Personalized antiplatelet therapy with P2Y\textsubscript{12} receptor inhibitors: benefits and pitfalls

Max-Paul Winter\textsuperscript{1}, Marek Koziński\textsuperscript{2}, Jacek Kubica\textsuperscript{2}, Daniel Aradi\textsuperscript{3}, Jolanta M. Siller-Matula\textsuperscript{1}

\textsuperscript{1}Department of Cardiology, Medical University of Vienna, Vienna, Austria
\textsuperscript{2}Department of Cardiology and Internal Medicine, Collegium Medicum of the Nicolaus Copernicus University, Bydgoszcz, Poland
\textsuperscript{3}Department of Cardiology, Heart Center Balatonfüred and Semmelweis University, Heart and Vascular Center, Budapest, Hungary

Abstract

Antiplatelet therapy with P2Y\textsubscript{12} receptor inhibitors has become the cornerstone of medical treatment in patients with acute coronary syndrome, after percutaneous coronary intervention and in secondary prevention of atherothrombotic events. Clopidogrel used to be the most broadly prescribed P2Y\textsubscript{12} receptor inhibitor with undisputable benefits especially in combination with aspirin, but a considerable number of clopidogrel-treated patients experience adverse thrombotic events in whom insufficient P2Y\textsubscript{12}-inhibition and a consequential high on-treatment platelet reactivity is a common finding. This clinically relevant limitation of clopidogrel has driven the increased use of new antiplatelet agents. Prasugrel (a third generation thienopyridine) and ticagrelor (a cyclopentyl-triazolo-pyrimidine) feature more potent and predictable P2Y\textsubscript{12}-inhibition compared to clopidogrel, which translates into improved ischemic outcomes. However, excessive platelet inhibition and consequential low on-treatment platelet reactivity comes at the price of increased risk of major bleeding. The majority of randomized clinical trials failed to demonstrate improved clinical outcomes with platelet function testing and tailored antiplatelet therapy, but results of all recent trials of potent antiplatelets and prolonged antiplatelet durations point towards a need for individualized antiplatelet approach in order to decrease thrombotic events without increasing bleeding. This review focuses on potential strategies for personalizing antiplatelet treatment.

Key words: antiplatelet therapy, P2Y\textsubscript{12} receptor inhibitors, acute coronary syndromes, platelet reactivity.

Atherothrombosis

Atherosclerotic plaque rupture or erosion is thought to be the initial step in the development of acute coronary syndrome (ACS). At the site of vascular injury (due to plaque rupture) exposed subendothelial matrix recruits and activates platelets [1]. Platelets adhere to exposed collagen and von Willebrand factor (vWF). Via the platelet glycoprotein (GP)-VI receptor and integrin α\textsubscript{2}β\textsubscript{1}, collagen can directly bind to and activate platelets, which leads to release of contents from the dense granules to the extracellular surrounding. Dense granules mostly consist of platelet agonists such as adenosine diphosphate (ADP), epinephrine, serotonin, thrombin, thromboxane A\textsubscript{2}, which in turn promote aggregation, recruitment, and further activation of circulating platelets. The α-granules contain fibrinogen, factor V and P-selectin. ADP binds to platelet P2Y\textsubscript{12} and P2Y1 receptors and by that amplifies the effect of other agonists such as thrombin [1–3]. Activation induces changes in platelet shape, increase of surface by pseudodopodia and secretion of further storage products. In the final step, GP IIb/IIIa is converted into its active form, which binds fibrinogen and vWF, leading to stable platelet aggregates and subsequent thrombus formation [4]. Additionally, the vascular injury exposes tissue factor which initiates the extrinsic clotting cascade and leads to generation of more thrombin and the propagation of the fibrin clot [5].

P2Y\textsubscript{12} receptor

The P2Y\textsubscript{12} receptor is a member of the P2Y purinergic G protein-coupled receptors (GPCR) family, which is activated by ADP, thromboxane A\textsubscript{2}, and the PAR-1 receptor agonists [6, 7]. Activation of the P2Y\textsubscript{1} receptor by ADP initiates a weak and transient phase of platelet aggregation whereas binding of ADP to the P2Y\textsubscript{12} amplifies dense granule secretion, expression of P-selectin and platelet aggregation [8]. Further stimulation of the P2Y\textsubscript{12} receptor sustains the activation of the GP IIb/IIIa and GP Ia/IIa receptors and stabilization of platelet aggregates [9, 10].

Corresponding author:
Jolanta Siller-Matula MD, PhD, Department of Cardiology, Medical University of Vienna, 1090 Vienna, Austria, phone: +43 1 40400 46140, fax: +43 1 40400 42160, e-mail: jolanta.siller-matula@meduniwien.ac.at
Received: 5.11.2015, accepted: 5.11.2015.
P2Y<sub>12</sub> receptor antagonism

Combination of aspirin with P2Y<sub>12</sub> receptor antagonists has been proven in a multitude of trials to have a favourable synergistic effect in patients after coronary stent implantation [11]. To date, ticlopidine, clopidogrel, prasugrel, ticagrelor and an intravenous compound, canagrelor, have been approved by the Food and Drug Administration (FDA) [1, 12, 13].

Ticlopidine

Ticlopidine, a first-generation thienopyridine, was the first FDA-approved P2Y<sub>12</sub> receptor inhibitor in clinical use [14]. It was the first drug that showed a decrease in major cardiovascular events in patients after stroke compared to aspirin or placebo, and in patients after percutaneous coronary intervention (PCI) compared to warfarin-based regimens [15]. Nevertheless, severe side effects like aplastic anaemia and agranulocytosis and slow onset of action limit the use of the compound and have led to the development of clopidogrel [16].

Clopidogrel

Clopidogrel, a second-generation thienopyridine-type irreversible inhibitor of the P2Y<sub>12</sub> receptor, has a more favourable safety profile compared to the ticlopidine. It is a pro-drug, requiring enteric and hepatic transformation by the cytochrome P450 (CYP) system to exert its antiplatelet effect. After absorption, up to 85% of clopidogrel is hydrolyzed by carboxyesterase-1 to an inactive metabolite, SR26334. The remaining approx. 15% of clopidogrel are metabolized to the active compound, R-130964, in a two-step process via formation of 2-oxo-clopidogrel. CYP 2C19 seems to have the most prominent role in this process, with less involvement of CYP2B6, CYP1A2, CYP3A/A5, and CYP2C9 [17, 18] (Figure 1). After administration of a 600 mg clopidogrel loading dose, the maximum achievable inhibition of ADP-induced platelet aggregation of 40–60% is achieved within 2 to 6 h [19].

Next generation P2Y<sub>12</sub> inhibitors

Despite the proven benefits of aspirin and clopidogrel, a non-negligible proportion of patients continue to experience recurrent ischemic events. These clinical failures have been attributed to response variability and to a relatively slow onset of action with clopidogrel and have prompted the development of new oral P2Y<sub>12</sub> inhibitors. Additionally, it has been shown that a moderate platelet inhibition by clopidogrel is insufficient to suppress an increase in ADP-induced platelet aggregation in the midmorning, in the period when myocardial infarction (MI), stroke and sudden cardiac death occur the most frequently [20–23]. Both prasugrel and ticagrelor have shown to have a more consistent, rapid and potent P2Y<sub>12</sub> receptor inhibition than clopidogrel, which translated into reduction in the ischemic events at the costs of bleeding events [12, 24–29].

Prasugrel

Prasugrel is a third generation thienopyridine, which acts as an irreversible inhibitor of the P2Y<sub>12</sub> receptor. Like clopidogrel, prasugrel is a pro-drug and requires hepatic bioactivation. The active metabolite is formed in a single-step oxidation via various CYP isoenzymes (CYP3A4/5, CYP2B6, CYP2C9, CYP2C9) [30] (Figure 1).

Ticagrelor

Ticagrelor is an antiplatelet agent that acts as an inhibitor of the P2Y<sub>12</sub> receptor without being a pro-drug. It is rapidly converted to the active metabolite in a rapid and irreversible manner. Ticagrelor has been shown to have a more rapid onset of action and a more potent antiplatelet effect compared to clopidogrel. The active metabolite is formed through a complex process involving multiple CYP isoenzymes, including CYP2C19, 2C9, 3A4/5, 2B6, and 2D6. Ticagrelor has been associated with a lower risk of bleeding compared to other P2Y<sub>12</sub> inhibitors, but it is more expensive and has a higher risk of gastrointestinal bleeding.

Figure 1. Metabolism of P2Y<sub>12</sub> receptor inhibitors

ADP – adenosine diphosphate, CYP – cytochrome 450.
P2Y12 receptors were identified on vascular smooth muscle cells. Therapy was associated with off-target effects [36]. Since the occurrence of MI, led to a hypothesis that ticagrelor, the PLATO trial, despite only a moderate decrease in clopidogrel [35].

Ticagrelor is active immediately after oral administration, which results in a more rapid onset of action and a more pronounced platelet inhibition compared to clopidogrel [34]. Ticagrelor is active immediately after oral administration, which results in a more rapid onset of action and a more pronounced platelet inhibition compared to clopidogrel [35].

The unprecedented mortality benefits observed in the PLATO trial, despite only a moderate decrease in the occurrence of MI, led to a hypothesis that ticagrelor therapy was associated with off-target effects [36]. Since P2Y12 receptors were identified on vascular smooth muscle cells (VSMCs), we and others have earlier demonstrated in animal and human models that ticagrelor, but not clopidogrel and prasugrel, prevents ADP-induced VSMC contraction [37]. Additionally, other groups have demonstrated that ticagrelor inhibited the uptake of adenosine by human erythrocytes [38] and also induced the release of adenosine triphosphate from human erythrocytes, that is, followed by its degradation to adenosine [39]. The former mechanism was proposed to explain the enhancement of adenosine-induced increase in coronary blood flow observed in a canine model by ticagrelor [38].

High on-treatment platelet reactivity

In clinical practice, antiplatelet drugs are administered to patients at standard doses, without monitoring their pharmacological response as it is done in case of warfarin therapy guided by INR-control [40]. This fixed-dose or better “one size fits all” approach with clopidogrel therapy is a remnant of clinical trials and does not take the inter-individual pharmacodynamic variability of ADP-pathway inhibitors into account [41]. Starting in 2003, studies suggested that the level of platelet inhibition, especially by clopidogrel, considerably varies between patients [41, 42].

Dependent on the assay used and the population studied, up to 25–50% of clopidogrel-treated patients fail to show adequate pharmacological response to clopidogrel and are not adequately protected from major adverse cardiac events (MACE) [43–45]. There is robust data showing an association between clopidogrel non-responsiveness or high on-treatment platelet reactivity (HPR) and adverse ischemic events, with the strongest association for short-term thrombotic events, like acute and subacute stent thrombosis, in patients after PCI [42, 46–55]. Nevertheless, the routine measurement of platelet reactivity has not been widely implemented and recommended in the guidelines. At least 40 studies demonstrated that ADP-induced platelet function testing is the best predictor of ischemic events in clopidogrel non-responders [54, 56–58]. Likewise, measurement of platelet function by light transmission aggregometry (LTA) in patients undergoing coronary stenting might predict adverse events [59–62]. Other tests, including the new generation impedance aggregometry test (Multiplate, MEA), VerifyNow™ and the vasodilator stimulated phosphoprotein (VASP) phosphorylation assay, have confirmed the association between poor clopidogrel responsiveness and increased risk of cardiac ischemic events during short- and long- term follow-up [46, 48, 63–69]. Nevertheless, lack of consensus concerning optimal method to quantify HPR and the best cut-off value associated with clinical risk has hindered the consideration of platelet function testing (PFT) in clinical guidelines. However, a recent analysis involving more than 20,000 patients after PCI tested uniformly-defined cutoff values for three relatively well-standardized assays (MEA, VerifyNow and VASP) and identified sharp cut points for HPR that were highly significant predictors of stent thrombosis and cardiovascular mortality [70].

Although new platelet aggregation inhibitors were invented to overcome HPR, it has been shown that this phenomenon is not exclusively true for clopidogrel treatment. In the acute phase of ST-elevation myocardial infarction (STEMI) 37% of the patients treated with prasugrel and 46% treated with ticagrelor exhibited HPR [69, 71–76]. Interestingly, a recent study has indicated that 12% of prasugrel-treated patients presented with the HPR phenotype [77], which might be explained by the fact that 43% of included patients displayed HPR under clopidogrel treatment and were switched to prasugrel [77]. Similarly, the TAILOR study as well as randomized trials in haemodialysis patients have shown that up to 20% of patients continued to exhibit HPR despite switch from clopidogrel to prasugrel [73, 74, 78]. Noteworthy, in the MADONNA study, direct switch to prasugrel from clopidogrel was associated with a satisfactory level of platelet inhibition by prasugrel in all patients [79]. Not surprisingly, however, the platelet inhibitory effect in patients treated with therapeutic hypothermia after cardiac arrest was reduced in prasugrel and ticagrelor treated patients reaching an incidence of HPR of 32% and 30%, respectively [80]. Interestingly, some studies indicated that in ACS patients with HPR while on clopidogrel ticagrelor produced stronger platelet inhibition compared with prasugrel [81]. Noteworthy, switching from ticagrelor main-
Max-Paul Winter et al. Personalized antiplatelet therapy with P2Y12 receptor inhibitors

Clinical factors associated with HPR

Drug-drug interactions, obesity, renal dysfunction, diabetes mellitus (DM), higher age, reduced left ventricular function, inflammation and the presence of an ACS are all associated with inadequate response to clopidogrel therapy and consequential HPR [85–90]. For further risk stratification, it has been suggested to use scoring systems that can integrate clinical risk factors and genetic variants identified by path models [91, 92].

Therefore, although the rate of HPR is lower with novel P2Y12-inhibitors, it is not an exclusive feature of clopidogrel. While clinical, genetic and demographic variables associated with HPR in clopidogrel-treated subjects are well defined and the worse clinical course in such patients is unquestionable, such factors and clinical impacts should be investigated and clarified in future trials in case of prasugrel and ticagrelor.

Figure 2. Effects of insulin on blood cells

PGE1 – prostaglandin E1, PG12 – prostaglandin I2, NO – nitric oxide, ADP – adenosine diphosphate, PAI-1 – plasminogen activator inhibitor 1.

Diabetes mellitus

Among all clinical risk factors accounting for HPR, DM has a unique position. DM is a strong independent predictor of short-term and long-term recurrent ischemic events and mortality in the ACS setting [105]. The reported negative impact on mortality includes all ACS subtypes and especially the increased risk for short-term ischemic events suggests an important role of platelet activation-aggregation.

It is well evidenced that platelets of DM patients exhibit an increased reactivity, caused by dysregulation of several signalling pathways by hyperglycaemia, insulin resistance, metabolic conditions and inflammation [106].

Direct insulin effect on platelets

In general, insulin exhibits anti-aggregatory effects and this antithrombotic effects are diminished in diabetic patients [107]. Insulin can exhibit direct anti-aggregatory effect via attenuation of the thrombin-induced Ca2+ response and the release of ADP as well as inhibition of the P2Y12 receptor [108, 109]. Furthermore, it enhances the platelet inhibitory effects of prostaglandin (PG) E1 and I2 (Figure 2) [110].

Hyperglycaemia

Hyperglycaemia has been shown to increase platelet reactivity in various ways (Figure 3). It induces P-selectin expression, alters membrane fluidity with subsequent platelet adhesion and activates protein C [106, 111]. In DM patients with ACS, glucose lowering therapy is proven beneficial independent of the treatment strategy [112, 113].

Insulin deficiency and resistance

Both insulin receptors and the insulin-like growth factor-1 (IGF-1) are expressed on thrombocytes. Binding of insulin to the platelets’ insulin receptor increases surface expression of adenylate cyclise-linked prostacyclin receptor, but due to the low Insulin receptor expression, the effect is negligible. IGF-1 is stored in the α-granules of platelets, which may contribute to the amplification of platelet aggregation after alpha granule release [114]. Other mechanisms how insulin resistance affect platelet aggregation include increased intracellular calcium with chanced platelet degranulation, impaired response to prostacyclin and nitric oxide [115, 116].
Metabolic conditions

The DM is often accompanied by obesity, dyslipidemia, and enhanced systemic inflammation, every single one of which may contribute to the increased platelet reactivity. Obesity may enhance platelet aggregation via similar pathomechanisms as insulin resistance: higher mean platelet volume, high blood leptin, increased intracellular calcium concentration [106].

HPR in diabetic patients

A multitude of trials have proven the benefit of clopidogrel in combination with aspirin in post-ACS DM patients. Nevertheless, HPR under clopidogrel therapy is more prevalent in diabetic compared with non-diabetic patients, especially in those requiring insulin therapy [105, 107]. Similar factors leading to increased platelet reactivity in DM patients also cause HPR to clopidogrel. To date, only small in vitro and ex vivo studies have identified the following factors to cause HPR: lack of response to insulin in platelets, changes in calcium metabolism, P2Y12 receptor signalling upregulation, increased exposure to ADP, and increased platelet turnover [106, 117, 118].

Another interesting mechanism for impaired P2Y12 inhibition mediated by clopidogrel among DM patients has been linked to attenuation of clopidogrel’s pharmacokinetics, which was characterized by lower plasma levels of clopidogrel active metabolite as compared with non-diabetic patients [119].

Low on-treatment platelet reactivity and the therapeutic window concept

Some studies postulated that there might be a therapeutic window for P2Y12 receptor blockers, indicating that while HPR is associated with thrombotic events, low on-treatment platelet reactivity (LPR) may be related to bleeding events [61, 64, 65, 120–122]. The two sides of the coin regarding P2Y12-inhibition, i.e. higher risk for thrombosis in HPR and higher risk for bleeding in LPR suggest that a sweet spot may exist for P2Y12-inhibition. Validation of such therapeutic window with patients having optimal platelet reactivity was recently reported in a collaborative analysis including more than 20,000 patients [70]. According to the results, patients with LPR had an absolute 1.2% lower risk for stent thrombosis and
2.7% lower risk for bleeding, compared to HPR and LPR, respectively [70].

Test systems used for assessment of the effect of antiplatelet drugs

The effect of clopidogrel on platelet function can be measured by platelet function testing and corresponds to the phenotype of its response. There are several test systems available for monitoring the effect of antiplatelet drugs, all characterizing different pathways of platelet activation, unfortunately with no option to reflect the complexity of platelet biology.

Platelet aggregometry

Platelet aggregometry is based on the stimulation of platelet aggregation with different agents. There are two commercially available techniques: optical and impedance aggregometry.

Light transmission aggregometry

Light transmission aggregometry (LTA) used to be the most widespread platelet function test. P2Y₁₂ receptor inhibition is measured by adding ADP and the change in the light transmittance is recorded. The maximal aggregation and the final aggregation responses can be measured and expressed as percentage (Table I). The widespread use and the reported good correlation between the measured aggregation responses and adverse events are the most important advantages of optical aggregometry. Time-consuming centrifugation steps as well as the large sample volume needed and variable reproducibility make this test less favourable. The proposed cutoff for HPR is > 70% of the maximal ADP-induced aggregation, but as LTA is not standardized according to the concentration of agonist, centrifuging time and speed, this sharp cut point is not generalizable for different centers. LTA is able to predict ischemic events with a sensitivity between 60–79%, with a specificity of 59–82% and an area under the receiver operating curve (AUC) of 0.73–0.85, and an odds ratio (OR) for ischemic events in the range of 3–35 [52, 56, 59, 123–125]. Additionally, LTA has been shown to predict stent thrombosis and bleeding events [47, 49, 51, 52].

Impedance aggregometry:

multiple electrode aggregometry

Multiple electrode aggregometry (MEA) is measuring whole blood platelet aggregation. ADP is used as agonist and, depending on the test, the antagonist PGE₁ may be added (high sensitivity ADP test (ADP-HS)). Changes in the electrical impedance caused by adhesion and aggregation of platelets on two independent electrode-set surfaces is measured and expressed as U (units) [100, 126, 127]. The cut-off values to separate patients with HPR in prior studies were around 46-50 U (Table II) [100, 126, 127]. MEA can predict stent thrombosis quite effectively (OR: 9–37; AUC: 0.78–0.92; sensitivity: 70–90% and specificity: 84–100%) [46, 48, 63]. Similarly to LTA, MEA has been shown to predict major bleedings (AUC: 0.61–0.74; sensitivity: 72–77% and specificity: 62–66%) [64, 65, 128, 129].

VASP phosphorylation

Measurement of VASP phosphorylation, that is a second messenger in one of the intracellular signalling pathways downstream of the P2Y₁₂ receptor, forms the basis of this assay (BioCytex, Marseille, France) [130, 131]. Serine 239-phosphorylated VASP is labelled with a monoclonal antibody followed by a secondary fluorescein isothiocyanate (FITC)-conjugated polyclonal goat-anti-mouse antibody and then measured using a flow cytometer. Platelet reactivity is expressed as platelet reactivity index (PRI%). Due to this unique technique, the VASP assay is highly reproducible even after 24 h of sample storage [90]. The VASP assay is the most specific assay for P2Y₁₂ signalling, because it evaluates the extent of P2Y₁₂ receptor inhibition without influencing the P2Y₁₂ receptor with agonist. The cut-off for VASP to separate patients with HPR is 50% (70) PRI [93]. A positive VASP test result corresponded to an OR = 1–23 [124, 131] to develop a stent thrombosis or MACE (AUC: 0.55–0.79) with high sensitivity (70–100%) [48, 132] but low specificity (25–37%) (Table III).

VerifyNow™

The VerifyNow™ assay (Accumetrics, San Diego, USA) measures the agonist-induced activation of platelets and their binding to fibrinogen-coated polystyrene beads. Once the platelets have bound to the beads, the platelet-bead complexes fall out of the solution and infrared-light transmittance increases. The assay uses ADP as agonist and PGE₁ as antagonist and results are reported as P2Y₁₂ reaction units (PRU) [133]. Beside the higher costs, the VerifyNow™ test shares the same advantages as the MEA, such as whole blood test condition, fast preparation time and small blood volume requirement. Although prior studies suggested 235 PRU to separate patients with HPR, data from the largest meta-analysis [70] and a sub-analysis of the GRAVITAS study suggest the benefit of a lower cutoff, 208 PRU (Table IV). VerifyNow™ has been shown to predict MACE (OR = 1–6.5; AUC: 0.56–0.87; sensitivity: 60–80% and specificity: 63–92%; Table IV) and major bleeding events (OR = 0.94; AUC = 0.84; sensitivity: 81% and specificity: 80%) [120, 134, 135] (Table IV).

Platelet Function Analyzer (PFA-100™)

The PFA-100™ (Dade Behring, Marburg, Germany) measures the time required for occlusion of a capillary tube by platelet aggregates (closure time – CT) under high shear rates (5000–6000 s⁻¹). To measure the effect of ADP antagonists, the membrane is coa-
Table I. Studies investigating the association of ischemic or bleeding events and clopidogrel response with use of light transmission aggregometry (LTA)

| Study author/acronym | Method/agonist  | N   | Population | Follow-up | Outcome | OR/HR | Cut-off value (%) | Prevalence of HPR/LPR (%) | AUC | PPV (%) | NPV (%) | Sensitivity (%) | Specificity (%) |
|----------------------|-----------------|-----|------------|-----------|---------|-------|-------------------|-----------------------------|-----|---------|---------|-----------------|-----------------|
| **Thrombosis**       |                 |     |            |           |         |       |                   |                             |     |         |         |                 |                 |
| Matetzky et al. [42] | LTA:ADP        | 60  | PCI + STEMI | 6 months  | MACE    | 6.00  | 103               | 25                          |     |         |         |                 |                 |
| Gurbe et al. [36]    | LTA:ADP        | 297 | Elective PCI| 2 years   | MACE    | 3.90  | 46                | 30                          | 0.77 | 63      | 82      |                 |                 |
| CREST [53]           | LTA:ADP        | 300 | History of ST vs. no ST | 6 months | MACE    | 2.60  | 60               |                             |     |         |         |                 |                 |
| PREPARE-POST STENTING [123] | LTA:ADP | 192 | Elective PCI | 6 months | MACE    | 2.70  | 67               | 25                          |     |         |         |                 |                 |
| CLEAR PLATELETS [62] | LTA:ADP        | 120 | Elective PCI | In hospital | Periprocedural MI | 50 |                   |                             |     |         |         |                 |                 |
| CLEAR PLATELETS-2 [58] | LTA:ADP | 100 | Elective PCI | In hospital | Periprocedural MI | 40 |                   |                             |     |         |         |                 |                 |
| Freer et al. [124]   | LTA:ADP        | 195 | NSTE-ACS + PCI | 1 month | MACE    | 8.00  | 70               | 27                          | 0.74 | 21      | 98      | 79               | 76               |
| Cuisset et al. [52]  | LTA:ADP        | 598 | NSTE-ACS + PCI | 1 month | ST     | 5.80  | 67               | 0.70                          | 4   | 99      | 70      | 68               |                 |
| Cuisset et al. [187] | LTA:ADP        | 306 | NSTE-ACS + PCI | 1 month | MACE    | 22.40 | 70               | 25                          |     |         |         |                 |                 |
| Cuisset et al. [54]  | LTA:ADP        | 190 | NSTEMI + PCI | In hospital | Periprocedural MI | 1.80 | 70               | 22                          |     |         |         |                 |                 |
| POPULAR [59]         | LTA:ADP        | 1049 | Elective PCI | 1 year | MACE    | 2.09  | 43               | 42                          | 0.73 | 12      | 94      | 60               | 59               |
| POPULAR [188]        | LTA:ADP        | 921  | Elective PCI | 1 year | MACE    | 2.65  | 43               | 15                          |     |         |         |                 |                 |
| Bliden et al. [125]  | LTA:ADP        | 100  | Elective PCI | 1 year | MACE    | 34.60 | 50               | 22                          | 0.86 | 73      | 91      |                 |                 |
| Lev et al. [57]      | LTA:ADP        | 150  | Elective PCI | In hospital | Myonecrosis | 1.87 | 70               | 24                          |     |         |         |                 |                 |
| Gori et al. [51]     | LTA:ADP        | 746  | PCI + DES   | 6 months | ST     | 3.15  | 70               | 12                          |     |         |         |                 |                 |
| Geisler et al. [189] | LTA:ADP        | 379  | PCI         | 3 months | MACE, death | 4.90 | 70               | 6                           |     |         |         |                 |                 |
| Geisler et al. [47]  | LTA:ADP        | 1019 | PCI         | 3 months | ST     | 2.21  | 42.5              | 33                          |     |         |         |                 |                 |
| Geisler et al. [86]  | LTA:ADP        | 1092 | PCI         | 1 month | MACE    | 1.71  | 47               | 33                          |     |         |         |                 |                 |
| EXCELSIOR [60]       | LTA:ADP        | 802  | Elective PCI | 1 month | MACE    | 6.70  | 32               | 25                          |     |         |         |                 |                 |
| EXCELSIOR [190]      | LTA:ADP        | 797  | Elective PCI | 1 year | MACE    | 3.0   | 34               | 27                          |     |         |         |                 |                 |
| Buonamici et al. [49] | LTA:ADP | 804 | PCI + DES   | 6 months | ST     | 3.08  | 70               | 13                          |     |         |         |                 |                 |
| Migliorini et al. [50] | LTA:ADP | 215 | PCI         | 3 years | CD, ST  | 3.82  | 70     | 19                          |     |         |         |                 |                 |
| Wang et al. [191]    | LTA:ADP        | 386  | Elective PCI + DES | 1 year | MACE    | 2.44  | 10 difference | 17                          |     |         |         |                 |                 |
| Wenaweser et al. [192] | LTA:ADP | 82   | History of ST vs. no ST | Case/control | 10 difference | 10 difference | | | | | | |
| **Bleeding**         |                 |     |            |           |         |       |                   |                             |     |         |         |                 |                 |
| Parodi et al. [61]   | LTA:ADP        | 298  | PCI + prasugrel | 6 months | TIMI major bleeding | 0.91 | 40               | 32                          |     |         |         |                 |                 |
| Chen et al. [193]    | LTA:ADP        | 45   | Surgery under clopidogrel | Blood transfusion | | | | | | | | |

ADP – adenosine diphosphate, AUC – area under the curve (of the receive operating curve – c-index), PPV – positive predictive value, NPV – negative predictive value, HPR – high platelet reactivity (prevalence is given for studies investigating thrombotic events), LPR – low platelet reactivity (prevalence is given for studies investigating bleeding events), PCI – percutaneous coronary intervention, NSTE-ACS – non ST-elevation acute coronary syndrome, STEMI-ST – elevation myocardial infarction, MACE – major adverse cardiac events, MI – myocardial infarction, ST – stent thrombosis, DES – drug eluting stent, CD – cardiac death, TIMI – thrombolysis in myocardial infarction, NS – not significant.
Table II. Studies investigating the association of ischemic or bleeding events and clopidogrel response with use of Multiplate Electrode Aggregometry (MEA)

| Study author/acronym | Method/agonist | N   | Population       | Follow-up | Outcome | OR/HR | Cut-off value | Prevalence of HPR/LPR (%) | AUC (PPV) (%) | NPV (NPV) (%) | Sensitivity (%) | Specificity (%) |
|----------------------|---------------|-----|------------------|-----------|---------|-------|--------------|---------------------------|---------------|---------------|----------------|-----------------|
| **Thrombosis**       |               |     |                  |           |         |       |              |                           |               |               |                |                 |
| Sibbing et al. [46]  | MEA:ADP       | 1608| Elective PCI     | 1 month   | ST      | 9.40  | 468AU*min = 47 U | 20                        | 0.78          | 70            | 84             |                 |
| Sibbing et al. [64, 65] | MEA:ADP   | 2533| Elective PCI     | 1 month   | ST      | 0.40  | 468AU*min = 47 U | 17                        |               |               |                |                 |
| Eshtehardi et al. [66]| MEA:ADP       | 219 | PCI              | 1 month   | MACE    |       | 309AU*min = 31 U | 15                         |               |               |                |                 |
| Müller-Schunk et al. [94] | MEA:ADP       | 50  | Neurointerventional stent | ST + TIA/ stroke |       |       | 52 U | 28                        |               |               |                |                 |
| Sibbing et al. [64, 65] | MEA:ADP   | 403 | PCI              | 1 year    | MACE    | 1.75  | 48 U | 19                        | 0.60          |               |                |                 |
| PEGASUS-PCI [63]     | MEA:ADP + PGE1 | 416 | PCI              | 1 year    | ST, MACE | 46 U | 38             | 0.78 7 100 70 67       |               |               |                |                 |
| Dineva et al. [67]   | MEA:ADP       | 603 | PCI              | 1 month   | ST      | 24.3  | 46 U | 18                        | 0.86          | 84            | 78             |                 |
| Siller-Matula et al. [48] | MEA:ADP + PGE1 | 416 | PCI              | 6 months  | ST      | 54 U | 14             | 0.92 5 100 86 100       |               |               |                |                 |
| PEGASUS-PCI [63]     | MEA:ADP + PGE1 | 416 | PCI              | 1 year    | ST, MACE | 36.9 | 48 U | 19                        | 0.90 13 100 90 83 |               |               |                |                 |
| **Bleeding**         |               |     |                  |           |         |       |              |                           |               |               |                |                 |
| Rahe-Meyer et al. [128]| MEA:ADP      | 60  | Cardiac surgery  | In hospital | Blood transfusion | 13 U | 33             | 0.74          | 77            | 63             |                 |
| Sibbing et al. [64, 65] | MEA:ADP   | 2533| PCI              | In hospital | TIMI major bleeding | 3.50 | 188AU*min = 19 U | 38                        | 0.61          | 2             | 99            | 62              |
| Ranucci et al. [129] | MEA:ADP       | 87  | Thienopyridine treatment | In hospital | Postoperative bleeding | 31 U | 40             | 0.71 29 92 72 66       |               |               |                |                 |
| PEGASUS-PCI [63]     | MEA:ADP + PG  | 416 | PCI              | 1 year    | TIMI major bleeding | Ns   | 20 U |                        |               |               |                |                 |

ADP – adenosine diphosphate, PGE1 – prostaglandin E1, AUC – area under the curve of the receiver operating curve – c-index, PPV – positive predictive value, NPV – negative predictive value, HPR – high platelet reactivity (prevalence is given for studies investigating thrombotic events), LPR – low platelet reactivity (prevalence is given for studies investigating bleeding events), PCI – percutaneous coronary intervention, MACE – major adverse cardiac events, ST – stent thrombosis, TIA – transient ischemic attack, TIMI – thrombolysis in myocardial infarction, NS – not significant.
Table III. Studies investigating the association of ischemic or bleeding events and clopidogrel response with use of vasodilator activated phosphoprotein assay (VASP)

| Study author/acronym | Method/agonist | $N$ | Population | Follow-up | Outcome | OR/HR | Cut-off value (%) | Prevalence of HPR/LPR (%) | AUC | PPV (%) | NPV (%) | Sensitivity (%) | Specificity (%) |
|----------------------|----------------|-----|------------|-----------|---------|-------|------------------|----------------------------|-----|---------|---------|----------------|----------------|
| **Thrombosis**       |                |     |            |           |         |       |                  |                            |     |         |         |                |                |
| Bonello et al. [132] | VASP assay     | 144 | PCI        | 6 months  | MACE    | 50    | 20               | 0.55                        | 100 | 100     | 25      |                |                |
| Bonello et al. [69]  | VASP assay     | 301 | ACS + PCI + prasugrel | 1 month | MACE    | 23.0  | 53.5             | 0.86                        | 92  | 88      | 77      |                |                |
| Siller-Matula et al. [48] | VASP assay | 416 | PCI        | 6 months  | ST      | NS    | 42               | 0.60                        | 1   | 100     | 100     | 37              |                |
| PEGASUS-PCI [63]     | VASP assay     | 416 | PCI        | 1 year    | MACE + ST | NS   | 42               | 0.62                        | 3   | 98      | 70      | 38              |                |
| Blindt et al. [131]  | VASP assay     | 99  | PCI at high ST risk | 6 months | ST      | 1.16  | 48               | 0.79                        | 80  | 73      |         |                |                |
| Freer et al. [124]   | VASP assay     | 195 | NSTE-ACS + PCI | 1 month | MACE    | 11.18 | 53               | 0.73                        | 12  | 99      | 93      | 50              |                |
| Barragan et al. [196]| VASP assay     | 46  | History of ST vs. no ST | 1 month | ST      |       |                  |                            |     |         |         |                |                |
| Cuisset et al. [52]  | VASP assay     | 598 | NSTE-ACS + PCI | 1 month | NS      |       |                  |                            |     |         |         |                |                |
| WILMAA [68]          | VASP assay     | 300 | PCI        | 6 months  | MACE    | 1.04  | 60               | 0.68                        | 8   | 99      | 94      | 37              |                |
| **Bleeding**         |                |     |            |           |         |       |                  |                            |     |         |         |                |                |
| Cuisset et al. [197] | VASP           | 597 | NSTEMI + PCI | 1 month | TIMI bleeding non-CABG related | 40 | 25               |                            |     |         |         |                |                |
| Mokhtar et al. [121] | VASP           | 346 | PCI        | In hospital | TIMI major bleeding non-CABG | 0.96 |                  |                            |     |         |         |                |                |
| Michelson et al. [71] | VASP          | 125 | ACS + PCI  | 3 days after PCI | Serious bleedings | 0.97 | 50               |                            |     |         |         |                |                |

AUC – area under the curve (of the receiver operating curve – c-index), PPV – positive predictive value, NPV – negative predictive value, PCI – percutaneous coronary intervention, NSTE-ACS – non ST-elevation acute coronary syndrome, MACE – major adverse cardiac events, ST – stent thrombosis, TIMI – thrombolysis in myocardial infarction, CABG – coronary artery bypass graft, HPR – high platelet reactivity (prevalence is given for studies investigating thrombotic events), LPR – low platelet reactivity (prevalence is given for studies investigating bleeding events), NS – not significant.
lagen/adenosine diphosphate (CADP) or collagen/ADP/PG1. To date, there is conflicting data concerning the reproducibility of the test [136–138]. The normal value for CADP-CT in treatment of naïve patients is 65–120 s [136]. Only small studies revealed the usefulness of the device for prediction of MACE (OR = 3–33) in clopidogrel users [139–142], but other studies found no association with clinical outcomes [59]. A closure time ≤ 72s has a sensitivity of 86%, and specificity of 76% [142] to detect ischemic events (Table V).

Cone and Platelet Analyzer
The Cone and Platelet Analyzer (DiaMed, Cressier, Switzerland) tests thrombocyte adhesion and aggregation under shear stress [143]. Adherent platelets are stained under flow conditions, the percentage of surface coverage (SC) and the average size (AS) of the objects are determined [144]. The variability is relatively low (< 5%). To date, no study could show that the CPA is sensitive enough to predict ischemic events in clopidogrel-treated patients (AUC: 0.53–0.62; Table V).

Plateletworks
The Plateletworks (Helena Laboratories, Beaumont, Texas) is based on counting platelets before and after ADP agonist incubation. The ratio between the aggregated platelets after stimulation and the platelet count in the reference tube is used as the degree of platelet aggregation [59]. One study investigated the predictive value of Plateletworks for ischemic events. In the POPULAR study, the Plateletworks assay predicted the composite of major ischemic events with a sensitivity of 63%, specificity of 59% und the AUC of 0.61 (Table V) [59].

Thrombelastography (TEG)
The TEG haemostasis analyser (Haemoscope Corp., Niles, Illinois) only measures platelet-fibrin clot strength and is therefore insensitive to P2Y12 inhibition and aspirin effect. P2Y12 receptor inhibitions can be measured only in modified protocols (Table V) [123, 125, 127, 145].

Limitations of platelet function testing
It is well known that technical factors, like type of anticoagulant or agonist used, time delay and pipetting errors, can influence the results of platelet testing [146, 147].

Beside all technical obstacles related to the procedure itself we must not forget that all these ex vivo tests do not reproduce the complexity of thrombocyte activation in vivo. Moreover, those tests ignore other platelet activating factors during ACS that might influence outcome, such as cytokines or other paracrine factors [148]. Because of this fact, one cannot assume that an in vitro observed clopidogrel effect will show the same efficacy in vivo, but vice versa one can prove at least the pharmacological efficacy, because if a drug fails to block ADP-in-
### Table V. Studies investigating the association of ischemic events and clopidogrel response with use of Cone and Platelet Analyzer (CPA), Plateletworks, Thromboelastography (TAG) or Platelet Function analyser 100 (PFA 100)

| Study author/acronym | Method/agonist | N    | Population | Follow-up | Outcome | OR/HR | Cut-off value | Prevalence of HPR (%) | AUC | PPV (%) | NPV (%) | Sensitivity (%) | Specificity (%) |
|----------------------|---------------|------|------------|-----------|---------|-------|---------------|----------------------|-----|---------|---------|---------------|----------------|
| **Thrombosis**       |               |      |            |           |         |       |               |                      |     |         |         |               |                |
| Matetzky et al. [42] | CPA           | 60   | PCI + STEMI | 6 months | MACE    | 6.00  | 9% difference | 25                   |     |         |         |               |                |
| POPULAR [59]         | CPA           | 910  | Elective PCI| 1 year   | MACE    | NS    | 8.4%          | 47                   | 0.56| 7       | 90      | 56            | 53             |
| POPULAR [59]         | CPA:ADP       | 905  | Elective PCI| 1 year   | MACE    | NS    | 3%           | 54                   | 0.53| 8       | 91      | 44            | 54             |
| PEGASUS-PCI [63]     | CPA:ADP       | 416  | PCI         | 1 year   | ST, MACE| NS    | 4.6%          | 61                   | 0.62| 3       | 98      | 90            | 36             |
| POPULAR [59]         | Plateletworks | 606  | Elective PCI| 1 year   | MACE    | 2.22  | 80.5%         | 43                   | 0.61| 13      | 94      | 63            | 59             |
| PREPARE-POST STENTING [123] | TEG:ADP    | 192  | Elective PCI| 6 months | MACE    | 22.60 | 67%           | 25                   | 0.88| 67      | 94      |               |                |
| Bliden et al. [125]  | TEG:ADP       | 100  | Elective PCI| 1 year   | MACE    | 26.80 | 70%           | 22                   | 0.88| 67      | 94      |               |                |
| POPULAR [59]         | PFA100:CADP   | 812  | Elective PCI| 1 year   | MACE    | NS    | 116 s         | 44                   | 0.50| 5       | 93      | 63            | 44             |
| PEGASUS-PCI [63]     | PFA100:CADP   | 416  | PCI         | 1 year   | ST, MACE| NS    | 105 s         | 38                   | 0.66| 4       | 98      | 70            | 61             |
| Chiu et al. [141]    | PFA100:CADP   | 144  | PCI         | 2 years  | MACE    | 5.3   | 95 s          |                      |     |         |         |               |                |
| Campo et al. [142]   | PFA100:CADP   | 135  | STEMI + PCI | 2 years  | MACE    | 4.5   | 72 s          | 0.85                 | 8.6 | 76      |         |               |                |
| Gianetti et al. [139]| PFA100:CADP   | 175  | ACS or CAD  | 6 months | MACE    | 22.9  | 82 s          | 25                   |     |         |         |               |                |
| Fuchs et al. [140]   | PFA100:CADP   | 208  | ACS         | 28 months| MACE    | 3.2   | 73 s          | 25                   |     |         |         |               |                |
| POPULAR [59]         | PFA100:Innovance | 588 | Elective PCI| 1 year   | MACE    | 299 s | 30            | 0.56                 | 5   | 90      | 61      | 29            |                |

ADP – adenosine diphosphate, CADP – collagen-adenosine diphosphate, HPR – high platelet reactivity, AUC – area under the curve (of the receiver operating curve – c-index), PPV – positive predictive value, NPV – negative predictive value, PCI – percutaneous coronary intervention, ACS – acute coronary syndrome, STEMI-ST – elevation myocardial infarction, MACE – major adverse cardiac events, ST – stent thrombosis, DES – drug eluting stent, CAD – coronary artery disease, NS – not significant.
duced aggregation in vitro, it will also fail in vivo. For that reason, platelet function assays cannot overcome the uncertainty of antithrombotic therapy efficacy in all patients.

It should be emphasized that the consensus regarding the optimal cut-off for HPR is necessary as well as standardization of methods before platelet function testing is introduced in clinical practice.

Genes associated with the response variability to clopidogrel

Cytochrome P450 genetic polymorphisms

Due to its complex metabolism, P2Y12 inhibitors involve multiple genes in absorption, activation, and inhibition of the receptor. Those detected gene variants have been shown to be associated with both bleeding and ischemic events.

Although CYP2C9 has an integral role in clopidogrel metabolism, the sparse data do not support the genotyping for CYP2C9*3 for prediction of events [87, 149].

CYP2C19*2 (loss of function allele), the most common known allele with 30% of Caucasians and up to 50% Asian being carriers, is associated with a reduced antiplatelet effect of clopidogrel and increased risk for adverse cardiovascular events [87, 150–154]. Although the CYP2C19*2 allele accounts only for 5–12% of the variation in the response to clopidogrel, several studies have shown an influence of CYP2C19*2 on clinical outcome [91, 95, 154–156]. Platelet function studies have shown a gene-dose effect in carriers of this polymorphism, showing that increase of dosage led to a sufficient level of platelet inhibition in heterozygous patients, whereas most homozygous patients failed to respond despite daily doses of 300 mg clopidogrel (Table VI) [157].

Due to a relatively low allele frequency (<1%), other identified CYP2C19 variants (*3–*8) have only a minor impact on HPR [149, 158, 159].

In contrast to CYP2C19*2, CYP2C19*17 is a gain of function mutation leading to intensified activation of clopidogrel and so-called ultra-metabolizers with exaggerated bioactivation of clopidogrel. Data on whether there is an association of CYP2C19*17 with haemorrhagic events is conflicting, and to date not convincing [120, 155, 156, 160, 161].

ABCB1

Thienopyridine absorption is mediated via the intestinal efflux transport pump P-glycoprotein encoded by the ABCB1 gene (MDR1). The influence of different ABCB1 alleles is unclear. Some studies have shown that patients harbouring genetic variants in ABCB1 (specifically homozygous for the C3435T variant), have lower levels of the active compound and higher rates of adverse clinical outcomes (Table VI). However, this finding could not be confirmed in several subsequent studies. Further studies are needed to clarify the impact of this gene on the antiplatelet effect of clopidogrel [34, 162, 163].

PON1

PON1 QQ192, a genetic variant in the gene encoding for the paraoxonase 1 (PON1) enzyme was linked to lower clopidogrel active metabolite concentrations in one study [164], which however was not confirmed in the following studies [91, 150, 165–167] (Table VI).

ITGB3

ITGB3 that encodes the integrin β3 of the GP Iib/IIa receptor has been linked with response variability of clopidogrel treatment and the risk of stent thrombosis [87]. Again, these results are challenged by another study that could not confirm these observations [158].

P2Y12

Genetic variations for the gene encoding the binding site for clopidogrel active metabolite on the P2Y12 receptor have shown a reduced efficacy of clopidogrel, but the clinical importance is doubtful [87, 158, 168].

IRS-1

Polymorphism of the insulin receptor substrate (IRS)-1 have been shown to be associated with hyperactive platelets and increased risk for ischemic events in patients with type 2 DM and stable coronary artery disease [169].

Studies investigating personalized antiplatelet treatment

The last decades of clopidogrel use have raised concerns that the “one dose fits all” approach is questionable in P2Y12-treated patients. There are numerous studies that linked HPR on clopidogrel to adverse ischemic events and gave credit to the need of platelet inhibition testing in case of clopidogrel. In multiple trials, it has been observed that ADP-antagonist induced platelet inhibition can be improved with increased clopidogrel loading and maintenance doses or simply by switching to novel compounds like prasugrel or ticagrelor. For example, increase to 150 mg maintenance dose of clopidogrel resulted in more intense inhibition of platelet aggregation than administration of the standard 75 mg dose in a subset of patients [170–172]. Nevertheless, it must be emphasized that increase in dosage is not sufficient in a number of patients, as it has been shown that even 900 mg loading doses of clopidogrel did not overcome HPR to clopidogrel in homozygous CYP2C19*2 allele carriers [157]. Adjusted loading doses of clopidogrel according to platelet monitoring were shown to achieve a reduction of MACE without an increase of bleeding complications,
| Study author/acronym | Polymorphism | N    | Population                  | Follow-up | Outcome | OR/HR | Prevalence (%) carriers | Prevalence (%) homozygote | Prevalence (%) heterozygote |
|----------------------|--------------|------|-----------------------------|-----------|---------|-------|-------------------------|---------------------------|---------------------------|
| Thrombosis: CYP2C19*2, *3, *4, *5 |
| AFIJI [152]          | 2C19*2       | 259  | MI (< 45 years of age)      | 6 months  | MACE    | 3.69  | 28                      | 0                         | 25                        |
| AFIJI [150]          | 2C19*2       | 371  | MI (< 45 years of age)      | 6 years   | MACE    | 2.26  | 31                      | 4                         | 26                        |
| TRITON TIMI-38 [153] | 2C19*2       | 1477 | PCI + ACS                   | 15 months | MACE    | 1.53  | 34                      |                           |                           |
| Oh et al. [202]      | 2C19*2       | 2146 | PCI + DES                   | 1 year    | MACE    | 2.62  | 47                      |                           |                           |
| Shuldiner et al. [154]| 2C19*2      | 227  | Elective PCI                | 1 year    | MACE    | 2.42  | 33                      | 2                         | 31                        |
| RECLOSE [151]        | 2C19*2       | 772  | PCI                         | 6 months  | ST      | 3.43  | 32                      | 3                         | 29                        |
| Harmsze et al. [149] | 2C19*2       | 176/420 | PCI (ST case/control) | 1 year    | ST      | 17    | 40                      | 5                         | 35                        |
| Sibbing et al. [203] | 2C19*2       | 2485 | PCI                         | 30 days   | ST      | 3.81  | 27                      | 2                         | 25                        |
| Sibbing et al. [165] | 2C19*2       | 127/1439 | PCI (ST case/control) | 30 days   | ST      | 2.27  | 25                      | 2                         | 23                        |
| ONASSIST [87]        | 2C19*2       | 123/246 | PCI (ST case/control) | ST        | NS      | 1.99  | 49                      | 16                        | 33                        |
| Harmsze et al. [96]  | 2C19*2       | 725  | Elective PCI                | 1 year    | MACE    | NS    | 31                      | 3                         | 28                        |
| Campo et al. [120]   | 2C19*2       | 300  | PCI                         | 1 year    | MACE    | NS    | 27                      | 2                         | 25                        |
| CHARISMA [156]       | 2C19*2       | 4819 | CAD or at high risk         | 2 years   | MACE    | NS    | 15                      |                           |                           |
| Tiroch et al. [204]  | 2C19*2       | 928  | MI                          | 1 year    | MACE    | NS    | 27                      | 2                         | 25                        |
| Sawada et al. [205]  | 2C19*2       | 300  | PCI + DES                   | 8 months  | MACE    | NS    | 42                      |                           |                           |
| Tello-Montolii et al. [206]| 2C19*2   | 428  | NSTE-ACS                    | 6 months  | MACE    | NS    | 28                      | 3                         | 25                        |
| Malek et al. [207]   | 2C19*2       | 261  | ACS                         | 1 year    | Death   | NS    | 21                      | 2                         | 19                        |
| PEGASUS-PCI [63]     | 2C19*2       | 436  | PCI                         | 1 year    | ST      | NS    | 20                      | 2                         | 18                        |
| Jeong et al. [159]   | 2C19*2 and *3| 266  | MI                          | 1 year    | MACE    | 2.81  | 45                      | 8                         | 37                        |
| FAST-MI [158]        | 2C19*2,3,4,5 | 2208 | PCI + MI                    | 1 year    | MACE    | 1.98  | 28                      | 2                         | 26                        |
| Yamamoto et al. [208] | 2C19*2 or *3| 123  | CAD                         | 12 months | MACE    | NS    | 44                      | 11                        | 33                        |
| CURE and ACTIVE [209]| 2C19*2 or *3 | 5059 | ACS or AF                   | 1 year    | MACE    | NS    | 20                      | 2                         | 18                        |
| PLATO [210]          | 2C19*2-*8    | 10285 | ACS                         | 30 days   | MACE    | 1.37  | 20                      | 2                         | 38                        |
| Harmsze et al. [149] | 2C9*3        | 176/420 | PCI (ST case/control) | 1 year    | ST      | 2.4   | 16                      | 1                         | 15                        |
| ONASSIST [87]        | 2C9*3        | 123/246 | PCI (ST case/control) | ST        | NS      | 17    | 0                       | 0                         | 17                        |
| Harmsze et al. [149] | CYP3A4*1B    | 176/420 | PCI (ST case/control) | 1 year    | ST      | NS    | 9                       | 2                         | 7                         |
| Suhr et al. [31]     | CYP3A5*3     | 348  | PCI                         | 6 months  | MACE    | 4.89  | 45                      |                           |                           |
| Harmsze et al. [149] | CYP3A5*3     | 176/420 | PCI (ST case/control) | ST        | NS      | 13    | 0                       | 0                         | 13                        |
| FAST-MI [158]        | CYP3A5*3     | 2208  | PCI + MI                    | 1 year    | MACE    | NS    | 17                      | 1                         | 16                        |
| Campo et al. [120]   | CYP3A5*3     | 300  | PCI                         | 1 year    | MACE    | NS    | 13                      | 1                         | 12                        |
| ONASSIST [87]        | CYP3A5*3     | 123/246 | PCI (ST case/control) | ST        | NS      | 20    | 4                       | 16                        | 36                        |
### Table VI. Cont.

| Study author/acronym | Polymorphism | N | Population | Follow-up | Outcome | OR/HR | Prevalence (%): carriers | Prevalence (%): homozygote | Prevalence (%): heterozygote |
|----------------------|--------------|---|------------|-----------|---------|-------|--------------------------|---------------------------|-----------------------------|
| **Bleeding: CYP2C19*17** |             |   |            |           |         |       |                          |                           |                             |
| Sibbing et al. [160]  | 2C19*17      | 1524 | PCI        | 30 days   | TIMI major bleeding | 1.8   | 41 | 5 | 36                         |
| Campo et al. [120]    | 2C19*17      | 300  | PCI        | 1 year    | TIMI major bleeding | 2.3   | 34 | 6 | 28                         |
| Harmsse et al. [212]  | 2C19*17      | 820  | Elective PCI | 1 year  | TIMI major bleeding | 2.7   |       |               |                             |
| Jeong et al. [159]    | 2C19*17      | 266  | MI         | 1 year    | TIMI major bleeding | NS    | 1  | 0 | 1                         |
| PLATO [210]           | 2C19*17      | 10285 | ACS       | 1 year    | Major bleeding     | 1.25  | 32 | 5 | 27                         |
| CURE and ACTIVE [209] | 2C19*17      | 5059 | ACS or AF  | 1 year    | Major bleeding     | NS    | 34 | 22 | 23                         |
| CHARISMA [156]        | 2C19*17      | 4819 | CAD or at high risk | 2 years | GUSTO severe bleeding | NS    | 22 | 4 | 30                         |
| PEGASUS-PCI [63]      | 2C19*17      | 436  | PCI        | 1 year    | TIMI major bleeding | NS    | 34 | 4 | 30                         |
| **Thrombosis: PON1**  |             |   |            |           |         |       |                          |                           |                             |
| Bouman et al. [164]   | PON1         | 1982 | ACS        | 1 year    | ST       | 12.80 | 54 | 13 | 41                         |
| EXCELSIOR [166]       | PON1         | 760  | Elective PCI | 1 year  | MACE     | NS    | 50 | 10 | 40                         |
| Sibbing et al. [165]  | PON1         | 127/1439 | PCI (ST case/control) | 30 days | ST | NS | 47 | 8 | 39                         |
| Campo et al. [163]    | PON1         | 300  | PCI        | 1 month   | MACE     | NS    | 76 | 27 | 49                         |
| Simon et al. [167]    | PON1         | 2210 | MI         | 1 year    | MACE     | NS    | 55 | 15 | 40                         |
| AFII [150]            | PON1         | 371  | M1 (< 45 years of age) | 6 years | MACE     | NS    | 72 | 41 | 29                         |
| **Thrombosis: ABCB1** |             |   |            |           |         |       |                          |                           |                             |
| TRITON TIMI 38 [213]  | ABCB1        | 2932 | ACS + PCI  | 15 months | MACE     | 1.72  | 73 | 23 | 50                         |
| FAST-MI [158]         | ABCB1        | 2208 | PCI + MI   | 1 year    | MACE     | 1.72  | 74 | 26 | 48                         |
| ONASSIST [87]         | ABCB1        | 123/246 | PCI (ST case/control) | ST | NS | 77 | 25 | 52                         |
| Jaitner et al. [162]  | ABCB1        | 66/1408 | PCI (ST case/control) | ST | NS | 78 | 29 | 49                         |
| Campo et al. [163]    | ABCB1        | 300  | PCI        | 1 year    | MACE     | NS    | 76 | 27 | 49                         |
| Harmsse et al. [149]  | ABCB1        | 176/420 | PCI (ST case/control) | ST | NS | 68 | 14 | 54                         |
| Jeong et al. [159]    | ABCB1        | 266  | MI         | 1 year    | MACE     | NS    | 54 | 13 | 41                         |
| Spiewak et al. [214]  | ABCB1        | 98   | ACS + PCI  | 1.7 years | MACE     | NS    | 72 | 21 | 51                         |
| Tioch et al. [204]    | ABCB1        | 928  | MI         | 12 months | MACE     | NS    | 82 | 29 | 49                         |
| **Thrombosis: ITGB3, P2Y12, IRS-1** |             |   |            |           |         |       |                          |                           |                             |
| ONASSIST [87]         | ITGB3        | 123/246 | PCI (ST case/control) | ST | NS | 16 | 0 | 36                         |
| FAST-MI [158]         | ITGB3        | 2208 | PCI + MI   | 1 year    | MACE     | NS    | 29 | 2 | 27                         |
| Ziegler et al. [215]  | P2Y12        | 137  | PAD        | 2 years   | Neurological event | 4.02 | 31 | 4 | 27                         |
| FAST-MI [158]         | P2Y12        | 2208 | PCI + MI   | 1 year    | MACE     | NS    | 25 | 3 | 25                         |
| ONASSIST [87]         | P2Y12        | 123/246 | PCI (ST case/control) | ST | NS | 32 | 5 | 27                         |
| Angiolillo et al. [169]| IRS-1        | 187  | DM + CAD   | 2 years   | MACE     | 2.88  | 31 | NN | NN                         |

AF – atrial fibrillation, PCI – percutaneous coronary intervention, NSTE-ACS – non ST-elevation acute coronary syndrome, MACE – major adverse cardiac events, MI – myocardial infarction, ST – stent thrombosis, PAD – periphery artery disease, DES – drug eluting stent, CAD – coronary artery disease, TIMI – thrombolysis in myocardial infarction, DM – diabetes mellitus, NS – not significant.
however this strategy is not as sufficient as switch to prasugrel or ticagrelor [79, 173, 174]. Concordant with this, intensified platelet inhibition with GP IIb/IIIa antagonists could be used as a “bridging strategy” at the time point of PCI [175] and showed to lower the incidence of MACE without increased in-hospital bleeding rates in smaller studies [176, 177].

Most importantly, three randomized clinical trials (ARCTIC, n = 2,440; GRAVITAS, n = 2,200; and TRIGGER-PCI, n = 423) investigated if the outcome can be influenced using individualized antiplatelet strategy. In the GRAVITAS trial, clopidogrel treated patients with HPR received either standard dosing of clopidogrel or a second clopidogrel loading dose of 600 mg plus a maintenance dose of 150 mg. Within the 6-month follow-up, no significant differences in event rates could be shown in this patient population with a low-to-moderate thrombotic risk [178]. The TRIGGER-PCI trial compared prasugrel versus clopidogrel in patients with low thrombotic risk. The trial had to be stopped prematurely, because an interim analysis indicated a lower than expected incidence of the primary endpoint. Therefore, no meaningful conclusions may be drawn regarding clinical events from this study [179]. The ARCTIC trial included patients with low to moderate thrombotic risk with planned coronary stenting, that were randomised to bedside platelet function monitoring versus no monitoring. In the monitoring arm, antiplatelet therapy was intensified by increasing the dose of aspirin or an additional loading dose followed by an increased maintenance dose of clopidogrel, by additional treatment with a GP IIb/IIIa inhibitor or by switching to prasugrel. Adjustment of antiplatelet therapy based on platelet function monitoring did not lead to any improvement in the composite endpoint of coronary ischemic events [180].

There are several possible explanations why these trials failed to show improved clinical outcome. Firstly, the three trials (GRAVITAS, TRIGGER-PCI, ARCTIC) only included low-to-moderate risk patients, whereas STEMI patients with a much higher ischemic risk were excluded. Moreover, in ARCTIC and GRAVITAS trials, only a minority of patients included had a non-ST-elevation-ACS (NSTE-ACS), whereas the TRIGGER-PCI trial included only patients with elective drug-eluting stent implantation during PCI and without procedural complications [179]. It is likely that exclusion of high-risk patients may have accounted in part for the negative study results. Based on these findings one can argue that intensified antiplatelet treatment might not be beneficial in patients with a low-to-moderate risk for thrombotic events, but improve outcome in higher-risk patients or in those with a high risk for stent thrombosis [181]. In line with this assumption, Aradi et al. could prove in a meta-regression analysis that the net clinical benefit of intensified P2Y$_{12}$ inhibition depends on the baseline risk for stent thrombosis [182]. This meta-analysis including 10 randomized trials with more than 4000 patients also proved that the intensified antiplatelet treatment was associated with a significant reduction in cardiovascular mortality, stent thrombosis and MI [182]. The net clinical benefit of a personalized antiplatelet treatment also has been shown in the MADONNA study [79, 183]. Similarly, individualisation of dual antiplatelet therapy minimised early thrombotic events in an all-comers PCI population without increasing bleeding in an IDEAL registry [184].

**Individualised antiplatelet therapy – algorithm approach**

Due to the lack of prospective double-blind randomised studies demonstrating an improvement in clinical outcome by personalised antiplatelet therapy, there is no recommendation regarding a routine approach of individualised antiplatelet therapy. To date, there is only a class IIb recommendation for platelet function testing to facilitate the choice of P2Y$_{12}$ inhibitor in selected patients on clopidogrel at high risk for thrombotic events [185].

The novel platelet inhibitors prasugrel and ticagrelor have been shown to be superior concerning platelet inhibition and reduction of thrombotic events and for that it is feasible to use those compounds in all ACS patients, especially those at high risk. Nevertheless the ACC/AHA guidelines recommend either clopidogrel or ticagrelor or prasugrel in interventionally managed ACS (all of them received a class IB recommendation) and because of that an individualized antiplatelet therapy is conceivable. For that purpose it might be useful to use an algorithm for personalised antiplatelet therapy in patients who are at high thrombotic risk. This global risk algorithm is based on clinical (PREDICT score), biological (platelet function) and genetic (CYP2C19*2 carrier status) information [186].

Nevertheless, this algorithm has not been tested prospectively yet.

**Conclusions**

Although the tailored antiplatelet treatment monitored by platelet function testing seems to be feasible, the contradictory results of smaller registry studies and larger randomized trials with regards to outcome leave a big uncertainty. It is tempting to speculate that the different study populations, follow-ups, treatment strategies, study endpoints or time-points of blood sampling and therapy adjustment might disguise the real effect of tailored treatment [181]. Therefore, further research is needed to define:

i) patient populations, which would benefit from the tailored antiplatelet strategy in terms of net clinical outcome,

ii) which time points of platelet function testing are most predictive for outcome,

iii) whether multiple testing is necessary,

iv) whether genotyping adds useful information,

v) how tailored antiplatelet strategy should be applied to patients with bleeding events,
vi) whether algorithm based approach to tailored antiplatelet strategy is feasible and improves net clinical outcome.

Conflict of interest
The authors declare no conflict of interest.

References
1. Franchi F, Angiolillo DJ. Novel antiplatelet agents in acute coronary syndrome. Nat Rev Cardiol 2015; 12: 30-47.
2. Raju NC, Eikelboom JW, Hirsh J. Platelet ADP-receptor antagonists for cardiovascular disease: past, present and future. Nat Clin Pract Cardiovasc Med 2008; 5: 766-80.
3. Davi G, Patrono C. Platelet activation and atherothrombosis. N Engl J Med 2007; 357: 2482-94.
4. Varga-Szabo D, Pleines I, Nieswandt B. Cell adhesion mechanisms in platelets. Arterioscler Thromb Vasc Biol 2008; 28: 403-12.
5. Monroe DM, Hoffman M, Roberts HR. Transmission of a procoagulant signal from tissue factor-bearing cell to platelets. Blood Coagul Fibrinolysis 1996; 7: 459-64.
6. Dorsam RT, Kunapuli SP. Central role of the P2Y12 receptor in platelet activation. J Clin Invest 2004; 113: 340-5.
7. Zhang K, Zhang J, Gao ZG, et al. Structure of the human P2Y12 receptor in complex with an antithrombotic drug. Nature 2014; 509: 109-18.
8. Rollini F, Franchi F, Angiolillo DJ. Switching P2Y-receptor inhibitors in patients with coronary artery disease. Nat Rev Cardiol 2015 Aug 18. doi: 10.1038/nrcardio.2015.113.
9. Gachet C. ADP receptors of platelets and their inhibition. Thromb Haemost 2001; 86: 222-32.
10. Ostrowska M, Adamski P, Kozinski M, et al. Off-target effects of glycoprotein lib/ila receptor inhibitors. Cardiol J 2014; 21: 458-64.
11. Siller-Matula JM, Delle-Karth G, Christ G, et al. Dual non-responsiveness to antiplatelet treatment is a stronger predictor of cardiac adverse events than isolated non-responsiveness to clopidogrel or aspirin. Int J Cardiol 2013; 167: 430-5.
12. Siller-Matula JM, Krumphuber J, Ilmia B. Pharmacokinetic, pharmacodynamic and clinical profile of novel antiplatelet drugs targeting vascular disease. Br J Pharmacol 2009; 159: 502-17.
13. Kubicz J, Kozinski M, Navarese EP, et al. Cangrelor: an emerging therapeutic option for patients with coronary artery disease. Curr Med Res Opin 2014; 30: 813-28.
14. Angiolillo DJ. The evolution of antiplatelet therapy in the treatment of acute coronary syndromes: from aspirin to the present day. Drugs 2012; 72: 2087-116.
15. Sharis PJ, Cannon CP, Loscalzo J. The antiplatelet effects of ticlopidine and clopidogrel. Ann Intern Med 1998; 129: 394-405.
16. Oto K, Kurohara K, Yoshihara M, et al. Agranulocytosis caused by ticlopidine and its mechanism. Am J Hematol 1991; 37: 239-42.
17. Huber K. Genetic variability in response to clopidogrel therapy: clinical implications. Eur Hear J 2010; 31: 2974-2976.
18. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, et al. Variability in individual responsiveness to clopidogrel: clinical implications, management, and future perspectives. J Am Coll Cardiol 2007; 49: 1505-16.
19. Jakubowski JA, Matsushima N, Asai F, et al. A multiple dose study of prasugrel (CS-747), a novel thienopyridine P2Y12 inhibitor, compared with clopidogrel in healthy humans. Br J Clin Pharmacol 2007; 63: 421-30.
20. Kozinski M, Bielis L, Wisniewska-Szmyt J, et al. Diurnal variation in platelet inhibition by clopidogrel. Platelets 2011; 22: 579-87.
21. Kasprzak M, Kozinski M, Bielis L, et al. Pantoprazole may enhance antiplatelet effect of enteric-coated aspirin in patients with acute coronary syndrome. Cardiol J 2009; 16: 535-44.
22. Navarese EP, Buffon A, Kozinski M, et al. A critical overview on ticagrelor in acute coronary syndromes. QJM 2013; 106: 105-15.
23. Kubicz A, Kasprzak M, Siller-Matula J, et al. Time-related changes in determinants of antiplatelet effect of clopidogrel in patients after myocardial infarction. Eur J Pharmacol 2014; 742: 47-54.
24. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009; 361: 1045-57.
25. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007; 357: 2001-15.
26. Jakubowski JA, Riesmeyer JS, Close SL, et al. TRITON and beyond: new insights into the profile of prasugrel. Cardiovasc Ther 2012; 30: e174-82.
27. Navarese EP, Verdia M, Schaffer A, et al. Ischaemic and bleeding complications with new, compared to standard, ADP-antagonist regimens in acute coronary syndromes: a meta-analysis of randomized trials. QJM 2011; 104: 561-9.
28. Siller-Matula JM, Petre A, Delle-Karth G, et al. Impact of preoperative use of P2Y12 receptor inhibitors on clinical outcomes in cardiac and non-cardiac surgery: a systematic review and meta-analysis. Eur Heart J Acute Cardiovasc Care 2015 May 5; doi: 10.1177/2048872615585516.
29. Gouya G, Arrich J, Wolzt M, et al. Antiplatelet treatment for prevention of cerebrovascular events in patients with vascular diseases: a systematic review and meta-analysis. Stroke 2014; 45: 492-503.
30. Schror K, Siller-Matula JM, Huber K. Pharmacokinetic basis of the antiplatelet action of prasugrel. Fundam Clin Pharmacol 2012; 26: 39-46.
31. Sugidachi A, Ogawa T, Kurihara A, et al. The greater in vivo antiplatelet effects of prasugrel as compared to clopidogrel reflect more efficient generation of its active metabolite with similar antiplatelet activity to that of clopidogrel’s active metabolite. J Thromb Haemost 2007; 5: 1545-51.
32. Kozinski M, Obonska K, Stankowska K, et al. Prasugrel overcomes high on-clopidogrel platelet reactivity in the acute phase of acute coronary syndrome and maintains its antiplatelet potency at 30-day follow-up. Cardiol J 2014; 21: 547-56.
33. Oprea AD, Popescu WM. P2Y12 receptor inhibitors in acute coronary syndromes: what is new on the horizon? Cardiol Res Pract 2013; 2013: 195456.
34. Wallentin L, James S, Storey RF, et al. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. Lancet 2010; 376: 1320-8.
35. Kowalczyk M, Banach M, Milhailidis DP, et al. Ticagrelor: a new platelet aggregation inhibitor in patients with acute coronary syndromes. An improvement of other inhibitors? Med Sci Monitor 2009; 15: MS24-30.
36. Adamski P, Kozinski M, Ostrowska M, et al. Overview of pleiotropic effects of platelet P2Y12 receptor inhibitors. Thromb Haemost 2014; 112: 224-42.
37. Grzesk G, Kozinski M, Navarese EP, et al. Ticagrelor, but not clopidogrel and prasugrel, prevents ADP-induced vascular smooth
muscle cell contraction: a placebo-controlled study in rats. Thromb Res 2012; 130: 65-9.

38. van Giezen JJ, Sidiayw J, Glaes P, Kirk I, Bjorkman JA. Ticagrelor inhibits adenosine uptake in vitro and enhances adenosine-mediated hyperemia responses in a canine model. J Cardiovasc Pharmacol Ther 2012; 17: 164-72.

39. Ohman J, Kudira R, Albinsson S, Olde B, Erlinge D. Ticagrelor induces adenosine triphosphate release from human red blood cells. Biochem Biophys Res Commun 2012; 418: 754-8.

40. Cattaneo M. High on-treatment platelet reactivity: definition and measurement. Thromb Haemost 2013; 109: 792-8.

41. Gurbel PA, Bilden KP, Hiatt BL, O’Connor CM. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. Circulation 2003; 107: 2908-13.

42. Matetzky S, Shenkman B, Guetta V, et al. Clopidogrel resistance is associated with increased risk of recurrent atherothrombotic events in patients with acute myocardial infarction. Circulation 2004; 109: 3171-5.

43. Tantry US, Bonello L, Aradi D, et al. Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. J Am Coll Cardiol 2013; 62: 2261-73.

44. Siller-Matula JM, Trenk D, Schror K, et al. Response variability to P2Y12 receptor inhibitors: expectations and reality. JACC Cardiovasc Interv 2013; 6: 1111-28.

45. Komosa A, Siller-Matula JM, Kowal J, et al. Comparison of the antiplatelet effect of two clopidogrel bisulfate formulations: pla-vix and generic-Egitromb. Platelets 2015; 26: 43-7.

46. Sibbing D, Braun S, Morath T, et al. Platelet reactivity after clopidogrel treatment assessed with point-of-care analysis and early drug-eluting stent thrombosis. J Am Coll Cardiol 2009; 53: 849-56.

47. Geisler T, Elke Schaeffeler E, Gawaz M, Schwab M. Genetic variation of platelet function and pharmacology: an update of current knowledge. Thromb Haemost 2013; 110: 876-87.

48. Gurbel PA, Antonino MJ, Bilden KP et al. Platelet reactivity to adenosine diphosphate and long-term ischemic event occurrence following percutaneous coronary intervention: a potential anti-platelet therapeutic target. Platelets 2008; 19: 595-604.

49. Lev EI, Patel RT, Maresh KJ, 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.

50. Gurbel PA, Bilden KP, Saucedo JF, et al. Bivalirudin and clopidogrel with and without epifibatide for elective stenting: effects on platelet function, thrombelastographic indexes, and their relation to periprocedural infarction results of the CLEAR PLATELETS-2 (Clopidogrel with Epifibatide to Arrest the Reactivity of Platelets) study. J Am Coll Cardiol 2009; 53: 648-57.

51. Breet NJ, van Werkum JW, Bouman HJ, et al. Comparison of platelet function tests in predicting clinical outcome in patients undergoing coronary stent implantation. JAMA 2010; 303: 754-62.

52. Hochholzer W, Trenk D, Bestehorn HP, 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: 1742-50.

53. Parodi G, Bellandi B, Venditti F, et al. Residual platelet reactivity, bleedings, and adherence to treatment in patients having coronary stent implantation treated with prasugrel. Am J Cardiol 2012; 109: 214-8.

54. Gurbel PA, Bilden KP, Zaman KA, et al. Clopidogrel loading with epifibatide to arrest the reactivity of platelets: results of the Clopidogrel Loading With Epifibatide to Arrest the Reactivity of Platelets (CLEAR PLATELETS) study. Circulation 2005; 111: 1153-9.

55. Siller-Matula JM, Delle-Karth G, Lang IM, et al. Phenotyping versus genotyping for prediction of clopidogrel efficacy and safety: the PEGASUS-PCI study. J Thromb Haemost 2012; 10: 529-42.

56. Sibbing D, Steinhuhl SR, Schulz S, et al. Platelet aggregation and its association with stent thrombosis and bleeding in clopidogrel-treated patients: initial evidence of a therapeutic window. J Am Coll Cardiol 2010; 56: 317-8.

57. Sibbing D, Schulz S, Braun S, et al. Antiplatelet effects of clopidogrel and bleeding in patients undergoing coronary stent placement. J Am Coll Cardiol 2010; 56: 275-83.

58. Esthehardt R, Windecker S, Cook S, et al. Dual low response to acetylsalicylic acid and clopidogrel is associated with myocardial and stent thrombosis after coronary stent implantation. Am Heart J 2010; 159: 891-8 e1.

59. Dineva D, Paskaleva I, Gotcheva N, et al. Assessment of platelet response with Multiplate impedance aggregometry in patients with coronary stents on Clopidogrel and aspirin treatment. Bulgarska Kardiologija 2011; 17: 16-25.

60. Freynhofer MK, Brozovic I, Bruno V, et al. Multiple electrode aggregometry and vasodilator stimulated phosphoprotein-phosphorylation assay in clinical routine for prediction of postprocedural major adverse cardiovascular events. Thromb Haemost 2011; 106: 230-9.

61. Bonello L, Pansieri M, Mancini J, et al. High on-treatment platelet reactivity after prasugrel loading dose and cardiovascular events after percutaneous coronary intervention in acute coronary syndromes. J Am Coll Cardiol 2011; 58: 467-73.

62. Aradi D, Kirtane A, Bonello L, et al. Bleeding and stent thrombosis on P2Y12-Inhibitors: collaborative analysis on the role of
platelet reactivity for risk stratification after percutaneous coronary intervention. Eur Heart J 2015; 36: 1762-71.

71. Michelson AD, Frelinger AL 3rd, Braunwald E, et al. Pharmacodynamic assessment of platelet inhibition by prasugrel vs. clopidogrel in the TRITON-TIMI 38 trial. Eur Heart J 2009; 30: 1753-63.

72. Bonello L, Mancini I, Pansieri M, et al. Relationship between post-treatment platelet aggregation and ischemic and bleeding events at one year follow-up in patients receiving prasugrel. J Thromb Haemost 2012; 10: 1999-2005.

73. Alexopoulos D, Xanthopoulou I, Davlouros P, et al. Prasugrel overcomes high on-clopidogrel platelet reactivity in chronic coronary artery disease patients more effectively than high dose (150 mg) clopidogrel. Am Heart J 2011; 162: 733-9.

74. Alexopoulos D, Panagiotou A, Xanthopoulou I, et al. Antiplatelet effects of prasugrel vs double clopidogrel in patients on hemodialysis and high on-treatment platelet reactivity. J Thromb Haemost 2011; 9: 2379-85.

75. Alexopoulos D, Xanthopoulou I, Gkizas V, et al. Randomized assessment of ticagrelor versus prasugrel antiplatelet effects in patients with ST-segment-elevation myocardial infarction. Circ Cardiovasc Interv 2012; 5: 797-804.

76. Parodi G, Valenti R, Bellandi B, et al. Comparison of prasugrel and ticagrelor loading doses in ST-segment-elevation myocardial infarction patients: RAPID (Rapid Activity of Platelet Inhibitor Drugs) primary PCI study. J Am Coll Cardiol 2013; 61: 1601-6.

77. Mayer K, Orban M, Bernlochner I, et al. Predictors of antiplatelet response to prasugrel during maintenance treatment. Platelets 2015; 26: 53-8.

78. Dridi NP, Johansson PI, Clemmensen P, et al. Prasugrel or double-dose clopidogrel to overcome clopidogrel low-response – The TAILOR (Thrombocytes And Individualization of ORal anti-platelet therapy in percutaneous coronary intervention) randomized trial. Platelets 2014; 25: 506-12.

79. Siller-Matula JM, Francesconi M, Dechant C, et al. Predictors of antiplatelet treatment after percutaneous coronary intervention: the MADONNA study. Int J Cardiol 2013; 167: 2018-23.

80. Ibrahim K, Christoph M, Schmeinck S, et al. High rates of prasugrel and ticagrelor non-responder in patients treated with therapeutic hypothermia after cardiac arrest. Resuscitation 2014; 85: 649-56.

81. Alexopoulos D, Galati A, Xanthopoulou I, et al. Ticagrelor versus prasugrel in acute coronary syndrome patients with high on-clopidogrel platelet reactivity following percutaneous coronary intervention: a pharmacodynamic study. J Am Coll Cardiol 2012; 60: 193-9.

82. Angiolillo DJ, Curzen N, Gurbel P, et al. Pharmacodynamic evaluation of switching from ticagrelor to prasugrel in subjects with stable coronary artery disease: results of the SWAP-2 Study. J Am Coll Cardiol 2014; 63: 1500-9.

83. Deharo P, Bassez C, Bonnet G, et al. Prasugrel versus ticagrelor in acute coronary syndrome: a randomized comparison. Int J Cardiol 2013; 170: e21-2.

84. Tomizawa A, Ohno K, Jakubowski J, et al. Comparison of antiplatelet effects of prasugrel and ticagrelor in cynomolgus monkeys by an ELISA-based VASP phosphorylation assay and platelet aggregation. Thromb Haemost 2013; 110: 769-76.

85. Angiolillo DJ. Antiplatelet therapy in diabetes: efficacy and limitations of current treatment strategies and future directions. Diabetes Care 2009; 32: 531-40.

86. Geisler T, Grass D, Bigalke B, et al. The residual platelet aggregation after deployment of intracoronary stent (PREDICT) score. J Thromb Haemost 2008; 6: 54-61.

87. Cayla G, Hulot JS, O’Connor SA, et al. Clinical, angiographic, and genetic factors associated with early coronary stent thrombosis. JAMA 2011; 306: 1765-74.

88. Neubauer H, Kaiser AF, Endres HG, et al. Tailored antiplatelet therapy can overcome clopidogrel and aspirin resistance: the BOchum Clopidogrel and Aspirin Plan (BOCLA-Plan) to improve antiplatelet therapy. BMC Med 2011; 9: 3.

89. Htu R, Fateh-Moghadam S, Bischofs C, et al. Low responsiveness to clopidogrel increases risk among CKD patients undergoing coronary intervention. J Am Soc Nephrol 2011; 22: 627-33.

90. Muller K, Aichele S, Herkommer M, et al. Impact of inflammatory markers on platelet inhibition and cardiovascular outcome including stent thrombosis in patients with symptomatic coronary artery disease. Atherosclerosis 2010; 213: 256-62.

91. Siller-Matula JM, Lang IM, Neunteufl T, et al. Interplay between genetic and clinical variables affecting platelet reactivity and cardiac adverse events in patients undergoing percutaneous coronary intervention. PLoS One 2014; 9: e102701.

92. Droppa M, Tschernow D, Muller KA, et al. Evaluation of clinical risk factors to predict high on-treatment platelet reactivity and outcome in patients with stable coronary artery disease (PREDICT-STABLE). PLoS One 2015; 10: e021620.

93. Siller-Matula JM, Lang I, Christ G, Jilma B. Calcium-channel blockers reduce the antiplatelet effect of clopidogrel. J Am Coll Cardiol 2008; 52: 1557-63.

94. Harmsze AM, Robijns K, van Werkum JW, et al. The use of amiodipine, but not of P-glycoprotein inhibiting calcium channel blockers is associated with clopidogrel poor-response. Thromb Haemost 2010; 103: 920-5.

95. Hochholzer W, Trenk D, Fromm MF, et al. Impact of cytochrome P450 2C19 loss-of-function polymorphism and of major demographic characteristics on residual platelet function after loading and maintenance treatment with clopidogrel in patients undergoing elective coronary stent placement. J Am Coll Cardiol 2010; 55: 2427-34.

96. Harmsze AM, van Werkum JW, Souverein PC, et al. Combined influence of proton-pump inhibitors, calcium-channel blockers and CYP2C19*2 on on-treatment platelet reactivity and on the occurrence of atherothrombotic events after percutaneous coronary intervention. J Thromb Haemost 2011; 9: 1892-901.

97. Gilard M, Arnaud B, Cornily JC, et al. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole Clopidogrel Aspirin) study. J Am Coll Cardiol 2008; 51: 256-60.

98. Cuisset T, Fiere C, Quillici J, et al. Comparison of omeprazole and pantoprazole influence on a high 150-mg clopidogrel maintenance dose the PACA (Proton Pump Inhibitors And Clopidogrel Association) prospective randomized study. J Am Coll Cardiol 2009; 54: 1149-53.

99. Siller-Matula JM, Jilma B, Schror K, et al. Effect of proton pump inhibitors on clinical outcome in patients treated with clopidogrel: a systematic review and meta-analysis. J Thromb Haemost 2010; 8: 2624-41.

100. Siller-Matula JM, Spiel AO, Lang IM, et al. Effects of pantoprazole and esomeprazole on platelet inhibition by clopidogrel. Am Heart J 2009; 157: 148.e1-5.

101. Teng R. Pharmacokinetic, pharmacodynamic and pharmacogenetic profile of the oral antiplatelet agent ticagrelor. Clin Pharmacokinet 2012; 51: 305-18.
102. Siller-Matula JM, Trenk D, Krahnebuhl S, et al. Clinical implications of drug-drug interactions with P2Y12 receptor inhibitors. J Thromb Haemost 2014; 12: 2-13.

103. Hobl EL, Stimpfl T, Ebner J, et al. Morphine decreases clopidogrel concentrations and effects: a randomized, double-blind, placebo-controlled trial. J Am Coll Cardiol 2014; 63: 630-5.

104. Kubica J, Adamski P, Ostrowska M, et al. Morphine delays ticagrelor exposure and action in patients with myocardial infarction: the randomized, double-blind, placebo-controlled IMPRESSION trial. Eur Heart J 2015 Oct 21; doi: 10.1093/eurheartj/ehv547

105. Roffi M, Chew DP, Mukherjee D, et al. Platelet glycoprotein Ib/IIa inhibitors reduce mortality in diabetic patients with non-ST-segment-elevation acute coronary syndromes. Circulation 2001; 104: 2767-71.

106. Ferreiro JL, Angiolillo DJ. Diabetes and antiplatelet therapy in acute coronary syndrome. Circulation 2011; 123: 798-813.

107. Angiolillo DJ, Bernardo E, Ramirez C, 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.

108. Fleming I, Schulz C, Fichtlscherer B, et al. AMP-activated protein kinase (AMPK) regulates the insulin-induced activation of the nitric oxide synthase in human platelets. Thromb Haemost 2003; 90: 863-71.

109. Ferreira IA, Mocking AI, Feijge MA, et al. Platelet dysfunction in type 2 diabetes. Arterioscler Thromb Vasc Biol 2006; 26: 417-22.

110. Vinik AI, Erbas T, Park TS, et al. Platelet dysfunction in type 2 diabetes. Diabetes Care 2001; 24: 1476-85.

111. Assert R, Scherl G, Bumbure A, et al. Regulation of protein kinase C by short term hyperglycaemia in human platelets in vivo and in vitro. Diabetologia 2001; 44: 188-95.

112. Malmberg K. Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study Group. BMJ 1997; 314: 1512-5.

113. Malmberg K, Ryden L, Wedel H, et al. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. Eur Heart J 2005; 26: 650-61.

114. Hirs I. Insulin-like growth factor-1 potentiates platelet activation via the IRS/PI3Kalpha pathway. Blood 2007; 110: 4243-52.

115. Ishida M, Ishida T, Ono N, et al. Effects of insulin on calcium metabolism and platelet aggregation. Hypertension 1996; 28: 209-12.

116. Betteridge DJ, El Tahir KE, Reckless JP, Williams KL. Platelets from diabetic subjects show diminished sensitivity to prostacyclin. Eur J Clin Invest 1982; 12: 395-8.

117. Li Y, Woo V, Bose R. Platelet hyperactivity and abnormal Ca(2+) homeostasis in diabetes mellitus. Am J Physiol Heart Circ Physiol 2001; 280: H1480-9.

118. Michno A, Bielarczyk H, Pawelczyk T, et al. Alterations of adenine nucleotide metabolism and function of blood platelets in patients with diabetes. Diabetes 2007; 56: 462-7.

119. Angiolillo DJ, Jakubowski JA, Ferreiro JL, et al. Impaired responsiveness to the platelet P2Y12 receptor antagonist clopidogrel in patients with type 2 diabetes and coronary artery disease. J Am Coll Cardiol 2014; 64: 1005-14.

120. Campo G, Parrinello G, Ferraresi P, et al. Prospective evaluation of on-clopidogrel platelet reactivity over time in patients treated with percutaneous coronary intervention relationship with gene polymorphisms and clinical outcome. J Am Coll Cardiol 2011; 57: 2474-83.

121. Mokhtar OA, Lemesle G, Armero S, et al. Relationship between platelet reactivity inhibition and non-CABG related major bleeding in patients undergoing percutaneous coronary intervention. Thromb Res 2010; 126: e147-9.

122. Cuisset T, Grosdidier C, Loudou AD, et al. Clinical implications of very low on-treatment platelet reactivity in patients treated with thienopyridine: the POBA study (predictor of bleedings with antiplatelet drugs). JACC Cardiovasc Interv 2013; 6: 854-63.

123. Gurbel PA, Bledin KF, Guyer K, et al. Platelet reactivity in patients and recurrent events post-stenting: results of the PREPARE POST-STEMING Study. J Am Coll Cardiol 2005; 46: 1820-6.

124. Frere C, Cuisset T, Quilici J, et al. ADP-induced platelet aggregation and platelet reactivity index VASP are good predictive markers for clinical outcomes in non-ST elevation acute coronary syndrome. Thromb Haemost 2007; 98: 838-43.

125. Bledin KF, Dichiara J, Tantry US, 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: 657-66.

126. Sibbing D, Braun S, Jawansky S, et al. Assessment of ADP-induced platelet aggregation with light transmission aggregometry and multiple electrode platelet aggregation before and after clopidogrel treatment. Thromb Haemost 2008; 99: 121-6.

127. Scharbert G, Auer A, Kozek-Langenecker S. Evaluation of the platelet mapping assay on rotational thromboelastometry ROTEM. Platelets 2009; 20: 125-30.

128. Rahe-Meyer N, Winterhalter M, Boden A, et al. Platelet concentrates transfusion in cardiac surgery and platelet function assessment by multiple electrode aggregometry. Acta Anaesthesiol Scand 2009; 53: 168-75.

129. Ranucci M, Baryshnikova E, Soro G, et al. Multiple electrode whole-blood aggregometry and bleeding in cardiac surgery patients receiving thienopyridines. Ann Thorac Surg 2011; 91: 129-9.

130. Siller-Matula J, Schror K, Wojta J, Huber K. Thienopyridines in cardiovascular disease: focus on clopidogrel resistance. Thromb Haemost 2007; 97: 385-93.

131. Blinda R, Stellbrink K, de Taeye A, et al. The significance of vasodilator-stimulated phosphoprotein for risk stratification of stent thrombosis. Thromb Haemost 2007; 98: 1329-34.

132. Bonello L, Paganeli F, Arpin-Bornet M, et al. Vasodilator-stimulated phosphoprotein phosphorylation analysis prior to percutaneous coronary intervention for exclusion of postprocedural major adverse cardiovascular events. J Thromb Haemost 2007; 5: 1630-6.

133. Jakubowski JA, Payne CD, Li YG, et al. The use of the VerifyNow P2Y12 point-of-care device to monitor platelet function across a range of P2Y12 inhibition levels following prasugrel and clopidogrel administration. Thromb Haemost 2008; 99: 409-15.

134. Price MJ, Endemann S, Gollapudi RR, et al. Prognostic significance of post-clopidogrel platelet reactivity assessed by a point-of-care assay on thrombotic events after drug-eluting stent implantation. Eur Heart J 2008; 29: 992-1000.

135. Marcucci R, Gori AM, Paniccia R, et al. Cardiovascular death and nonfatal myocardial infarction in acute coronary syndrome pa-
tients receiving coronary stenting are predicted by residual platelet reactivity to ADP detected by a point-of-care assay: a 12-month follow-up. Circulation 2009; 119: 237-42.

136. Jilma B. Platelet function analyzer (PFA-100): a tool to quantify congenital or acquired platelet dysfunction. J Lab Clin Med 2001; 138: 152-63.

137. Madsen EH, Schmidt EB, Maurer-Spurej E, Kristensen SR. Effects of aspirin and clopidogrel in healthy men measured by platelet aggregation and PFA-100. Platelets 2008; 19: 335-41.

138. Grove EL, Hvas AM, Johnsen HL, et al. A comparison of platelet function tests and thromboxane metabolites to evaluate aspirin response in healthy individuals and patients with coronary artery disease. Thromb Haemost 2010; 103: 1245-53.

139. Gianetti J, Parri MS, Sbrana S, et al. Platelet activation predicts recurrent ischemic events after percutaneous coronary angioplasty: a 6-months prospective study. Thromb Res 2006; 118: 487-93.

140. Fuchs I, Frossard M, Spiel A, et al. Platelet function in patients with acute coronary syndrome (ACS) predicts recurrent ACS. J Thromb Haemost 2006; 4: 2547-52.

141. Chiu FC, Wang TD, Lee JK, et al. Prognostic value of serial platelet reactivity measurements on long-term clinical outcome in patients with ST-elevation myocardial infarction undergoing primary PCI. J Thromb Haemost 2008; 6: 1826-41.

142. Campo G, Valgimigli M, Frangione A, et al. Relationship between cytochrome P450 2C19 genetic polymorphisms and response to clopidogrel. Eur J Intern Med 2011; 22: 471-7.

143. Panzer S, Eichelberger B, Koren D, et al. Monitoring survival and function of transfused platelets in Bernard-Soulier syndrome by flow cytometry and a cone and plate(let) analyzer (Impact-R). Transfusion 2007; 47: 103-6.

144. Varon D, Lider O, Dardik R, et al. Inhibition of integrin-mediated platelet aggregation, fibrinogen-binding, and interactions with extracellular matrix by nonpeptidic mimetics of Arg-Gly-Asp. J Thromb Haemost 2006; 4 Suppl. 1: 230-7.

145. Craft RM, Chavez JJ, Bresee SJ, et al. A novel modification of the Thrombelastograph assay, isolating platelet function, correlates with optical platelet aggregation. J Lab Clin Med 2004; 143: 301-9.

146. Cattaneo M. Resistance to antiplatelet drugs: molecular mechanisms and laboratory detection. J Thromb Haemost 2007; 5 Suppl. 1: 230-7.

147. Sumaya W, Daly RL, Mehra S, et al. No association of ABCB1 C3435T genotype with clopidogrel response or risk of stent thrombosis in patients undergoing coronary stenting. J Thromb Haemost 2011; 4: 585-94.

148. Schror K, Huber K, Hohlfeld T. Functional testing methods for the antiplatelet effects of aspirin. Biomark Med 2011; 5: 31-42.

149. Harmsse AM, van Werkum JW, Ten Berg JM, et al. CYP2C19*2 and CYP2C9*3 alleles are associated with stent thrombosis: a case-control study. Eur Heart J 2010; 31: 3046-53.

150. Hulot JS, Collet JP, Cayla G, et al. CYP2C19 but not PON1 genetic variants influence clopidogrel pharmacokinetics, pharmacodynamics, and clinical efficacy in post-myocardial infarction patients. Circ Cardiovasc Interv 2011; 4: 422-8.

151. Giusti B, Gori AM, Marcucci R, et al. Relation of cytochrome P450 2C19 loss-of-function polymorphism to occurrence of drug-eluting coronary stent thrombosis. Am J Cardiol 2009; 103: 806-11.

152. Collet JP, Hulot JS, Pena A, et al. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. Lancet 2009; 373: 309-17.

153. Mega JL, Close SL, Vivriott SD, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. N Engl J Med 2009; 360: 354-62.

154. Shuldiner AR, O’Connell JR, Bliden KP, et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. JAMA 2009; 302: 849-57.

155. Siller-Matula JM, Delle-Karth G, Lang IM, et al. Phenotyping vs. genotyping for prediction of clopidogrel efficacy and safety: the PEGASUS-P CI-study. J Thromb Haemost 2012; 10: 529-42.

156. Simon T, Verstuyft C, Mary-Krause M, et al. Genetic determinants of response to clopidogrel and cardiovascular events. N Engl J Med 2009; 360: 363-75.

157. Jaitner J, Morath T, Byrne RA, et al. No association of ABCB1 C3435T genotype with clopidogrel response or risk of stent thrombosis in patients undergoing coronary artery disease. Eur Heart J 2009; 306: 2221-8.

158. Fontana P, Dupont A, Gandrille S, et al. Adenosine diphosphate-induced platelet aggregation and P2Y12 receptor inhibitors. J Thromb Haemost 2015; 13: 984-95.

159. Varon D, Lider O, Dardik R, et al. Inhibition of integrin-mediated platelet aggregation, fibrinogen-binding, and interactions with extracellular matrix by nonpeptidic mimetics of Arg-Gly-Asp. J Thromb Haemost 2003; 11: 1030-6.

160. Campo G, Ferraresi P, Marchesini J, et al. Relationship between CYP2C19 genetic polymorphisms and response to clopidogrel and cardiovascular events. JAMA 2011; 306: 989-95.
182. Aradi D, Komocsi A, Price MJ, et al. Efficacy and safety of in-180. Collet JP, Cuisset T, Range G, et al. Bedside monitoring to adjust
179. Trenk D, Stone GW, Gawaz M, et al. Impact of platelet reactivity on cardiovascular outcomes in patients with type 2 diabetes mellitus and coronary artery disease. J Am Coll Cardiol 2011; 58: 30-9.
178. Price MJ, Berger PB, Teirstein PS, et al. Standard- vs high-dose
177. Cuisset T, Frere C, Quilici J, et al. Glycoprotein IIb/IIIa inhibitors
176. Valgimigli M, Campo G, de Cesare N, et al. Intensifying platelet
175. Christ G, Hafner T, Siller-Matula JM, et al. Platelet inhibition
174. Bonello L, Camoin-Jau L, Arques S, et al. Adjusted clopi-
173. Bonello L, Camoin-Jau L, Armero S, et al. Tailored clopidogrel
172. Angiolillo DJ, Bernardo E, Palazuelos J, et al. Functional impact of high clopidogrel maintenance dosing in patients undergoing elective percutaneous coronary interventions. Results of a randomized study. Thromb Haemost 2008; 99: 161-8.
171. Angiolillo DJ, Bernardo E, Palazuelos J, et al. Functional impact of high clopidogrel maintenance dosing in patients undergoing elective percutaneous coronary interventions. Results of a randomized study. Thromb Haemost 2008; 99: 161-8.
170. Bonello L, Camoin-Jau L, Armero S, et al. Adjusted clopi-
169. Angiolillo DJ, Bernardo E, Zanoni M, et al. Impact of insulin re-
168. Angiolillo DJ, Bernardo E, Zanoni M, et al. Impact of insulin re-
ceptor substrate-1 genotypes on platelet reactivity and cardio-
vascular outcomes in patients with type 2 diabetes mellitus and coronary artery disease. J Am Coll Cardiol 2011; 58: 30-9.
167. von Beckerath N, Kastrati A, Wieczorek A, et al. A double-blind, randomized study on platelet aggregation in patients treated with a daily dose of 150 or 75 mg of clopidogrel for 30 days. Eur Heart J 2007; 28: 1814-9.
166. Angiolillo DJ, Bernardo E, Sabate M, et al. Impact of platelet reactivity on cardiovascular outcomes in patients with type 2 diabetes mellitus and coronary artery disease. J Am Coll Cardiol 2007; 50: 1541-7.
165. Angiolillo DJ, Bernardo E, Palazuelos J, et al. Functional impact of high clopidogrel maintenance dosing in patients undergoing elective percutaneous coronary interventions. Results of a randomized study. Thromb Haemost 2008; 99: 161-8.
164. Bonello L, Camoin-Jau L, Arques S, et al. Adjusted clopi-
163. Valgimigli M, Campo G, de Cesare N, et al. Intensifying platelet
162. Angiolillo DJ, Bernardo E, Palazuelos J, et al. Functional impact of high clopidogrel maintenance dosing in patients undergoing elective percutaneous coronary interventions. Results of a randomized study. Thromb Haemost 2008; 99: 161-8.
161. Bonello L, Camoin-Jau L, Armes S, et al. Tailored clopidogrel
160. Collet JP, Cuisset T, Range G, et al. Bedside monitoring to adjust
159. Trenk D, Hochholzer W, Fromm M, et al. Cytochrome P450
158. Valgimigli M, Campo G, de Cesare N, et al. Intensifying platelet
157. Christ G, Hafner T, Siller-Matula JM, et al. Platelet inhibition
156. Bonello L, Camoin-Jau L, Arques S, et al. Adjusted clopi-
155. Valgimigli M, Campo G, de Cesare N, et al. Intensifying platelet
154. Christ G, Hafner T, Siller-Matula JM, et al. Platelet inhibition
153. Bonello L, Camoin-Jau L, Arques S, et al. Adjusted clopi-
152. Valgimigli M, Campo G, de Cesare N, et al. Intensifying platelet
151. Angiolillo DJ, Bernardo E, Zanoni M, et al. Impact of insulin re-
cceptor substrate-1 genotypes on platelet reactivity and cardio-
vascular outcomes in patients with type 2 diabetes mellitus and coronary artery disease. J Am Coll Cardiol 2011; 58: 30-9.
ing after non-ST elevation acute coronary syndrome. Shifting from antiplatelet resistance to bleeding risk assessment? Euro-Intervention 2009; 5: 325-9.

198. Park DW, Lee SW, Yun SC, et al. A point-of-care platelet function assay and C-reactive protein for prediction of major cardiovascular events after drug-eluting stent implantation. J Am Coll Cardiol 2011; 58: 2630-9.

199. Cuisset T, Hamilos M, Sarma J, et al. Relation of low response to clopidogrel assessed with point-of-care assay to periprocedural myonecrosis in patients undergoing elective coronary stenting for stable angina pectoris. Am J Cardiol 2008; 101: 1700-3.

200. Patti G, Nasca A, Mangiacapra F, et al. Point-of-care measurement of clopidogrel responsiveness predicts clinical outcome in patients undergoing percutaneous coronary intervention results of the ARMYDA-PRO (Antiplatelet therapy for Reduction of Myocardial Damage during Angioplasty-Platelet Reactivity Predicts Outcome) study. J Am Coll Cardiol 2008; 52: 1128-33.

201. Gurbel PA, Erlinge D, Ohman EM, et al. Platelet function during extended prasugrel and clopidogrel therapy for patients with ACS treated without revascularization: the TRILOGY ACS Platelet Function Substudy. JAMA 2012; 308: 1785-94.

202. Oh IY, Park KW, Kang SH, et al. Association of cytochrome P450 2C19*2 polymorphism with clopidogrel response variability and cardiovascular events in Koreans treated with drug-eluting stents. Heart 2011; 98: 139-44.

203. Sibbing D, Stegherr J, Latz W, et al. Cytochrome P450 2C19 loss-of-function polymorphism and stent thrombosis following percutaneous coronary intervention. Eur Heart J 2009; 30: 916-22.

204. Tiroch KA, Sibbing D, Koch W, et al. Protective effect of the CYP2C19 *17 polymorphism with increased activation of clopidogrel on cardiovascular events. Am Heart J 2010; 160: 506-12.

205. Sawada T, Shinke T, Shite J, et al. Impact of cytochrome P450 2C19*2 polymorphism on intra-stent thrombus after drug-eluting stent implantation in Japanese patients receiving clopidogrel. Circ J 2011; 75: 99-105.

206. Tello-Montoliu A, Jover E, Marin F, et al. Influence of CYP2C19 polymorphisms in platelet reactivity and prognosis in an unselected population of non ST elevation acute coronary syndrome. Rev Esp Cardiol 2012; 65: 219-26.

207. Malek LA, Przytulski I, Spiewak M, et al. Cytochrome P450 2C19 polymorphism, suboptimal reperfusion and all-cause mortality in patients with acute myocardial infarction. Cardiology 2010; 117: 81-7.

208. Yamamoto K, Hokimoto S, Chitose T, et al. Impact of CYP2C19 polymorphism on residual platelet reactivity in patients with coronary heart disease during antiplatelet therapy. J Cardiol 2011; 57: 194-201.

209. Pare G, Mehta SR, Yusuf S, et al. Effects of CYP2C19 genotype on outcomes of clopidogrel treatment. N Engl J Med 2010; 363: 1704-14.

210. Wallentin L, James S, Storey RF, et al. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. Lancet 2010; 376: 1320-8.

211. Suh JW, Koo BK, Zhang SY, et al. Increased risk of atherothrombotic events associated with cytochrome P450 3A5 polymorphism in patients taking clopidogrel. CMAJ 2006; 174: 1715-22.

212. Harmsze AM, van Werkum JW, Hackeng CM, et al. The influence of CYP2C19*2 and *17 on on-treatment platelet reactivity and bleeding events in patients undergoing elective coronary stenting. Pharmacogenet Genomics 2012; 22: 169-75.

213. Mega JL, Close SL, Wiviott SD, et al. Genetic variants in ABCB1 and CYP2C19 and cardiovascular outcomes after treatment with clopidogrel and prasugrel in the TRITON-TIMI 38 trial: a pharmacogenetic analysis. Lancet 2010; 376: 1312-9.

214. Spiewak M, Malek LA, Kostrzewa G, et al. Influence of C3435T multidrug resistance gene-1 (MDR-1) polymorphism on platelet reactivity and prognosis in patients with acute coronary syndromes. Kardiol Pol 2009; 67: 827-34.

215. Ziegler S, Schillinger M, Funk M, et al. Association of a functional polymorphism in the clopidogrel target receptor gene, P2Y12, and the risk for ischemic cerebrovascular events in patients with peripheral artery disease. Stroke 2005; 36: 1394-9.