Review paper

Personalized antiplatelet therapy with P2Y$_{12}$ receptor inhibitors: benefits and pitfalls

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Abstract

Antiplatelet therapy with P2Y$_{12}$ 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$_{12}$ 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$_{12}$-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$_{12}$-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$_{12}$ 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 α2β1, 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$_2$, 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 P2Y12 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 pseudopodia 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$_{12}$ receptor

The P2Y$_{12}$ receptor is a member of the P2Y purinergic G protein-coupled receptors (GPCR) family, which is activated by ADP, thromboxane A$_2$ and the PAR-1 receptor agonists [6, 7]. Activation of the P2Y$_1$ receptor by ADP initiates a weak and transient phase of platelet aggregation whereas binding of ADP to the P2Y$_{12}$ amplifies dense granule secretion, expression of P-selectin and platelet aggregation [8]. Further stimulation of the P2Y$_{12}$ receptor sustains the activation of the GP IIb/IIIa and GP Ia/IIa receptors and stabilization of platelet aggregates [9, 10].

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P2Y$_{12}$ receptor antagonism

Combination of aspirin with P2Y$_{12}$ 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, cangrelor, 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$_{12}$ 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$_{12}$ 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$_{12}$ 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$_{12}$ 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$_{12}$ 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$_{12}$ 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, CYP2C19, CYP2C9) [30] (Figure 1).
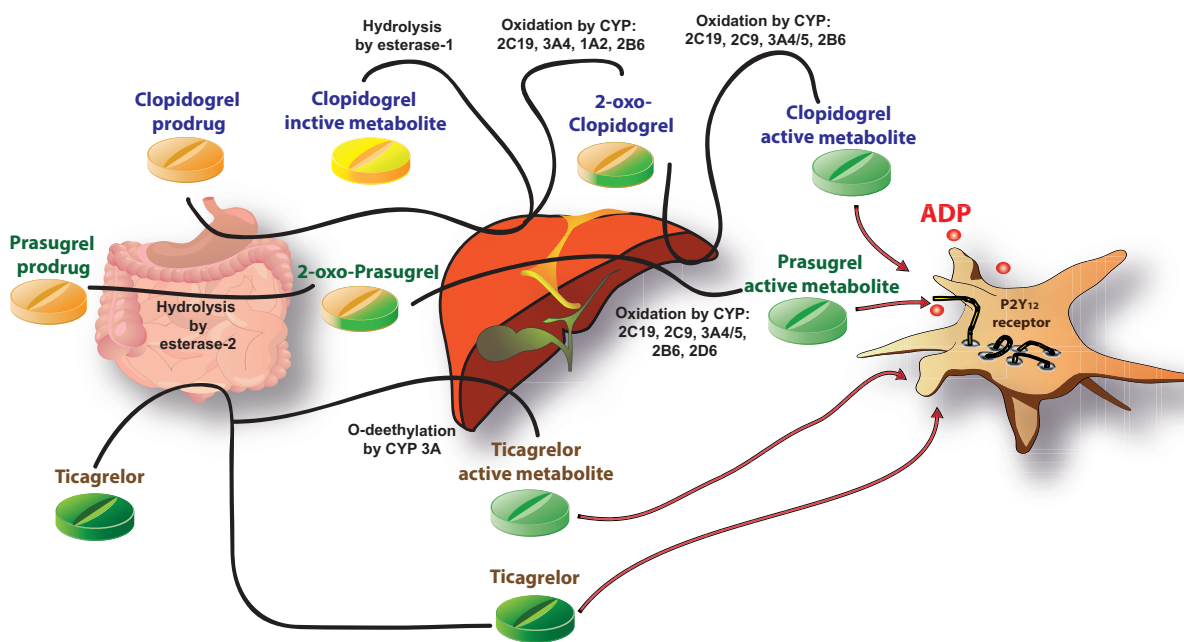

Figure 1. Metabolism of P2Y$_{12}$ receptor inhibitors
ADP – adenosine diphosphate, CYP – cytochrome 450.

It's worth noting that the known functional genetic CYP variants do not significantly affect formation of the active metabolite of prasugrel, that is faster and more efficient resulting in greater *in vivo* antiplatelet potency compared to clopidogrel [31, 32].

Ticagrelor

Ticagrelor, a cyclopentyl-triazolo-pyrimidine, is an oral antagonist of the P2Y$_{12}$ receptor, and unlike clopidogrel and prasugrel it is an active, noncompetitive antagonist of the P2Y$_{12}$ receptor. As an active drug ticagrelor does not require hepatic bioactivation, but has a metabolite (AR-C124910XX) formed by metabolism via CYP3A4, with also anti-aggregatory effects [33] (Figure 1). Genetic factors including *CYP2C19* and *ABCB1* polymorphisms do not influence the clinical outcome of ticagrelor-treated patients [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 P2Y$_{12}$ 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-

tenance dose to prasugrel maintenance dose was associated with a lower level of platelet inhibition as compared to continued ticagrelor therapy [82]. Nevertheless, at day 7 there was no difference in HPR frequency between the prasugrel and ticagrelor groups [82]. In ACS patients one month after the event ticagrelor was more effective than prasugrel in a pharmacodynamic study [83]. Interestingly, the antiplatelet activity of ticagrelor's active metabolite was more potent compared to ticagrelor or prasugrel's active metabolite in both humans and nonhuman primates [84].

Therefore, although the rate of HPR is lower with novel P2Y$_{12}$-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.

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].

Drug-drug interactions

It has been shown that certain proton pump inhibitors such as omeprazole, calcium channel blockers, ke-

toconazole and rifampicin may significantly influence clopidogrel metabolism [87, 93–102]. Interestingly, morphine co-medication in ACS is a strong predictor of HPR in patients treated with clopidogrel, prasugrel and ticagrelor. This effect might be partially explainable by the impaired or delayed absorption of those drugs induced by opioid-induced gastroparesis [76, 103, 104].

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 Ca^{2+} response and the release of ADP as well as inhibition of the P2Y$_{12}$ 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].
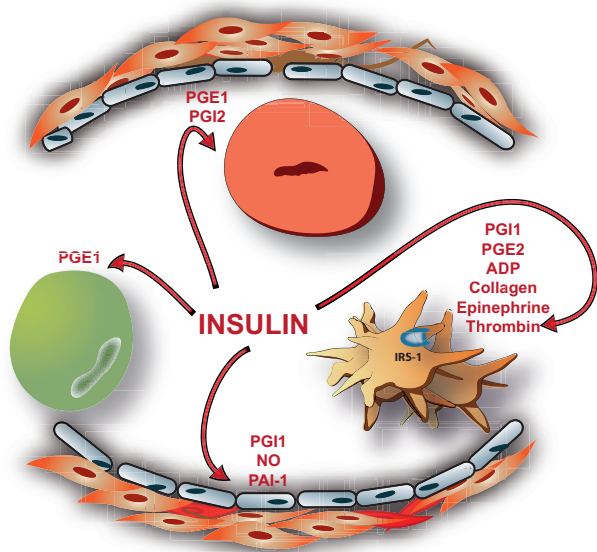

Figure 2. Effects of insulin on blood cells
PGE1 – prostaglandin E1, PGI2 – prostaglandin I2, NO – nitric oxide, ADP – adenosine diphosphate, PAI-1 – plasminogen activator inhibitor 1.
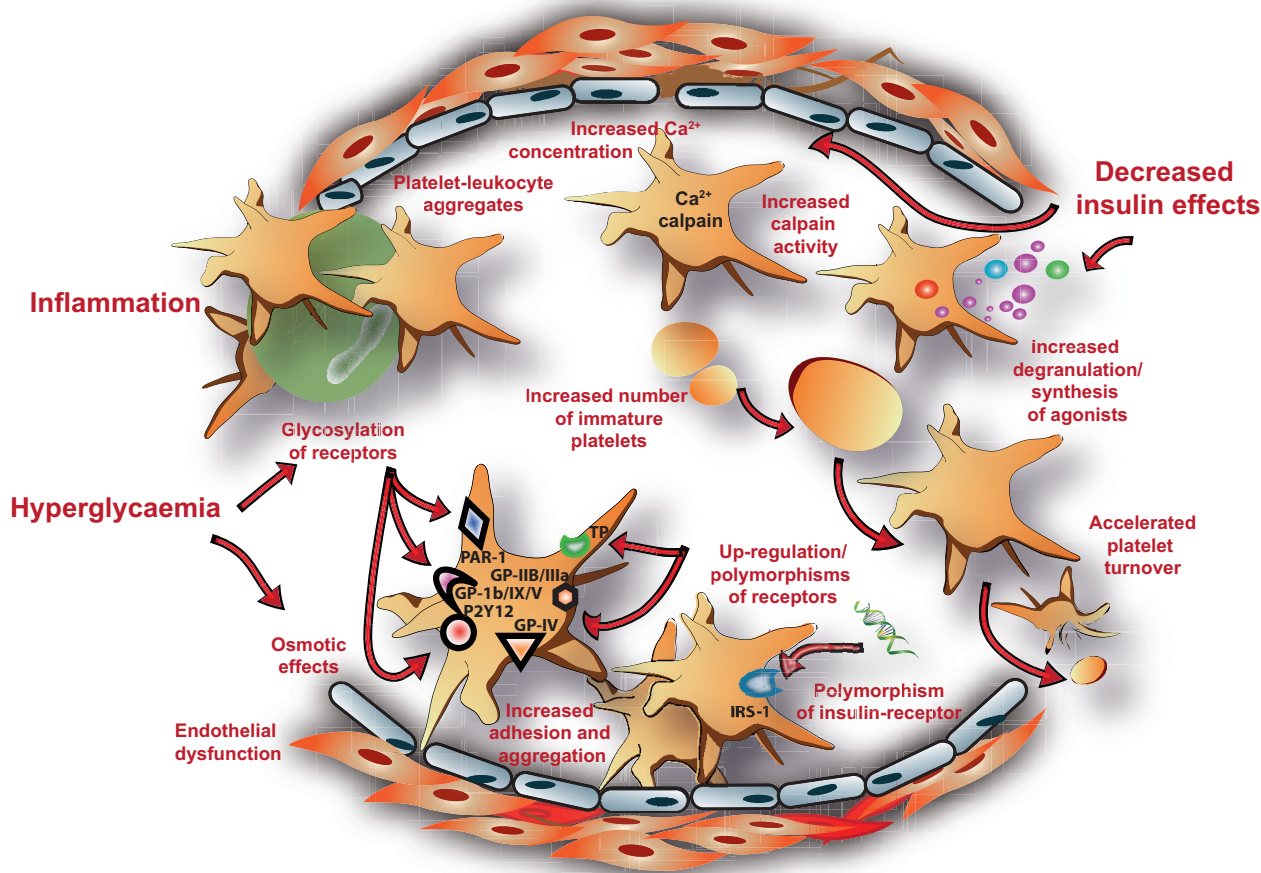
Figure 3. Effects of hyperglycaemia on platelets

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, P2Y$_{12}$ receptor signalling upregulation, increased exposure to ADP, and increased platelet turnover [106, 117, 118].

Another interesting mechanism for impaired P2Y$_{12}$ 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 P2Y$_{12}$ 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 P2Y$_{12}$-inhibition, i.e. higher risk for thrombosis in HPR and higher risk for bleeding in LPR suggest that a sweet spot may exist for P2Y$_{12}$-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. P2Y$_{12}$ 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 P2Y$_{12}$ 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 P2Y$_{12}$ signalling, because it evaluates the extent of P2Y$_{12}$ receptor inhibition without influencing the P2Y$_1$ 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 P2Y$_{12}$ 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 coated with col-

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					
Gurbel et al. [56]	LTA:ADP	297	Elective PCI	2 years	MACE	3.90	46	30	0.77			63	82
CREST [53]	LTA:ADP	100	History of ST vs. no ST				42	60					
PREPARE-POST STENTING [123]	LTA:ADP	192	Elective PCI	6 months	MACE	2.70	67	25				37	79
CLEAR PLATELETS [62]	LTA:ADP	120	Elective PCI	In hospital	Periprocedural MI		50						
CLEAR PLATELETS-2 [58]	LTA:ADP	200	Elective PCI	In hospital	Periprocedural MI		40						
Frere 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	106	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	14	27					
Buonamicci 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						
RECLOSE 2-ACS [61]	LTA:ADP	1789	ACS + PCI	2 years	MACE	1.49	70	16		15	91		
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		40						

ADP – adenosine diphosphate, 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, 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 (%)	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. [194]	MEA:ADP	50	Neurointerventional stent		ST + TIA/ stroke		52 U	28					
Siller-Matula et al. [195]	MEA:ADP	403	PCI	1 year	MACE	1.75	48 U	19	0.60				
PEGASUS-PCI [63]	MEA:ADP	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	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 infraction, 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	25	0.86	92	100	88	77
Siller-Matula *et al.* [48]	VASP assay	416	PCI	6 months	ST	NS	42	63	0.60	1	100	100	37
PEGASUS-PCI [63]	VASP assay	416	PCI	1 year	ST, MACE	NS	42	62	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
Frere *et al.* [124]	VASP assay	195	NSTE-ACS + PCI	1 month	MACE	11.18	53	54	0.73	12	99	93	50
Barragan *et al.* [196]	VASP assay	46	History of ST vs. no ST	1 month	ST		50						
Cuisset *et al.* [52]	VASP assay	598	NSTE-ACS + PCI	1 month	ST	NS			0.61				
WILMAA [68]	VASP assay	300	PCI	6 months	MACE	1.04	60	62	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 infraction, 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.

Table IV. Studies investigating the association of ischemic or bleeding events and clopidogrel response with use of VerifyNow assay

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													
Price et al. [134]	VerifyNow	380	PCI	6 months	MACE	6.50	235 PRU	32	0.71		99	78	68
Campo et al. [120]	VerifyNow	300	PCI	1 year	MACE	1.02	239 PRU	13	0.87	43	98	81	92
Park et al. [198]	VerifyNow	2849	PCI + DES	2.2 years	MACE	NS	235 PRU	58					
Marcucci et al. [135]	VerifyNow	683	ACS + PCI	1 year	MACE	2.52	240 PRU	32	0.66	12	96	61	70
POPULAR [59]	VerifyNow	1055	Elective PCI	1 year	MACE	2.53	236 PRU	38	0.62	13	94	60	63
POPULAR [188]	VerifyNow	422	Elective PCI	1 year	MACE	2.5	236 PRU	25					
Cuisset et al. [199]	VerifyNow	120	Elective PCI	In hospital	Periprocedural MI	4.60	< 15% inhibition	25					
ARMYDA PRO [200]	VerifyNow	160	PCI	1 month	MACE	6.10	240 PRU		0.56			81	53
TRILOGY ACS Platelet Function Substudy [201]	VerifyNow	2564	ACS treated conservatively	30 months	MACE	NS	208 and 230 PRU	Clopidogrel: 45–55% Prasugrel: 10–15%	0.54 (for 178 PRU)			47	59
Bleeding													
Campo et al. [120]	VerifyNow	300	PCI	1 year	TIMI major bleeding	0.94	85 PRU	25	0.84	21	98	81	80

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, ACS – acute coronary syndrome, MACE – major adverse cardiac events, MI – myocardial infarction, ST – stent thrombosis, DES – drug eluting stent, TIMI – thrombolysis in myocardial infraction, NS – not significant.

lagen/adenosine diphosphate (CADP) or collagen/ADP/PGE1. To date, there is conflicting data concerning the reproducibility of the test [136–138]. The normal value for CADP-CT in treatment of naive 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 P2Y$_{12}$ inhibition and aspirin effect. P2Y$_{12}$ 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	Prevelance 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				74	89
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			86	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	NS	299 s	30	0.56	5	90	61	29

ADP – adenosine diphosphate, CADP – collagen-adenosine doiphosphate, 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, P2Y$_{12}$ 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 β$_3$ of the GP IIb/IIIa 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].

P2Y$_{12}$

Genetic variations for the gene encoding the binding site for clopidogrel active metabolite on the P2Y$_{12}$ receptor have shown a reduced efficacy of clopidogrel, but the clinical importance is doubtable [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 P2Y$_{12}$-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,

Table VI. Studies investigating the genotype and its association with bleeding or ischemic events

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	1.7	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	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	100	PCI + DES	8 months	MACE	NS	42		
Tello-Montoliu 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	416	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		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	18
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	17
Harmsze et al. [149]	CYP3A4*1B	176/420	PCI (ST case/control)	1 year	ST	NS	9	2	7
Suh et al. [211]	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	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

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
Harmsze 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		
CHARISMA [156]	2C19*17	4819	CAD or at high risk	2 years	GUSTO severe bleeding	NS	22		
PEGASUS-PCI [63]	2C19*17	416	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			
AFIJI [150]	PON1	371	MI (< 45 years of age)	6 years	MACE	NS	55	15	40
Thrombosis: ACBC1									
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	2.16	76	32	44
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	77	25	52
PLATO [210]	ABCB1	10285	ACS	1 year	MACE	NS	76	27	49
Harmsze et al. [149]	ABCB1	176/420	PCI (ST case/control)	1 year	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
Tiroch 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	0.52	16	0	16
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 planed 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.

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