 78, 79, 99). Although most studies have evaluated a 600 mg loading dose, there are some studies which have evaluated a 900 mg loading dose (72, 78). However, these loading dose regimens given in clopidogrel-naïve patients provided platelet inhibition only marginally higher than those obtained with a 600 mg loading dose which has been attributed to the limited ability to absorb such a high dose (72).

In patients undergoing elective PCI, a high-maintenance-dose (150 mg/day) dose regimen of clopidogrel was found to be associated with enhanced platelet inhibition compared to the currently recommended 75 mg/day (74, 75, 77). The benefit of this higher maintenance dose was observed in patients with higher levels of post-treatment platelet reactivity with 75 mg (74). The OPTIMUS (Optimizing antiPlatelet Therapy In diabetes MellitusUS) study evaluated type 2 diabetes mellitus patients with high platelet reactivity while in their chronic phase of treatment in which a 150 mg clopidogrel maintenance dose resulted in higher platelet inhibition compared with 75 mg dosing (75). In a recently published observational study (100), Lemésle et al. evaluated the impact of a 600-mg loading dose followed by a high maintenance dose (150 mg/day) during the first 15 days after PCI compared with standard dosing in a non-selected cohort of patients (n=2,954) who underwent PCI with coronary stenting. At two-month follow-up, the high dose of clopidogrel was significantly associated with a decrease in the composite endpoint of death, MI and stent thrombosis without a significant increase in bleeding events.

Currently, PCI guidelines provide a class I recommendation (level of evidence C) for a 600 mg clopidogrel loading dose (3). The guidelines provide a class IIB recommendation (level of evidence C) for considering therapy with 150 mg clopidogrel maintenance dose in patients in whom a stent thrombosis might result in a catastrophic or lethal event if <50% inhibition is observed. The ongoing CURRENT/OASIS-7 (Clopidogrel optimal loading dose Usage to Reduce recurrent EveNts/Optimal Antiplatelet Strategy for InterventionS; NCT00335462) will evaluate the efficacy of higher loading and maintenance doses of clopidogrel in NSTEACS patients undergoing PCI. Several currently ongoing clinical trials are evaluating safety and/or efficacy of a tailored treatment with high clopidogrel maintenance dose in patients with inadequate response to clopidogrel. These include GRAVITAS (Gauging Responsiveness with a VerifyNow Assay; Impact on Thrombosis And Safety; NCT00645918), ARCTIC (Double Randomization of a Monitoring Adjusted Antiplatelet Treatment Versus a Common Antiplatelet Treatment for DES Implantation, and Interruption Versus Continuation of Double Antiplatelet Therapy; NCT00827411), and DANTE (Dual Antiplatelet Therapy Tailored on the Extent of Platelet Inhibition, NCT00774475).

### b) Triple antiplatelet therapy

The addition of a third antiplatelet agent may be considered in the acute and maintenance phase of therapy. In the acute phase of therapy, addition of a glycoprotein IIb/IIIa inhibitor may be considered. Addition of a glycoprotein IIb/IIIa inhibitor achieves enhanced platelet inhibition in patients receiving aspirin and a loading dose of clopidogrel (irrespectively of using 600 mg or 300 mg as loading dose) (20). Recently, Cuisset et al. evaluated the effect of adding abciximab to dual antiplatelet therapy in clopidogrel non-responders (n=149) referred for elective PCI. The rate of cardiovascular events at one month was significantly lower when abciximab was added compared to conventional dual antiplatelet therapy (101). The 3T/2R trial (presented at the European Society of Cardiology Congress 2008 in Munich, Germany) randomised poor responders (n=263) to aspirin or clopidogrel who underwent elective PCI to receive a tirofiban bolus or placebo (102). Patients treated with tirofiban had significant lower increase of troponins within 48 hours (primary endpoint), as well as significant reduction of major adverse cardiovascular events within 30 days.

In the maintenance phase of therapy, triple antiplatelet therapy achieved with the adjunctive use of cilostazol, a phosphodiesterase III inhibitor, may be considered. Recently, the OPTIMUS-2 study showed that in a diabetic population cilostazol markedly enhances inhibition of P2Y$_{12}$ signalling (103). These findings may contribute to the reduced stent thrombosis rates observed with this triple antiplatelet treatment regimen compared to standard dual antiplatelet therapy (104). In addition, triple antiplatelet therapy has been associated with better outcomes, mainly driven by reduced target lesion revascularisation rates, in patients treated with both bare-metal and drug-eluting stents without any increase in bleeding (105–107). These benefits appear to be more marked in higher risk subjects, such as diabetes (108). Cilostazol therapy, however, is limited by its high prevalence of side effects (e.g. headache, gastrointestinal disturbances, palpitations) (103).

### c) New P2Y$_{12}$ receptor antagonists

Several newer P2Y$_{12}$ receptor antagonists are currently under different phases of clinical development (e.g. prasugrel, cangrelor, ticagrelor, elinogrel). Description of these agents goes beyond the scope of this manuscript and described in details elsewhere (109–111). These agents have more potent inhibitory effects than clopidogrel, even when used at high doses, and have less variability in interindividual response profiles (112). Prasugrel, a third generation thienopyridine with more favorable pharmacokinetic profiles and consequently better pharmacodynamic responses compared to clopidogrel, has already completed its phase III investigation and received approval for clinical use by regulatory authorities. The TRITON-TIMI 38 (Trial to Assess
Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel – Thrombolysis In Myocardial Infarction (TIMI) 38) trial showed that in high-risk acute coronary syndrome patients undergoing PCI, a loading dose of 60 mg of prasugrel followed by a 10 mg maintenance dose, was associated with significantly reduced rates of ischaemic events, including stent thrombosis, compared to standard dose clopidogrel (113). This, however, occurred at the expense of an increased risk of major bleeding. Nevertheless, the net clinical benefit analysis, defined as the composite of efficacy and bleeding end points (death from any cause, non-fatal MI, non-fatal stroke, and TIMI major haemorrhage), still favored prasugrel. In this trial, prasugrel showed a special benefit in patients with diabetes mellitus (114) and STEMI (115). On the contrary, there was no net benefit in patients weighing less than 60 kg patients or ≥75 years of age and a net harm was shown in patients with a history of stroke or transient ischaemic attack (115). If prasugrel yields better clinical outcomes in clopidogrel non-responders undergoing elective PCI is currently under investigation. The results of ongoing clinical investigations with the other P2Y12 receptor antagonists (e.g. cangrelor, ticagrelor, elinogrel) will dictate their potential use in the clinical setting.

Conclusions

There is strong evidence supporting the presence of variability in individual response profiles to clopidogrel therapy and its clinical sequelae. Mechanisms leading to variable clopidogrel-induced antiplatelet effects which may in turn impact clinical outcomes are likely multifactorial, including genetic, cellular, and clinical factors. Further studies however are warranted to better define this phenomenon for which a standardised definition is still lacking. The latter will provide a stronger basis for the future endeavor of overcoming this phenomenon and set the basis for individualised antiplatelet treatment regimens, particularly in high-risk patients (116–118).

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