

ADP-receptor blockade: A case for personalised pharmacotherapy?

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Summary

The dual antiplatelet therapy consisting of aspirin and the ADP-receptor blocker clopidogrel is the current standard medication after acute coronary events. However, clopidogrel is characterised by a high interindividual response variability, insufficient inhibition of platelet aggregation in a significant number of patients, relatively slow onset of efficacy and potential interaction with different co-medication via diverse hepatic cytochrome enzymes. In various trials, response variability of clopidogrel was translated into a higher rate of recurrent cardiovascular events. Different clinical and non-genetic factors contribute to the phenomenon of clopidogrel response variability. An individualised anti-thrombotic pharmacotherapy taking these factors into account, including the definition of status of response, verification of the efficacy by standardised platelet function testing, intensified or alternative platelet

inhibition would be the ultimate goal for patients treated with clopidogrel. Currently, new drugs are on the way and promise a more consistent efficacy and smaller amount of response variability. However, the bleeding risk in subgroups of patients and further side effect profile remains to be clearly defined. Therefore, risk stratification models are warranted to identify patients who benefit from personalised pharmacotherapy in terms of improved clinical net benefit. In this review, we discuss treatment failure of clopidogrel based on platelet function testing, the mechanism of established and new ADP-blockers as well as new therapeutic principles.

Keywords

ADP-receptor blockers, thienopyridines, clopidogrel, response variability, prasugrel, platelet function testing.

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Received: June 1, 2009

Accepted after major revision: November 2, 2009

Prepublished online: January 13, 2010

doi:10.1160/TH09-06-0340

Thromb Haemost 2010; 103: 496–506

Introduction

Coronary artery disease (CAD) remains the major cause for mortality and morbidity in the industrialised world. Coronary thrombosis following the rupture of atherosclerotic plaques or endothelial injury is the leading cause of acute coronary syndromes (ACS). Platelets play a pivotal role in atherothrombotic complications. Besides other therapeutic principles, inhibition of the platelet adenosine diphosphate (ADP) receptor is one major antiplatelet therapeutic mechanism to control platelet-mediated coronary thrombosis. The thienopyridines are ADP-receptor blockers which directly act on the platelet surface membrane by blocking the ADP activation pathway (1, 2). So far, ADP-receptor antagonists comprise the thienopyridine group, which includes ticlopidine, clopidogrel, prasugrel and elinogrel, and the adenosine triphosphate (ATP) analogs cangrelor and ticagrelor (► Table 1). Clopidogrel has largely replaced the first generation thienopyridine ticlopidine because of highly different side-effect profiles (e.g. less bone marrow toxicity) and pharmacological properties (3–5). Current evidence-based antiplatelet therapy with low-dose aspirin and clopidogrel results in a significant mortality reduction in randomised clinical trials among patients with acute cardiovascular events (6–8). Clopidogrel acts via selective and irreversible inhibition of the ADP P2Y₁₂ receptor.

The clinical benefit of clopidogrel has been shown in numerous large-scale trials. However, the established drug therapy with this ADP receptor blocker has several shortcomings including the high interindividual response variability, even insufficient efficacy in some patients, relatively low onset of action and potential interaction with cardiac co-medication. This is translated into a considerable number of cardiovascular events despite clopidogrel treatment.

Mechanism of ADP-receptor blockade

Platelets contain large amounts of ADP in their storage granules (9). ADP is an important mediator of both physiologic haemostasis and thrombosis. During secretion, ADP is released and reinforces the activation of platelets. Platelet activation leads to multiple responses that play a critical role in arterial thrombosis and associated inflammatory responses, including platelet aggregation, dense and alpha granule secretion and pro-coagulant activity (10, 11).

ADP receptors are located on the membrane of blood platelets. Platelets reveal three types of receptors: P2Y₁ and P2Y₁₂, which interact with ADP, and P2X₁, a receptor that reacts with ATP (12, 13).

Table 1: Characteristics of ADP-receptor antagonists (ticlopidine, clopidogrel and prasugrel) and the ATP-analog ticagrelor.

Drug	Ticlopidine	Clopidogrel	Prasugrel	Ticagrelor
Bioavailability (%)	80–90	>50	80–100	?
Protein binding (%)	98	94–98	?	?
Half-life (hours)	12.6	7–8	3.7 ^a	12
Metabolism	90% hepatic, no active metabolites	Hepatic active metabolites	Hepatic active metabolites, 70% renal excretion	Orally active
Onset of antiaggregation	<4 days	2 hours	30 minutes	2 hours
Steady state of aggregation	8–11 days	3–7 days ^b	3 days	2–3 days
Phase	approved	approved	3	3
Reversibility	-	-	-	+

^a Median half-times reported for the active metabolite R-138727. ^b After administration of loading dose (300 mg to 600 mg).

ADP-receptors are G-protein-coupled (G_x) and belong to the seven-transmembrane domain receptor family. The P2Y₁ receptor is coupled to G_q and initiates ADP-induced platelet activation (14). It leads to a change in platelet shape. Activation of the P2Y₁₂ receptor results in glycoprotein (GP) IIb/IIIa activation and stabilisation of the platelet aggregate. The interaction of thienopyridines is specific and irreversible for P2Y₁₂. Activation of this receptor is associated with dephosphorylation of intraplatelet vasodilator-stimulated phosphoprotein (VASP). Blocking of P2Y₁₂ prevents the platelet activation process pathway.

Like all thienopyridines, clopidogrel is a prodrug and thus not active *in vitro*. After oral administration it is absorbed from the intestine, limited by an intestinal efflux transporter P-glycoprotein coded by the ABCB1 gene (15). Some metabolites (only about 15%) are formed by hepatic conversion via diverse cytochrome P450 (CYP) isoforms to exert the typical antiplatelet efficacy (16).

Response variability to ADP-receptor blockade

The existence of variability in clopidogrel-induced inhibition of platelet aggregation has been described profoundly in the current literature (17–21). The clinical definition of “resistance” to clopidogrel (better: “treatment-failure”) is based on the occurrence of ischaemic events despite adequate medication. The laboratory definition is based on the results of laboratory testing of platelet reactivity. In general, platelet response to clopidogrel is represented as a normal, bell-shaped (Gaussian) distribution (► Fig. 1). However, mostly arbitrarily chosen cut-off points in platelet function tests have been used to divide patients with inadequate response to clopidogrel (“clopidogrel-responders” versus “low-responders”) (22). The term “non-responders or “resistant” is inadequate since it describes the laboratory finding of a complete failure of antiplatelet medication to block the target receptor. Moreover, there is a lack of a consistent standard definition of inadequate platelet response to clopidogrel. Therefore, comparison of laboratory results of different studies on clopidogrel-“low-re-

sponders” remains difficult. In general, various data show that after an initial “loading dose” of clopidogrel, 5% to 44% of patients fail to achieve a sufficient antiplatelet effect (19, 23–27).

Response variability to antiplatelet medication is especially clinically relevant since patients with higher levels of residual, i.e. post-treatment platelet activity (RPA) have been shown to be at increased risk for recurrent ischaemic events (16–20, 28). Recently, we were able to demonstrate in 379 patients undergoing coronary stent implantation that low response, defined as platelet aggregation >70% measured at least 6 hours after administration of a loading dose of 600 mg clopidogrel, was associated with an enhanced occurrence of cardiovascular events and death (23) (► Fig. 2). Moreover, the occurrence of early stent thrombosis which is related to high morbidity and mortality, is directly influenced by the degree of post-interventional RPA (29, 30).

Laboratory testing of clopidogrel's individual efficacy

In general, there is lack of standardisation of measurement techniques and cut-off values to define patient's response to clopidogrel. In literature, there is also a wide variety of time-points defined for measurement of platelet reactivity. Since platelets can be activated by several different pathways, none of the tests is able to monitor all potential ways of platelet activation and aggregation. Measurement of ADP-induced light transmission aggregation (LTA) has been widely applied and can be considered as the gold-standard method. However, this assay is operator-dependent, time-consuming and not standardised. Since clopidogrel targets the P2Y₁₂ receptor and by this enhancing VASP-phosphorylation (VASP-P), flow cytometric analysis of the degree of VASP-P is considered more specific to monitor P2Y₁₂ dependent platelet inhibition (32). However, limitations to this method are the costs, need of sample preparation and special laboratory equipment (flow-cytometry). Various studies demonstrated a good correlation between estimates of the thienopyridine effect on platelet function assessed by VASP and LTA (33–35).

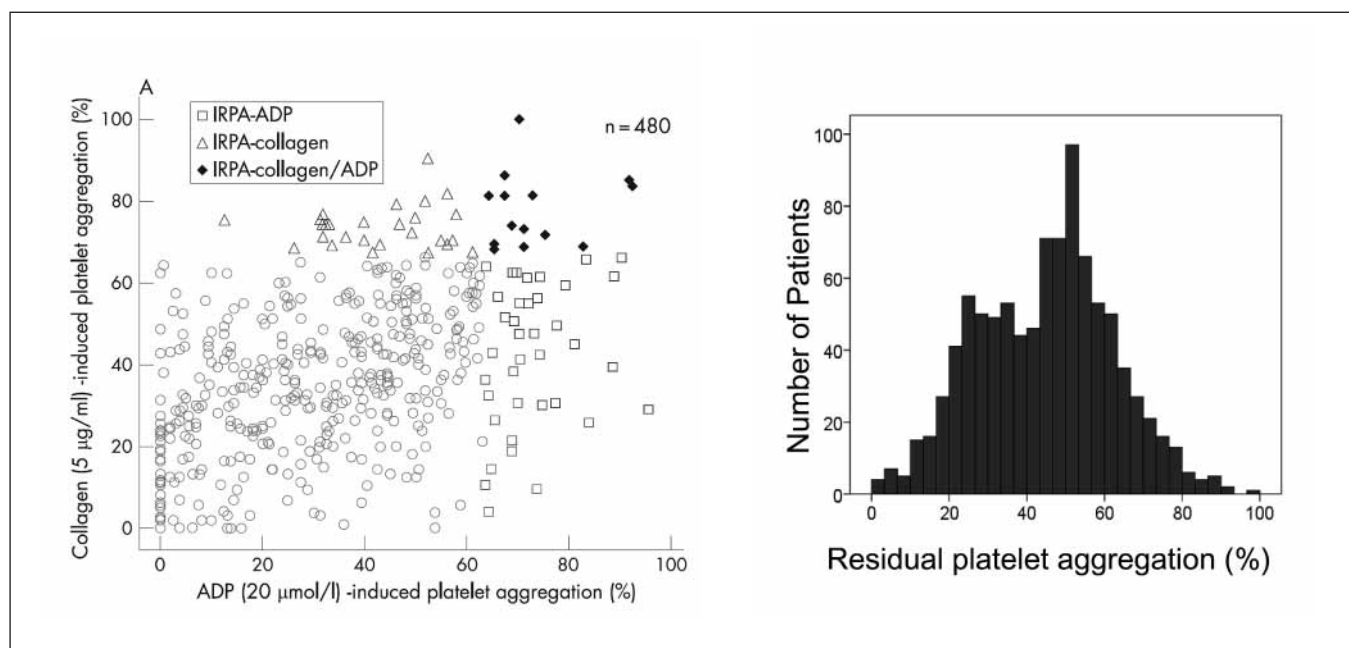


Figure 1: Distribution of platelet response to dual antiplatelet therapy. A) A scatter plot showing ADP- and collagen-induced post-treatment platelet aggregation in a study of 480 patients. IRPA, increased residual platelet aggregation. B) In the patient population, the residual platelet aggregation (RPA) shows a normal but wide-spread distribution. Adapted from Geisler et al. *Heart* 2008; 94: 743–747.

Point-of-care platelet function test like the Multiple electrode aggregometry (MEA) and VerifyNow P2Y12 have been tested for their significance in cardiovascular cohorts. MEA is a device to measure agonist-induced platelet aggregation in whole blood by means of impedance aggregometry (38). Recent data indicate a prognostic relevance of the measured results and suggest a possible differentiation between atherothrombotic and bleeding risk (31, 37). The VerifyNow is a cartridge assay based on the turbidometric

measurement of platelet aggregation to fibrinogen-coated microbeads upon agonist stimulation (36). It was recently evaluated in the larger POPULAR study to compare the prognostic relevance of eight different assays (MEA was not included in this study) and was able to detect high platelet reactivity and CV-events beside LTA and PlateletWorks[®] (presented at the American Heart Association 2009 Scientific Sessions). On behalf of recent data, user-friendly point-of-care devices (like MEA and VerifyNow) are the favourable methods for clinical routine as they combine practicability and correlation with prognosis of clopidogrel treated patients. They should be further evaluated for effects of therapy adjustment on behalf of measured results.

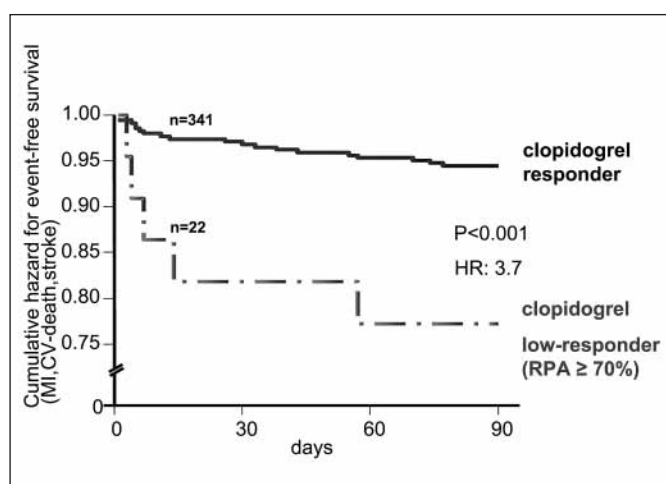


Figure 2: Response variability to clopidogrel: effect on recurrent cardiovascular events. Cumulative event-free survival in patients undergoing coronary stenting in an analysis of death from cardiovascular causes at three months according to response to clopidogrel. MI, myocardial infarction. Adapted from Geisler et al. *Eur Heart J* 2006; 27: 2420–2425.

Mechanisms of clopidogrel response variability

Multiple reasons seem to account for interindividual differences in platelet response to clopidogrel therapy and many of them still need to be elucidated. In general, mechanisms of treatment failure include non-genetic (i.e. clinical) and genetic factors (► Fig. 3).

First of all, clinical factors comprise the patient's compliance and dosing regime. Poor compliance presents an obvious risk factor for ischaemic events (22, 39). Especially in patients with high doses of antiplatelet therapy, minor bleeding complications during everyday activities may endorse non-compliance (40). Besides, various gastrointestinal or haematologic diseases resulting in a poor intestinal clopidogrel absorption or increased turn-over of blood platelets must also be taken into account. Also the presence

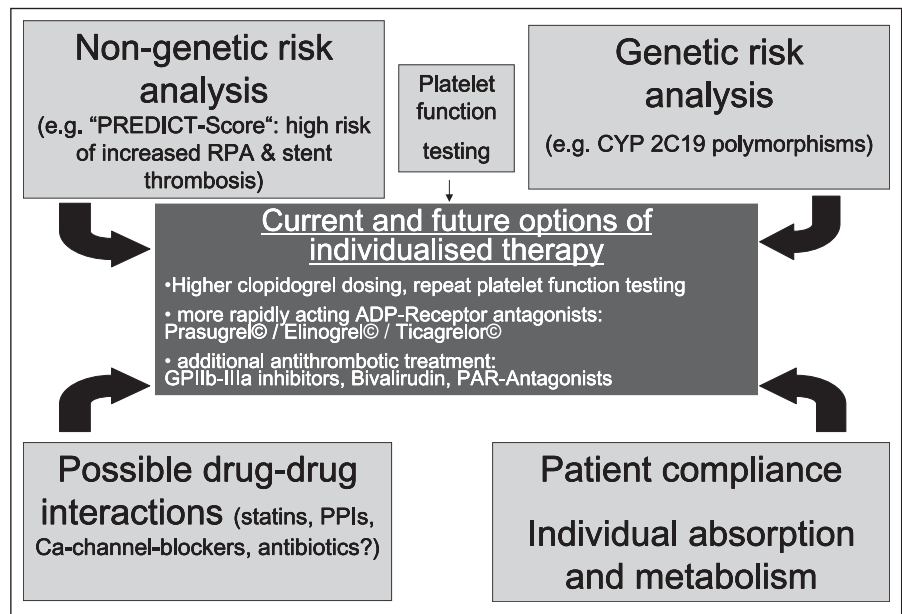


Figure 3: Contributing factors of variable platelet response to clopidogrel treatment. Diverse genetic (e.g. cytochrome polymorphisms) and non-genetic factors (e.g. clinical risk factors, pharmacological interactions) contribute to the phenomenon of variable response to clopidogrel.

of specific cardiovascular risk factors has been associated with lower clopidogrel efficacy. In a large study of 1092 consecutive patients with planned percutaneous coronary intervention (PCI), we identified age >65 years, type 2 diabetes, decreased left ventricular ejection fraction, renal insufficiency and ACS for prediction of persistent high RPA after dual antiplatelet therapy with aspirin and clopidogrel (41). By using a factor-weighted model, we developed the PREDICT-score (residual platelet aggregation after deployment of intracoronary stent). With a score higher than 4 score levels, the risk for persistent RPA was significantly increased (► Fig. 4). Especially diabetes mellitus must be considered as a high risk factor for a low response to clopidogrel (42, 43). It is well established that platelet function in diabetic patients significantly differs from non-diabetic individuals. In a study of 485 consecutive patients with symptomatic CAD, we found that diabetes mellitus is significantly associated with a lower response to a 600-mg clopidogrel loading dose (44). In other trials, a high body mass index (BMI) has been associated with increased baseline platelet activity and lower clopidogrel-effects (45, 46). Clinical factors that influence the response rate of clopidogrel also include the patient's general metabolic status. The individual baseline metabolic activity of the CYP enzyme system may determine the degree of intrahepatic activation of clopidogrel. Co-medication with substrates, inhibitors (e.g. ketoconazole (47), erythromycin) or inducers (e.g. rifampicin) of hepatic CYP isoforms can interact with intrahepatic activation of clopidogrel, thus diminishing its antiplatelet effect. So far, lipophilic statins (48), proton pump inhibitors (PPI) (49, 50) and calcium channel blockers (51, 52) are suspected to significantly interact with clopidogrel due to the same hepatic metabolic cytochrome pathway. However, data are inconsistent and some large trials have failed to demonstrate a clinical effect of these potential interactions. In our large study of 1155 patients undergoing PCI, peri-procedural co-administration of sta-

tins in addition to clopidogrel did not increase the RPA and did not worsen the rate of clinical events in these patients (53). In an analysis of platelet function in consecutive patients undergoing PCI treated with dual antiplatelet therapy, we were recently able to demonstrate a significant attenuation of clopidogrel-dependent platelet inhibition in patients with PPI co-medication (54), especially also in patients with pantoprazole intake. Our data stand in contrast to the study of Sibbing et al demonstrating significant effects of concomitant PPI treatment on platelet response to clopidogrel only for omeprazole, but not for pantoprazole or esomeprazole (55). However, further large-scale, prospective randomised trials are needed and definitive conclusions about a clopidogrel-PPI interaction may not yet be drawn.

Besides clinical factors, genetic factors have been shown to significantly influence the response variability to clopidogrel. Clopidogrel is an inactive prodrug and after absorption it requires in vivo-conversion to an active metabolite. Functional genetic polymorphisms of enzymes involved in intestinal absorption have been associated with variations in the interindividual clopidogrel response rate. The ABCB1 gene encodes for the intestinal efflux transporter P-glycoprotein (multidrug resistance transporter) which is involved in clopidogrel absorption. A lower clopidogrel efficacy was reported for its genetic variants (5, 56, 57). In another study, the presence of two variant alleles of ABCB1 was associated with a higher rate of 1-year cardiovascular events in patients who had presented with an acute myocardial infarction (MI) (58). Variants of genes encoding for platelet membrane receptors have also been associated with modified clopidogrel efficacy in smaller studies, partly with inconsistent findings. These include polymorphisms in genes coding P2Y12, the platelet fibrinogen receptor GP IIb/IIIa and receptor for thrombin (25, 59). Not only genetic polymorphisms of the P2Y12 receptor, but also differences in its occupancy seem to be associated with variability in clopidogrel re-

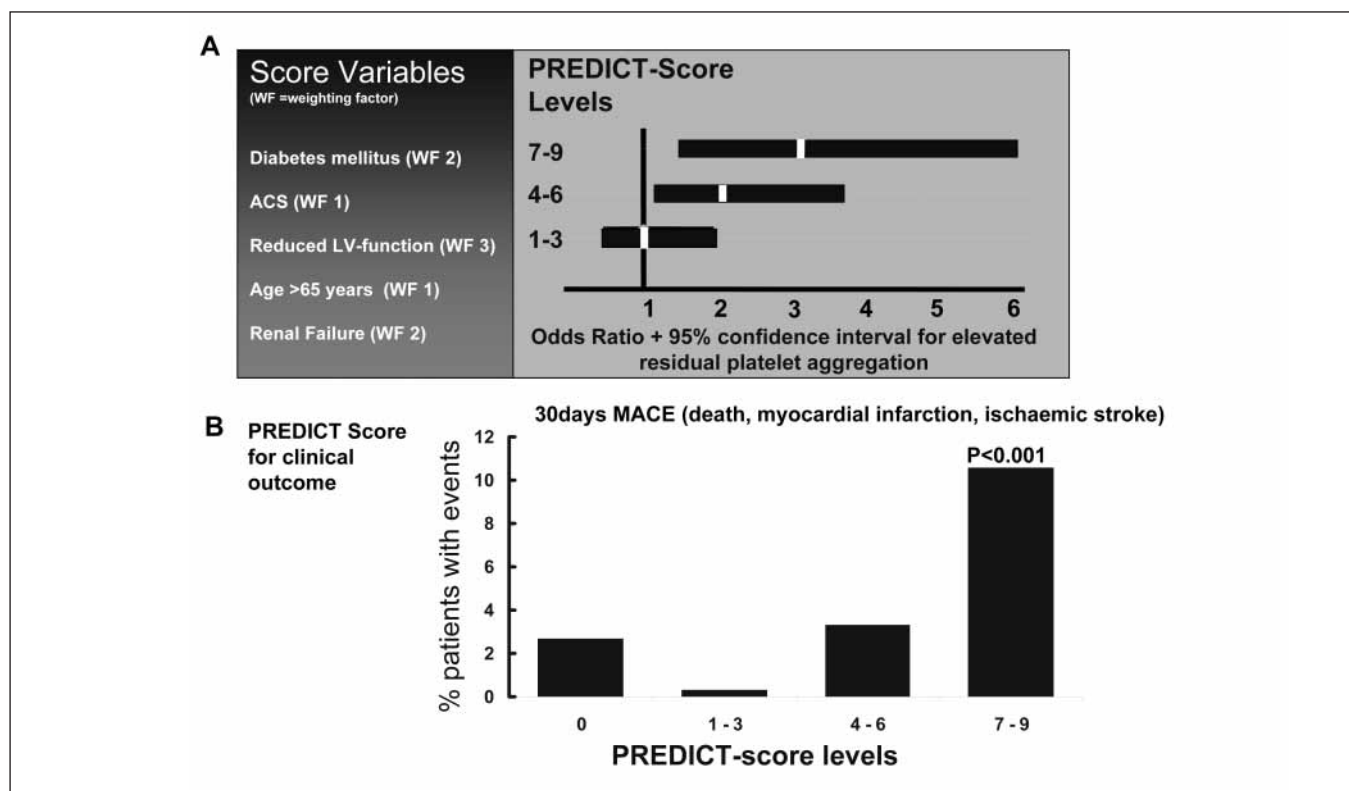


Figure 4: Introduction of the PREDICT- (residual platelet aggregation after deployment of intracoronary stent) score in patients undergoing coronary stenting. A) The PREDICT score provides a good tool to estimate residual platelet activity (RPA) after a clopidogrel loading dose. The easily available score variables comprise diabetes mellitus, acute coronary

syndrome, reduced left ventricular ejection fraction, age >65 years and renal failure, which are assigned different weighting factors. B) Higher score levels are significantly associated with short-term outcome (30 days major adverse cardiovascular events). Adapted from Geisler et al. *J Thromb Haemost* 2008; 6: 54–61.

sponse (60). Moreover, genes codifying hepatic cytochrome P450 isoenzymes have been associated with variations in the interindividual clopidogrel response rate. Different CYP isoforms (CYP3A4, CYP3A5, CYP2C9, CYP2C19) are involved in clopidogrel metabolism and may be determinants of its response (58, 61–63). The most consistent findings are reported for CYP2C19. A study with healthy individuals demonstrated that carriage of the cytochrome P450 2C19 loss of function variant CYP2C19*2 is associated with reduced responsiveness to clopidogrel (64). To assess the effect of this pharmacogenetic determinant on clinical outcomes after ACS, a study on 2209 consecutive patients was performed (21). Carriers of two CYP2C19 loss-of-function alleles revealed significantly more recurrent cardiovascular events compared to non-carriers at a one year follow up, especially patients who had undergone PCI. In another study with 259 young patients (<45 years) with MI, the CYP2C19*2 genetic variant was identified as a major determinant of future prognosis (65). Besides diminished platelet inhibition, significantly lower levels of the active clopidogrel metabolite have been identified in carriers of the CYP2C19 loss of function allele (61). In the study of Trenk et al. (62), carriers of the CYP2C19*2 polymorphism revealed a significantly higher RPA on clopidogrel treatment. Elevated RPA (>14%) at pre-discharge resulted in a 3.0fold increase in the 1-year inci-

dence of death and MI. To investigate an association between responsiveness to clopidogrel with genotypes of cytochrome CYP2C19, CYP3A4 and CYP3A5, we recently performed genotyping in 237 patients undergoing PCI (66). Since not only CYP2C19, but also the cytochrome P450 enzyme family (CYP3A) is involved in the bioactivation of clopidogrel (67), we also took polymorphisms of these enzymes into account. We found that CYP2C19*2 carriers showed a significantly increased RPA with especially an even higher association in combination with non-genetic risk factors.

Overcoming the limitations of inadequate clopidogrel response

Variability in platelet response to clopidogrel treatment is an emerging clinical challenge and may have fatal consequences in patients with recent coronary stent implantation in terms of recurrent ischaemic events. Therefore, an individualised pharmacotherapy which overcomes this phenomenon is crucial. However, the management of patients with low response to clopidogrel is still unclear and not guideline-based. Initially, it is important to assure

the individual patient's compliance. Concerning potential drug-drug interactions of co-medication, our approach is to avoid high dosing of lipophilic statins that are metabolised via CYP P450 and to use PPIs only if indicated and other than omeprazole which are less likely to significantly interact with the antiplatelet effect of clopidogrel.

Furthermore, increase of the clopidogrel loading dose >300 mg has been associated with better outcomes (68). A loading dose of 600 mg clopidogrel has been demonstrated to achieve optimal antiplatelet effect (69, 70). This was confirmed by data from the CURRENT-OASIS 7 trial (clinicaltrials.gov, NCT00335452), which were presented most recently. In this trial, patients with unstable angina or ACS undergoing coronary angiography within the first 72 hours were randomised to a 600 mg versus 300 mg clopidogrel loading dose and 150 mg per day for seven days versus 75 mg clopidogrel per day respectively. Here, the clopidogrel high-dose regimen significantly reduced the risk of stent thrombosis and MI without increasing the risk of fatal bleeding.

Based on these results, we would recommend to consequently apply a loading dose of 600 mg clopidogrel, as it is recommended in PCI guidelines (7). Moreover, the time-frame to achieve full antiplatelet effect is >6 hours for 300 mg clopidogrel, but only two hours for a 600 mg loading dose (28). Studies have demonstrated that clopidogrel loading doses higher than 600 mg are not associated with an additional significant suppression of platelet function, possibly due to limitations in absorption ability (69). To ensure a sufficient clopidogrel effect, there is also a discussion about an increase of the clopidogrel maintenance dose. Some studies demonstrated an intensified platelet inhibition in patients undergoing PCI when a high maintenance dose of 150 mg clopidogrel was applied (71, 72). Since the benefit of this treatment regimen was especially observed in patients with high RPA (71) and with diabetes mellitus (72), this approach may be especially worthwhile in these patient groups. PCI guidelines also suggest a 150 mg clopidogrel maintenance dose in patients with <50% inhibition of platelet aggregation with high risk of a stent thrombosis (7). Many studies are currently under way which assess safety and efficacy of higher maintenance doses in patients with inadequate response to clopidogrel and these results are eagerly expected.

Also laboratory methods of determination of platelet reactivity or response to thienopyridines are an important component of developing a personalised pharmacotherapy in patients undergoing PCI. However, since there is no standardisation in the assessment of platelet inhibition, current guidelines do not consequently recommend platelet function testing to evaluate the inhibitory effect of antiplatelet medication (73, 74). Recently, an algorithm was developed to optimise clopidogrel response according to impedance aggregometry in patients with planned coronary intervention (75). In this study, the incidence of clopidogrel low responders in patients undergoing elective coronary stenting was reduced from 23.6% to 5% when administering an additional 600 mg clopidogrel loading dose plus a 150 mg clopidogrel maintenance dose, otherwise changing to ticlopidine. This approach might be helpful to reduce the incidence of clopidogrel resistance in the particular patient collective. However, clinical event rate was not registered in

this trial. In contrast, data of Bonello et al. (76, 77) showed a reduction in post-PCI major adverse cardiovascular events (MACE) and rate of stent thrombosis, when low responders, according to VASP assay, received up to three additional loading doses of 600 mg clopidogrel before PCI. The design of these trials was randomised (VASP-guided group and controls), multicentric, initially included 162 patients (76), subsequently 429 patients (77). Interestingly, the rate of minor and major bleeding was not significantly influenced. Nevertheless, the study collective was small and the event-rate lower than expected. In conclusion, when personalised antiplatelet therapies based on individual platelet function analysis are applied, it would be adequate to increase the dose of the ADP-receptor blocker in patients with insufficient inhibition of platelet aggregation, to check platelet reactivity again and when indicated, take further steps like switching to another antiplatelet treatment.

However, laboratory testing of response to clopidogrel bares the limitations of a variety of assays with in general not transferable results and sometimes weak correlation (78). Besides, platelet function testing cannot be performed in every institution. Therefore, in the process of risk stratification and therapeutic decision, clinical risk scores entirely based on clinical data and independent of platelet function tests might be another helpful tool. Thereby, evaluation of platelet reactivity by assessment of easily available clinical data may be integrated into the concept of personalised pharmacotherapy. Our recently developed PREDICT score allows to estimate the probability of high RPA and the risk for short-term ischaemic events from easily available data, weighted according to their influence (e.g. weighing factor 1 for advanced age and ACS, 2 for renal insufficiency and diabetes mellitus and 3 for compromised ejection fraction) (41). We further evaluated the prognostic role of our score by a follow-up regarding MACE in 1038 patients. Patients identified at high risk of increased RPA (score =4) revealed a significantly worse outcome (log rank $p < 0.001$). For additional evaluation of risk prediction for RPA, genetic analysis was added. In our study, we subsequently included genotyping for CYP2C19*2 to our PREDICT variables. By logistic regression analysis, we were able to demonstrate a significant association of non-genetic risk factors (chi-square 5.32; $p = 0.021$) and CYP2C19*2 (chi-square 21.31, $p < 0.0001$) with RPA. For the combination of both, the association was even higher (chi-square 25.85; $p < 0.0001$) (► Fig. 5). Furthermore, we are currently evaluating in a small study collective if additional genetic analysis improves the risk prediction for recurrent ischaemic events. Therefore, performance of a genetic analysis may be another brick in the concept of personalised antiplatelet therapy. Further trials are warranted to evaluate clinical scores and the effects of tailored antiplatelet therapy on behalf of clinical and genetic risk analysis.

Additionally, the development of new therapeutic agents acting via ADP-receptor blockade might be a new gleam of hope to improve antiplatelet treatment. Besides others, the new antiplatelet drugs prasugrel, elinogrel and ticagrelor are currently under clinical evaluation.

Prasugrel is a thienopyridine of the third generation and can already be used for limited clinical indications. Equally to clopidogrel and ticlopidine, prasugrel needs conversion into an active drug

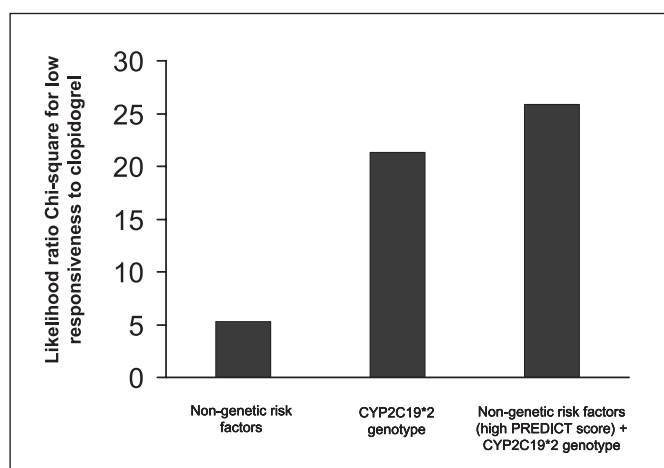


Figure 5: Better prediction of low response to antiplatelet therapy by genetic (CYP2C19*2 polymorphism) and non-genetic (PREDICT-Score) risk analysis. The combination of non-genetic risk analysis (PREDICT score) and genetic analysis (genotyping for CYP2C19 loss of function alleles) is a superior tool for evaluation of elevated RPA after clopidogrel intake. Adapted from Geisler T et al. *Pharmacogenomics* 2008; 9: 1251–1259.

metabolite. The first step in the generation of prasugrel's active metabolite is the formation of the thiolactone, R-95913, which is formed following the rapid hydrolysis of prasugrel by esterases in the intestine, liver, and plasma. R-95913 is subsequently metabolised via oxidation by intestinal and hepatic cytochrome P-450 enzymes in a single step that leads to ring opening, a formation of the SH-containing active metabolite R-138727. This active metabolite is detected in human plasma very early, approximately 15 minutes after a loading dose of 60 mg and reaches its peak plasma concentration at about 30 minutes. Within 1 hour after a 60 mg

loading dose of prasugrel, the therapeutic effect of platelet inhibition is reached (79). While the active metabolite of prasugrel inhibits the platelet P2Y₁₂ receptor to a similar extent as the active metabolite of clopidogrel, the *in vivo*-generation of the active metabolite of prasugrel is more efficient. Therefore, preclinical and clinical studies showed a more rapid, potent and consistent inhibition of platelet function for prasugrel compared to clopidogrel (80, 81) (► Fig. 6). The differences were observed both with the standard 300 mg clopidogrel loading dose and the loading dose of 600 mg clopidogrel compared with 60 mg prasugrel. Overall, variability of platelet inhibition after prasugrel intake was significantly lower compared to clopidogrel (82). The JUMBO trial TIMI 26, a phase 2, randomised, double-blind safety trial of prasugrel versus clopidogrel in patients undergoing elective or urgent PCI showed that prasugrel and clopidogrel both equally resulted in low rates of bleeding (83). In the TRITON TIMI 38 trial among patients with ACS receiving PCI, prasugrel therapy was associated with significantly reduced rates of ischaemic events, including stent thrombosis, but with an increased risk of major bleeding (including fatal bleeding) (84). The latter was especially observed in patients with prior stroke or transitory ischaemic attack and in older patients (>75years) as well as patients with low body weight (<60kg). However, the overall mortality did not differ significantly between the two groups and the net clinical weighing up both efficacy and bleeding endpoints still favored prasugrel. It seems that most benefit from prasugrel occurs early (e.g. prevention of ischaemia), but most harm (e.g. bleeding complication) occurs late (85). Results of the TIMI 38 trial also suggest that careful dosing of prasugrel will be the key to success for this new antiplatelet drug. In a real-world setting, this must especially be considered in the large collective of our elderly patients with multiple co-existing conditions, as well as in patients with cerebrovascular disease or low body weight. Furthermore, it has to be considered that even in clopidogrel, the largest safety issue in combination with low-dose aspirin is moderate

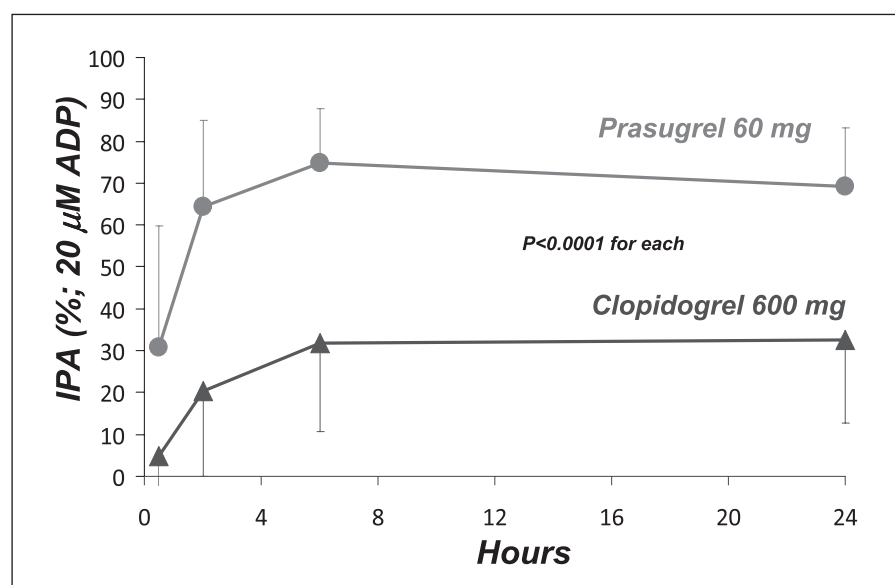


Figure 6: Comparison of the onset of antiplatelet effect after loading dose of clopidogrel versus prasugrel. After application of a loading dose, prasugrel shows a significantly more rapid and more intense 20 μ M ADP-induced inhibition of platelet aggregation (light grey line) as compared to clopidogrel (dark grey line). Adapted from Wiviott SD et al. *Circulation* 2007; 116: 2923–2932.

to severe bleeding, which can be as high as 35% depending on the study collective (e.g. in patients requiring heart surgery) (86).

In patients undergoing PCI included in the TIMI 44 trial, loading with 60 mg prasugrel resulted in greater platelet inhibition compared to a 600 mg clopidogrel loading dose. Also, maintenance therapy with prasugrel 10 mg/d showed a greater antiplatelet effect compared to 150 mg clopidogrel daily (87). Besides, the drug-drug interaction profile of prasugrel may be superior to clopidogrel. In a recent study, lansoprazole affected the degree of inhibition of platelet aggregation after a loading dose of clopidogrel, but not after prasugrel (88). For a personalised pharmacotherapy in patients with PCI, we would consider prasugrel in patients with high RPA after clopidogrel loading measured by platelet function testing and in high risk patients (e.g. with high risk of stent thrombosis or re-infarction, diabetics). However, the decision to continue with clopidogrel or to switch to prasugrel is currently an individual decision based on appropriate selection of patients (89). Platelet function testing will also facilitate the decision for the appropriate antiplatelet substance. A study which is based on platelet function testing using VerifyNow, the TRIGGER-PCI (clinicaltrials.gov, NCT00910299) study, is currently under way. Here, the efficacy of prasugrel versus clopidogrel for reduction of adverse cardiovascular events is assessed in patients with high platelet reactivity on clopidogrel after drug-eluting stent implantation.

The thienopyridine **elinogrel** (PRT060128) is currently under investigation as another new antiplatelet therapeutic option (90). In contrast to clopidogrel, it can be administered orally and intravenously. Moreover, it is supposed to be immediately active resulting in a rapid onset of action and it is a reversible P2Y₁₂ antagonist. Phase 1 clinical study (safety and efficacy of antiplatelet therapy prior to primary PCI in ST-segment elevation myocardial infarction [STEMI] patients, ERASE-MI) has been completed in July 2008 (91). 70 patients were randomised to an i.v. bolus of placebo versus elinogrel. In this collective, elinogrel was well tolerated and revealed a predictable, dose-dependent inhibition of platelet aggregation. The phase 2 safety and efficacy study of elinogrel in 800 patients with non-urgent PCI (INNOVATE-PCI) has been already started (92). After diagnostic angiography, patients scheduled for PCI are randomised to clopidogrel or to one of three dose levels of elinogrel. Estimated completion date will be fall 2009, results are expected at the beginning of 2010.

ATP analogs are a new class of antiplatelet medication, since ATP is the natural antagonist of ADP-induced platelet aggregation via binding of the ADP P2Y₁₂ receptor. These substances are no thienopyridines. **Ticagrelor** is a prototype of a new chemical class named cyclopentyl-triazolo-pyrimidines. This substance is derived from ATP, reversibly interacts with the platelet P2Y₁₂ receptor and almost completely inhibits ADP-induced platelet aggregation *ex vivo*. In contrast to the group of thienopyridines, ticagrelor does not require metabolic conversion to an active form. Like prasugrel, ticagrelor results in a more rapid onset of antiplatelet effect and reveals a higher degree of platelet inhibition (higher potency: 90–95% versus 60%) compared to clopidogrel. Additionally, in patients treated with clopidogrel, ticagrelor further suppresses platelet aggregation (93).

Ticagrelor has recently been evaluated in the Dose Confirmation Study Assessing Anti-Platelet Effects of AZD6140 Versus Clopidogrel in NSTEMI (DISPERSE-2) study, a randomised phase 2 study that compared ticagrelor (90 mg or 180 mg twice daily) with clopidogrel (300 mg loading dose, 75 mg daily maintenance) for 4–12 weeks in 990 patients with ACS (94). Here, no significant difference of bleeding risk was detected in total and especially also in patients who received either clopidogrel or ticagrelor within 24h of coronary artery bypass surgery. However, if surgery was performed 1–5 days after the last dose, patients treated with ticagrelor revealed a significantly lower risk of major bleeding (36% versus 64% for clopidogrel users). Thus, the use of ticagrelor as a reversible agent may provide more flexibility for the timing of surgery than the thienopyridines and may help to overcome perioperative bleeding risk. With regard to side effects, ticagrelor was associated with a dose-dependent greater incidence of persistent dyspnoea: 6% of patients in the ticagrelor groups versus 2% of clopidogrel-users. The cause of dyspnoea is not fully understood yet but might be related to ticagrelor's ATP-like effects. Additionally, significantly more but mostly asymptomatic ventricular pauses >2.5 seconds and a mild increase in uric acid levels were observed in the ticagrelor group. Ticagrelor (180 mg loading dose, 90 mg twice daily maintenance dose) was compared with clopidogrel (300–600 mg loading dose, 75 mg daily maintenance dose) in the PLATO trial, a large phase 3 trial including over 18,000 patients with ACS (clinicaltrials.gov, NCT00391872) (95). Compared with clopidogrel, ticagrelor significantly reduced the rate of primary end point (death from vascular causes, myocardial infarction or stroke). The rate of overall major bleeding was not increased but the rate of non-procedure-related bleeding.

Cangrelor is a reversible, intravenously applied, competitive antagonist of the P2Y₁₂ receptor without the need of metabolic activation. Like prasugrel and ticagrelor, cangrelor had proven a greater antiplatelet effect and more rapid onset of effect compared to clopidogrel. However, the Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition (CHAMPION) trials (clinicaltrials.gov, NCT00385138) have been prematurely terminated since intermediate results failed to demonstrate a superior effect compared to placebo and the active comparator, respectively. However, cangrelor may play a role in perioperative bridging in the future. Currently, the Bridge study is evaluating the safety profile of cangrelor before coronary artery bypass grafting in terms of perioperative bleeding (clinicaltrials.gov, NCT00767507).

Along with those new P2Y₁₂ antagonists, inhibitors of the other platelet receptor for ADP (P2Y₁) and of the receptor for ATP (P2X₁) are currently on the way. Data from P2Y₁ and P2X₁ knockout mice and unselective P2Y₁ and P2X₁ antagonists have shown that this may also prove to be effective targets for antithrombotic drugs in the future (96). Altogether, the results of ongoing trials including new antiplatelet drugs are eagerly awaited. The development of new antiplatelet drugs may be a hopeful new step towards an individualised pharmacotherapy, especially for patients with low response to clopidogrel or genetic polymorphisms resulting in loss-of-function alleles.

Summary and conclusions

Dual antiplatelet therapy consisting of aspirin and the ADP-receptor antagonist clopidogrel is the current standard therapeutic principle after coronary stent implantation for the prevention of recurrent cardiovascular events. However, diverse data supports the existence of high variability in individual response to clopidogrel with up to 44% of patients revealing an inadequate "low response". A universal definition of inadequate clopidogrel response, however, is lacking and it is unclear how to assess this variable response. There are many different platelet function tests with diverse advantages and disadvantages and results that cannot be compared easily. The response variability to clopidogrel is clinically relevant since high levels of RPA were demonstrated to correlate with recurrent cardiovascular events. Contributing factors to individual differences in clopidogrel response are multiple, non-genetic (e.g. clinical) and genetic. Therefore, an individualised pharmacologic approach which takes all factors into account represents a major challenge. There are different possibilities to overcome limitations of inadequate clopidogrel response. Besides assuring the patient's compliance, the choice of co-medication that potentially interacts with clopidogrel is crucial. Furthermore, increase of clopidogrel loading and maintenance doses to achieve further inhibition of platelet aggregation are other options, and algorithms of such a tailored antiplatelet therapy are currently under development and will be considered in future guidelines. In situations when platelet function testing is not available or in combination with laboratory testing, clinical scores for evaluation of high risk of RPA despite clopidogrel intake might be useful tools for therapeutic decision-making in the future. Also genetic risk analyses (testing for CYP polymorphisms) can be applied but results are hardly available at an early phase of antiplatelet therapy. Furthermore, new platelet inhibitors may overcome the problem of inadequate response, relatively low onset of action and oral application. Currently, new therapeutic agents acting on the ADP receptor are already available (prasugrel) or are on the way. Their targets, the ADP receptors (P2Y1 and P2Y12) are located on the platelet surface membrane and trigger platelet aggregation via down-regulation of adenylyl cyclase. The thienopyridines ticlopidine, clopidogrel and the novel substance prasugrel all act as ADP receptor blockers but have widely differing side-profiles and pharmacological properties, especially with regard to the onset of action. In contrast to thienopyridines, ATP-analogons do not require conversion into an active form. So far, results of diverse trials indicate that these new drugs reveal a smaller amount of response variability and seem to be more potent in the degree of platelet inhibition. Side effects are possibly mediated via A1 adenosine receptors which do not occur with the irreversibly acting P2Y12 antagonists. However, the bleeding risk in particular subgroups has to be taken into consideration. Also for reasons of cost-effectiveness the use of novel antiplatelet substances can not be applied as a routine alternative. Thus, strategies have to be developed to identify patients who benefit from personalised pharmacotherapy consisting of intensified (dose increase) or alternative antiplatelet therapies. Platelet function point-of-care testing or non-genetic and genetic risk analysis might be suitable approaches to achieve this goal.

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