How to improve the concept of individualised antiplatelet therapy with P2Y<sub>12</sub> receptor inhibitors – is an algorithm the answer?

Jolanta M. Siller-Matula<sup>1</sup>; Dietmar Trenk<sup>2</sup>; Karsten Schrör<sup>3</sup>; Meinrad Gawaz<sup>4</sup>; Steen D. Kristensen<sup>5</sup>; Robert F. Storey<sup>6</sup>; Kurt Huber<sup>7</sup>; for the European Platelet Academy

<sup>1</sup>Department of Cardiology, Medical University of Vienna, Austria; <sup>2</sup>Clinics of Cardiology and Angiography II, Universitäts-Klinikum Schleswig-Holstein, Campus Lübeck, Germany; <sup>3</sup>Institut für Pharmakologie und Klinische Pharmakologie, Heinrich-Heine-Universität, Düsseldorf, Germany; <sup>4</sup>Medizinische Klinik III, Department of Cardiology and Cardiovascular Diseases, Eberhard Karls University, Tübingen, Germany; <sup>5</sup>Department of Cardiology, Aarhus University Hospital, Denmark; <sup>6</sup>Department of Cardiovascular Science, University of Sheffield, UK; <sup>7</sup>3rd Medical Department, Cardiology and Emergency Medicine, Wilhelminen hospital, Vienna, Austria

Summary

Within the past decade, high on-treatment platelet reactivity (HTPR) on clopidogrel and its clinical implications have been frequently discussed. Although it has been previously assumed that HTPR is a phenomenon occurring only in patients treated with clopidogrel, recent data show that HTPR might also occur during treatment with prasugrel or ticagrelor in the acute phase of ST-elevation myocardial infarction. Moreover, it has been postulated that there is a therapeutic window for P2Y<sub>12</sub> receptor blockers, thus indicating that HTPR is associated with thrombotic events whereas low on-treatment platelet reactivity (LTPR) is associated with bleeding events. The current paper focuses on tools to identify risk factors for HTPR (pharmacogenetic testing, clinical scoring and drug-drug interactions) and on the use of platelet function testing in order to identify patients who might not respond adequately to clopidogrel. The majority of recent clinical randomised trials have not supported the hypothesis that platelet function testing and tailored antiplatelet therapy are providing a favourable clinical outcome. These trials, mainly performed in low-to-moderate risk patients, will be reviewed and discussed. Finally, an algorithm based on current knowledge is suggested, which might be of use for design of clinical trials.

Keywords

Platelet reactivity, clopidogrel, prasugrel, ticagrelor

Purpose of this review

The purpose of this review is to: i) provide a critical literature review regarding high on-treatment platelet reactivity (HTPR) to P2Y<sub>12</sub> receptor inhibitors, ii) to discuss studies, which applied personalised antiplatelet treatment with P2Y<sub>12</sub> receptor inhibitors, iii) to provide possible explanations why has the concept of personalised anti-platelet therapy with P2Y<sub>12</sub> receptor inhibitors failed so far, and iv) to propose an algorithm for personalised antiplatelet treatment with P2Y<sub>12</sub> receptor inhibitors, which might be of interest when designing future trials.

Introduction

Platelet function studies have shown that 30–50% of patients (dependent on the assay used) have HTPR while on clopidogrel treatment (1, 2). Studies including more than 20,000 patients have demonstrated an association between HTPR and adverse ischaemic events with the strongest association for short-term thrombotic events in patients undergoing percutaneous coronary intervention (PCI) (odds ratio [OR] 2–10) (3–13). Adenosine diphosphate (ADP)-induced platelet function testing has been established as the best predictor of ischaemic events in patients treated with dual antiplatelet therapy (5, 9, 11, 14–17). Nevertheless, although associations have been reported, an independent association between HTPR, platelet reactivity and outcome has not been consistently demonstrated. Although it has been previously assumed that HTPR is a phenomenon occurring only on treatment with clopidogrel, recent data show that in special clinical situations such as in the acute phase of ST-elevation myocardial infarction (STEMI) a substantial proportion (30–40%) of patients treated with prasugrel or ticagrelor exhibited HTPR (18–24), which was associated with adverse ischaemic outcome in one of these studies (20). In detail, roughly 46% (ticagrelor) and 37% (prasugrel) of patients suffering from STEMI and treated with one of the new P2Y<sub>12</sub>-receptor antagonists exhibited HTPR when assessed 2 hours (h) after the loading dose, thus demonstrating no consistent efficacy in reducing platelet function during or shortly after primary PCI (23).

Some recent studies postulate that there might be a therapeutic window for P2Y<sub>12</sub>-receptor blockers, indicating that HTPR is associated with thrombotic events, whereas low on-treatment platelet reactivity (LTPR) may be related to bleeding events (25–30) (▶ Figure 1). For better understanding of its clinical importance, this association has to be confirmed in future trials.
Several clinical and demographic variables are associated with HTPR in patients treated with clopidogrel. These factors include obesity, renal dysfunction, diabetes, higher age, reduced left ventricular function, inflammation and the presence of an acute coronary syndrome (ACS) (31–36) (Figure 2). Drug-drug interactions may also contribute to variability in response to clopidogrel or ticagrelor. For instance, certain proton-pump inhibitors such as omeprazole, calcium channel blockers, ketoconazole or rifampicin interact with clopidogrel metabolism (33, 37–46). Whereas ketoconazole, rifampicin, clarithromycin or dexamethasone have an impact on ticagrelor pharmacokinetics, ticagrelor itself increases the plasma levels of the CYP3A4 substrates simvastatin and lovastatin, of the p-glycoprotein substrate digoxin and also of cyclosporine (45). Interestingly, concomitant use of morphine was a strong predictor of HTPR in patients treated with clopidogrel, prasugrel and ticagrelor, indicating that impaired or delayed absorption of those drugs induced by morphine might be the underlying mechanism of slower action onset in STEMI patients (24, 47).

From multiple candidate genes being involved in absorption, activation, and inhibition of the receptor by P2Y$_{12}$ antagonists, CYP2C19*2 (loss of function allele) has been associated with a reduced antiplatelet effect of clopidogrel and increased risk for adverse cardiovascular events in several studies (33, 48–52). However, other reports could not confirm the impact of CYP2C19*2 on clinical outcome (15, 53). This discrepancy might be explained by the fact that the CYP2C19*2 allele accounts only for 5–12% of the variation in the response to clopidogrel (39, 52). Moreover, while the majority of heterozygote carriers had a sufficient level of platelet inhibition by increased clopidogrel dosage, a much higher proportion of homozygotes failed to respond (i.e. < 230 P2Y12 reaction units (PRU) by VerifyNow test) despite daily doses of 300 mg clopidogrel (54). Other CYP2C19 variants (*3 -*8) have a low allele frequency in Caucasians (<1%) and contribute thereby only to a minor extent to HTPR (55–57). In contrast, in East Asians up to 17% of patients are carriers of the CYP2C19*3 allele, which also plays a role as a predictor of HTPR (57). Another explanation might be that the CYP2C19*2 allele has been shown to be important mainly in the acute phase of myocardial infarction, whereas in a chronic stable phase it does not appear to be significant (58).

Data on the clinical impact of a gain-of-function mutation (CYP2C19*17), which is responsible for an intensified activation of clopidogrel, are conflicting so far (15, 27, 59, 60). Whether polymorphisms of other genes are involved in the metabolism or action of clopidogrel (e.g. the intestinal efflux transport pump P-glycoprotein pump encoded by the ABCB1 gene (33, 55, 58, 61–63), the ITGB3 encoding the integrin Beta3 of the GpIIb/IIIa receptor (33, 55), the P2Y12 receptor (33, 55, 64) is a matter of debate. Although the P-glycoprotein pump and the CYP4S0 system are also involved in the transport and metabolism of prasugrel and ticagrelor (Figure 3), polymorphisms of the responsive gens did not impact on clinical outcome of ticagrelor or prasugrel treated patients (58, 65).

Studies investigating personalised antiplatelet treatment

Undoubtedly, a growing body of evidence underlines a considerable concern surrounding the one-size-fits-all strategy with clopidogrel. The majority of published data linked clopidogrel non-responsiveness to adverse ischaemic events especially in patients undergoing PCI, which led to the suggestion that the magnitude of platelet in-
by clopidogrel can be monitored and adjusted appropriately using different approaches. Several studies have demonstrated that the inhibition of ADP-induced platelet aggregation in patients on standard doses of clopidogrel can be improved with higher loading or maintenance doses of clopidogrel, or by switching to prasugrel or ticagrelor (▶Table 1). Administration of a 150 mg maintenance dose of clopidogrel resulted in more intense inhibition of platelet aggregation than administration of the 75 mg maintenance dose in a major subset of patients but not in all (66–68). In line with these findings, tailored treatment with up to four repeated loading doses of clopidogrel or a single reloading and a double maintenance dose of clopidogrel overcame HTPR to the conventional-dose clopidogrel therapy (69–71). Nevertheless, doubling the clopidogrel maintenance dose did not reach the same inhibition level as the one achieved in patients with an adequate response (67, 68, 72, 73). Moreover, the enhanced platelet reactivity persisted over time in some patients and the antiplatelet effect was not uniform (67, 68, 73). Interestingly, adding cilostazol to aspirin and clopidogrel was more effective than 150 mg maintenance dose of clopidogrel (74). Novel P2Y₁₂ receptor inhibitors achieved stronger platelet inhibition in patients with HTPR to clopidogrel and only prasugrel and ticagrelor are currently approved for clinical use. With regard to genotype-based personalised treatment, increased loading doses up to 900 mg or maintenance doses up to 300 mg have been show to overcome HTPR under clopidogrel treatment in heterozygous carriers of CYP2C19*2 allele but not in homozygous carriers (54, 75).

An impact on clinical outcome with individualised antiplatelet therapy has been tested in some smaller studies (▶Table 1). Guided therapy with up to four clopidogrel re-loadings in the group of patients with HTPR resulted in a reduction of major adverse cardiac events without an increase in major bleeding complications (69–71). In line with this finding, intensified platelet inhibition with GP IIb/IIIa antagonists lowered the incidence of major adverse cardiac events without increased bleeding rates (76, 77). In contrast, guided antiplatelet therapy did not improve patient outcomes in the large-scale GRAVITAS [Gauging Responsiveness With A VerifyNow Assay-Impact On Thrombosis And Safety] trial (78). Patients with HTPR under clopidogrel treatment were randomised to standard dosing of clopidogrel or to receive a second clopidogrel loading dose of 600 mg and were treated with a double maintenance dose of 150 mg of clopidogrel throughout the study. This approach, tested in more than 2,200 patients, showed no differences in event rates during six months follow-up in a patient population with a low-to-moderate thrombotic risk.

The TRIGGER-PCI [Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel] trial, which compared prasugrel versus clopidogrel in patients with HTPR to clopidogrel after elective DES implantation without procedural complications (low thrombotic risk), was stopped prematurely for futility after randomisation of 423 patients, because an interim analysis indicated a lower than expected incidence of the primary endpoint. However, platelet aggregation data from TRIGGER-PCI clearly demonstrated that HTPR could be corrected by switching from clopidogrel to prasugrel (79).

The TRILOGY ACS [The Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syn-
dromes] platelet substudy among medically managed patients with ACS but no ST-segment elevation, confirmed that the use of prasugrel was associated with lower platelet reactivity than clopidogrel. Although platelet reactivity showed association with the occurrence of ischaemic outcomes in univariate and survival analyses, there was no independent association between platelet reactivity and ischaemic events (80).

In contrast, a meta-analysis of 10 randomised trials in 4,213 patients showed that the intensified antiplatelet treatment was associated with a significant reduction in cardiovascular mortality, stent thrombosis and myocardial infarction (81). Interestingly, meta-regression analysis revealed that the net clinical benefit of the intensified treatment significantly depended on the baseline risk for stent thrombosis.

In the recently published open-label ARCTIC [Double Randomisation of a Monitoring Adjusted Antiplatelet Treatment Versus a Common Antiplatelet Treatment for DES Implantation, and Interruption Versus Continuation of Double Antiplatelet Therapy] trial, 2,440 patients scheduled for coronary stenting, who were at low-to-moderate thrombotic risk, were randomised to bedside platelet function monitoring versus no monitoring. In the monitoring arm, antiplatelet therapy could be intensified in patients with HTFR under aspirin or clopidogrel, either by increasing the dose of aspirin or an additional loading dose followed by an increased maintenance dose of clopidogrel, by switching to prasugrel, or by additional treatment with GP IIb/IIIa inhibitors. Despite the fact that platelet reactivity could be reduced, the strategy of therapy adjustment based on platelet function monitoring did not

Figure 3: Metabolic pathways and binding to the P2Y<sub>12</sub> receptor by clopidogrel, prasugrel and ticagrelor. Adenosine diphosphate (ADP), cytochrome P450 (CYP).
lead to any improvement in the composite endpoint of coronary ischaemic events (82).

Currently, several studies are underway to evaluate the association between genetic profiling or platelet function testing and clinical outcome (Table 2). With respect to genetic testing, it has to be mentioned that it is currently not clear whether a combination of different polymorphisms (e.g. CYP2C19*2 and CYP2C19*17) have any clinical implication and that the determination of single polymorphisms therefore might not represent the full truth.

Why has the concept of individualised anti-platelet therapy failed so far?

Reasons related to risk classification of the study population

The ADAPT-DES [Assessment of Dual AntiPlatelet Therapy With Drug Eluting Stents] registry indicated that platelet function assessment in patients with stable CAD treated with clopidogrel is unlikely to provide benefit, whereas this approach may be feasible in patients with high-risk ACS (83). In line with the latter, a meta-regression analysis revealed that the net clinical benefit of the intensified treatment largely depends on the baseline risk for stent thrombosis (81). Importantly, large randomised controlled trials (GRAVITAS, TRIGGER-PCI, ARCTIC, TRILOGY-ACS) included low-to-moderate risk patients whereas high-risk patients, such as those with STEMI, were excluded (Table 1). In the ARCTIC study, patients with NSTE-ACS represented only 25% of the study population (84). The TRIGGER-PCI trial included only patients with elective DES-PCI without procedural complications (79). Also the GRAVITAS trial enrolled stable patients undergoing elective PCI (60%) and a minor proportion of patients with NSTE-ACS (40%) (78). In the TRILOGY ACS platelet substudy, the post-ACS patients treated conservatively (about half without diagnostic angiography) probably also are low- or moderate-risk patients (80). Therefore, exclusion of high-risk patients may have accounted for the negative study results.

Based on the above considerations, intensified antiplatelet treatment does not seem to be efficacious in patients with a low-to-moderate risk for thrombotic events (such as elective PCI or conservatively-treated patients included days after a NSTE-ACS) but might improve outcome in higher-risk patients or in those with a high risk for stent thrombosis (predisposing factors: diabetes, ACS, multiple stenting and multivessel disease).

Reasons related to the limitations of platelet function testing

The one major limitation of platelet function testing is the lack of consensus regarding the optimal cut-off for HTPR and low standardisation of methods (Table 3). Another problem with platelet function testing arises as some factors can influence the results, the most important of which are technical (anticoagulant used and time delay) and chemical (agonist used and its concentration) (85, 86).

Another shortcoming of platelet function testing ex vivo are the experimental conditions under which most of these assays are performed. Platelets are taken out from their natural environment and subsequently re-stimulated by one selected stimulus, in case of ADP-antagonist, by ADP and clot formation is then determined. These procedures ignore the multiplicity of platelet stimuli, acting simultaneously in vivo as well as the secretory function of platelets, i.e. the paracrine release of mediators (e.g. thromboxane A2, serotonin, others), which might act on non-platelet targets with consequences for the clinical outcome. These procedures also ignore the different platelet-activating situations in ACS vs stable angina as well as the interaction with white cells or plasmatic cytokines (87). They do allow predictions for the pharmacological efficacy of a given drug – an ADP-antagonist: if the drug does not block ADP-induced aggregation in vitro, it will also fail to do so in vivo. However, the opposite conclusion cannot be drawn – i.e. that a compound that works in vitro is also expected to work in vivo to prevent platelet-dependent thrombus formation. The latter, however, is what investigators and physicians really want to know, at least with some predictive certainty. To improve this certainty is the goal of individualised antiplatelet treatment by platelet function testing. However, this goal is clearly not reached by performing platelet function assays as surrogates of the efficacy of antithrombotic treatment in all cardiovascular patients at risk of thrombosis. High-risk patients on clopidogrel, such as diabetics, might be one group where platelet function testing is useful but still not predictive enough because of the very low event-rate in patients on stable conditions. In any case, general agreement on the type of assay to be performed and its cut-off values is another highly desirable precaution. Although it is already proven that platelet hyperreactivity is a key risk factor for arterial thrombosis, the question remains, whether and for what extent this hyperreactivity remains because non-ADP-agonists, such as thrombin, are major stimuli for platelet-dependent thrombus formation in certain clinical conditions. For example, thrombin contributes to initial platelet activation in ACS. Huge amounts of thrombin can be generated after generation and release of tissue factor from the ruptured plaque area (88). One possible solution would be to use modified thrombelastography (TEG) assay (e.g. a platelet mapping assay), which allows measurement of platelet–fibrin clot strength and is sensitive to P2Y12 receptor inhibition as the contribution of P2Y12 receptor to the thrombus formation is measured by the addition ADP. The advantage with TEG is the fact that the test assesses several aspects of thrombus formation and the interaction between platelets and coagulation system. Nevertheless, still the disadvantage of the modified TEG is a low standardisation. Therefore, the tests might provide only incomplete answers to the really burning question of clinical efficacy of antiplatelet drugs and its predictability. Another problem arises as platelet function testing represents predictive tests (pre-symptomatic testing; the condition is not present at the time of testing) for which no established measures of performance are given. Therefore, it might not be surprising that the positive predictive values (PPV) of phenotyping are low for stent thrombosis when assessed before the event occurs (pre-symptomatic testing: PPV=5–15%), whereas it increases when the test is performed...
at the time of stent thrombosis (symptomatic testing: PPV=50\%) (11).

Noteworthy, in the larger trials investigating intensified antiplatelet treatment, which were in most cases negative, the VerifyNow assay system was used (Table 1). Whether the use of other assay methods with subsequent intensification of antiplatelet treatment will improve outcome has to be investigated in future studies. Also, the use of hirudin anticoagulation might enhance the accuracy of the VerifyNow P2Y12 assay in a clinical trial setting (86).

### Table 1: Studies investigating guided antiplatelet treatment.

<table>
<thead>
<tr>
<th>Study author/-Acronym (ref.)</th>
<th>Population</th>
<th>n</th>
<th>Follow-up</th>
<th>Outcome</th>
<th>Method</th>
<th>Cut-off value</th>
<th>Study type</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRAVITAS (78)</td>
<td>PCI for CAD or NSTE-ACS</td>
<td>2214</td>
<td>6 months</td>
<td>MACE</td>
<td>VerifyNow</td>
<td>230 PRU</td>
<td>CRT: 300/75 mg clopidogrel vs 600/75 mg clopidogrel in patients with HTPR</td>
</tr>
<tr>
<td>TRIGGER-PCI (79)</td>
<td>elective PCI</td>
<td>423</td>
<td>6 months</td>
<td>MACE; bleeding</td>
<td>VerifyNow</td>
<td>208 PRU</td>
<td>CRT: prasugrel (loading of 60 mg and maintenance 10 mg) vs. clopidogrel (maintenance 75 mg) in patients with HTPR</td>
</tr>
<tr>
<td>Valgimigli et al. (76)</td>
<td>elective PCI</td>
<td>263</td>
<td>in hospital</td>
<td>MACE</td>
<td>VerifyNow</td>
<td>235 PRU</td>
<td>CRT: tirofiban vs placebo in patients with HTPR</td>
</tr>
<tr>
<td>Alexopolus et al. (21)</td>
<td>CAD with clopidogrel treatment</td>
<td>31</td>
<td>1 month</td>
<td>level of platelet inhibition</td>
<td>VerifyNow</td>
<td>235 PRU</td>
<td>randomised, crossover: 10 mg prasugrel vs 150 mg clopidogrel in patients with HTPR</td>
</tr>
<tr>
<td>Alexopolus et al. (22)</td>
<td>HD with clopidogrel treatment</td>
<td>21</td>
<td>1 month</td>
<td>level of platelet inhibition</td>
<td>VerifyNow</td>
<td>235 PRU</td>
<td>randomised, crossover: 10 mg prasugrel vs 150 mg clopidogrel*</td>
</tr>
<tr>
<td>ARCTIC (82)</td>
<td>PCI with DES</td>
<td>2440</td>
<td>1 year</td>
<td>MACE</td>
<td>VerifyNow</td>
<td>235 PRU</td>
<td>CRT: guided: clopidogrel (600 mg reloading and 75 mg or 150 mg maintenance) or prasugrel (60 mg loading and 10 mg maintenance) or GP IIb/IIIa inhibitors vs non-guided: clopidogrel (maintenance 75 mg) in patients with HTPR</td>
</tr>
<tr>
<td>Capranzano et al. (115)</td>
<td>clopidogrel treatment + age &gt; 75</td>
<td>100</td>
<td></td>
<td>level of platelet inhibition</td>
<td>VerifyNow</td>
<td>230 PRU</td>
<td>observational: prasugrel in patients with HTPR</td>
</tr>
<tr>
<td>Bonello et al. (70)</td>
<td>PCI</td>
<td>162</td>
<td>1 month</td>
<td>MACE</td>
<td>VASP assay</td>
<td>50%</td>
<td>CRT: guided (repeated loading with clopidogrel 600 mg) vs non-guided group</td>
</tr>
<tr>
<td>Bonello et al. (69)</td>
<td>PCI</td>
<td>429</td>
<td>1 month</td>
<td>MACE, ST, bleeding</td>
<td>VASP assay</td>
<td>50%</td>
<td>CRT: guided (repeated loading with clopidogrel 600mg) vs. non-guided group</td>
</tr>
<tr>
<td>VASP-02 (73)</td>
<td>elective PCI</td>
<td>153</td>
<td>1 month</td>
<td>MACE, level of platelet inhibition</td>
<td>VASP assay</td>
<td>69%</td>
<td>observational: 150 mg clopidogrel in patients with HTPR</td>
</tr>
<tr>
<td>Ferreira et al. (116)</td>
<td>DMII</td>
<td>30</td>
<td></td>
<td>level of platelet inhibition</td>
<td>VASP assay</td>
<td>50%</td>
<td>observational: cilostazol vs 150 mg clopidogrel in patients with HTPR</td>
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<tr>
<td>Kozinski et al. (117)</td>
<td>ACS+PCI</td>
<td>71</td>
<td>1 month</td>
<td>level of platelet inhibition</td>
<td>VASP assay</td>
<td>50%</td>
<td>parallel-group, open-label study; patients with HTPR were assigned to prasugrel (30 mg loading dose, 10 mg maintenance dose) or clopidogrel (150 mg maintenance dose for 6 days and thereafter 75 mg maintenance dose)</td>
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<td>Trenk et al. (72)</td>
<td>elective PCI</td>
<td>117</td>
<td>14 days</td>
<td>level of platelet inhibition</td>
<td>LTA</td>
<td>14%</td>
<td>observational: 150 mg clopidogrel vs control in patients with HTPR</td>
</tr>
<tr>
<td>ACCEL-RESISTANCE (74)</td>
<td>PCI</td>
<td>60</td>
<td>1 month</td>
<td>level of platelet inhibition</td>
<td>LTA</td>
<td>50%</td>
<td>CRT: adjunctive cilostazol vs 150 mg clopidogrel in patients with HTPR</td>
</tr>
<tr>
<td>Cuisset et al. (77)</td>
<td>elective PCI</td>
<td>149</td>
<td>1 month</td>
<td>MACE</td>
<td>LTA</td>
<td>70%</td>
<td>CRT: GP IIb/IIIa antagonists vs control in patients with HTPR</td>
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</table>
not typing Infarct Patients to Adjust and Normalize Thienopyridine Treatment], and another trial evaluating ticagrelor use in patients with the CYP2C19 loss of function allele in PCI patients is still ongoing (TAILOR-PCI [Tailored Antiplatelet Therapy Following PCI]). In the GIANT trial, which has been presented at Transcatheter Cardiovascular Therapeutics 25th Annual Scientific Symposium, 272 patients received assay-guided antiplatelet therapy adjustment. The one-year composite endpoint was about five times higher for the CYP2C19 loss of function allele in PCI patients (up to 4 loading doses with 600 mg clopidogrel or 1 loading dose with prasugrel in patients with HTPR). Nevertheless, we are still awaiting the publication of the original paper.

Nevertheless, prospective randomised double-blind trials with use of pharmacogenetic profiling to guide antiplatelet drug regimen are, to our knowledge, not yet registered. It seems that both genotyping and phenotyping provide complementary information to stratify risk (90). The TARGET-PCI [Thrombocyte Activity Reassessment and GEneTyping for PCI] study, a randomised open label study to guide antiplatelet therapy, was designed to investigate a strategy of simultaneous pheno- and genotyping. Unfortunately, the trial has been terminated due to the lack of financial support.

### Reasons related to the protocol for personalised therapy

Another possible explanation for the negative results of some recent large trials is the fact that the study protocols allowed only singular switch to other drug or dose (Table 2). The latter aspect is mirrored in the GRAVITAS trial, in which 40% of patients in the guided group displayed HTPR phenotype despite high dose clopidogrel (78). Interestingly, in TRIGGER-PCI, less than 6% of patients with HTPR on clopidogrel had still HTPR after switching to prasugrel (79). Therefore, it is not surprising that this inadequate personalised therapy failed to show a significant benefit. Although in the ARCTIC trial platelet function was measured repeatedly, other aspects might have accounted for unsuccessful outcome as the fact that only 3.3% of patients were switched to prasugrel (79). Therefore, it is not surprising that this inadequate personalised therapy failed to show a significant benefit.

### Table 1: Continued

<table>
<thead>
<tr>
<th>Study author/ - Acronym (ref.)</th>
<th>Population</th>
<th>n</th>
<th>Follow-up</th>
<th>Outcome</th>
<th>Method</th>
<th>Cut-off value</th>
<th>Study type</th>
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<tr>
<td>Matezky et al. (118)</td>
<td>MI</td>
<td>200</td>
<td>10 weeks</td>
<td>level of platelet inhibition</td>
<td>LTA</td>
<td>80 %</td>
<td>observational: 600/150 mg clopidogrel in patients with HTPR</td>
</tr>
<tr>
<td>Gurbel et al. (119)</td>
<td>stable CAD + previous PCI</td>
<td>20</td>
<td>7 days</td>
<td>level of platelet inhibition</td>
<td>LTA</td>
<td>43 %</td>
<td>observational: single dose elinogrel 60 mg in patients with HTPR</td>
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<tr>
<td>RESPOND (120)</td>
<td>stable CAD + clopidogrel</td>
<td>41</td>
<td>1 month</td>
<td>level of platelet inhibition</td>
<td>LTA</td>
<td>43 %</td>
<td>CRT: crossover: ticagrelor 180/90 mg vs clopidogrel 600/75 mg</td>
</tr>
<tr>
<td>MADONNA (71)</td>
<td>PCI</td>
<td>798</td>
<td>1 month</td>
<td>ST, MACE, TIMI major bleeding</td>
<td>MEA</td>
<td>50 U</td>
<td>Non-randomised, controlled: non-guided vs guided group (up to 4 loading doses with 600 mg clopidogrel or 1 loading dose with prasugrel in patients with HTPR)</td>
</tr>
<tr>
<td>Aradi et al. (91)</td>
<td>ACS+PCI</td>
<td>741</td>
<td>1 year</td>
<td>ST, MACE, BARC major bleeding</td>
<td>MEA</td>
<td>46 U</td>
<td>observational: 600/150 mg clopidogrel vs prasugrel in patients with HTPR</td>
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<td>Neubauer (121)</td>
<td>elective PCI</td>
<td>161</td>
<td>level of platelet inhibition</td>
<td>IA</td>
<td>5 U</td>
<td>observational: 600/150 mg clopidogrel vs ticlopidine in patients with HTPR</td>
<td></td>
</tr>
<tr>
<td>BOCLA Plan (34)</td>
<td>PCI</td>
<td>504</td>
<td>level of platelet inhibition</td>
<td>IA</td>
<td>5 U</td>
<td>observational: 600/150 mg clopidogrel vs ticlopidine vs prasugrel in patients with HTPR</td>
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<tr>
<td>CLOVIS-2 (75)</td>
<td>MI</td>
<td>109</td>
<td>in hospital</td>
<td>level of platelet inhibition</td>
<td>CYP2C19 *2</td>
<td>*1/*2 and *2/*2</td>
<td>CRT: 300 vs 900 mg clopidogrel</td>
</tr>
<tr>
<td>ELEVATE TIMI-56 (54)</td>
<td>clopidogrel treatment</td>
<td>333</td>
<td>1 month</td>
<td>level of platelet inhibition</td>
<td>CYP2C19 *2</td>
<td>*1/*2 and *2/*2</td>
<td>CRT: 75, 150, 225, or 300 mg clopidogrel in *2 carriers vs. 75 or 150 mg clopidogrel in *2 non-carriers</td>
</tr>
<tr>
<td>RAPID-GENE (122)</td>
<td>PCI</td>
<td>200</td>
<td>7 days</td>
<td>level of platelet inhibition</td>
<td>CYP2C19 *2</td>
<td>*1/*2 and *2/*2</td>
<td>CRT: 10 mg prasugrel in *2 carriers vs 75 mg clopidogrel in *2 non-carriers</td>
</tr>
<tr>
<td>ACCEL-AMI-2C19 (123)</td>
<td>MI</td>
<td>126</td>
<td>30 days</td>
<td>level of platelet inhibition</td>
<td>CYP2C19 *2</td>
<td>*1/*2 and *2/*2</td>
<td>CRT: adjunctive cilostazol vs high maintenance-dose clopidogrel</td>
</tr>
<tr>
<td>ACCEL-2C19 (124)</td>
<td>elective PCI</td>
<td>134</td>
<td>30 days</td>
<td>level of platelet inhibition</td>
<td>CYP2C19 *2/*3</td>
<td>*1/*2 and *2/*2 and *2/*3</td>
<td>CRT: adjunctive cilostazol vs high maintenance-dose clopidogrel</td>
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</tbody>
</table>

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Thrombosis and Haemostasis 113.1/2015
The combined incidence of bleeding and thrombotic complications during 12 months

<table>
<thead>
<tr>
<th>Identifier</th>
<th>Acronym</th>
<th>Title</th>
<th>Population</th>
<th>Test</th>
<th>n</th>
<th>Treatment strategy</th>
<th>Primary endpoint</th>
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<tr>
<td>NCT00774475</td>
<td>DANTE</td>
<td>Dual Antiplatelet Therapy Tailored on the Extent of Platelet Inhibition</td>
<td>UA/STEMI undergoing PCI with stent implantation</td>
<td>VerifyNow</td>
<td>442</td>
<td>Active Comparator: clopidogrel 150 mg/day; Control Comparator: clopidogrel 75 mg/day</td>
<td>Composite of cardiovascular death, non-fatal myocardial infarction, target lesion vessel revascularisation by PCI or coronary bypass at 6 and 12 months</td>
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<tr>
<td>NCT01515345</td>
<td>IDEAL-PCI</td>
<td>Individualizing Dual Antiplatelet Therapy after PCI</td>
<td>PCI</td>
<td>MEA</td>
<td>1,000</td>
<td>Switch to prasugrel or ticagrelor in patients with HTPR</td>
<td>ST, bleedings</td>
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<tr>
<td>NCT00995514</td>
<td>GeCCO</td>
<td>Genotype Guided Comparison of Clopidogrel and Prasugrel Outcomes Study</td>
<td>ACS</td>
<td>CYP2C19*2</td>
<td>14,600</td>
<td>Active comparator: prasugrel 10mg/day; Control comparator: clopidogrel 75mg/day</td>
<td>Composite of cardiovascular death, nonfatal MI, or non-fatal stroke at 6 months</td>
</tr>
<tr>
<td>NCT01452152</td>
<td>PAPI-2</td>
<td>Pharmacogenomics of Anti-platelet Intervention-2</td>
<td>PCI</td>
<td>CYP2C19*2</td>
<td>7,200</td>
<td>Intervention group: CYP2C19 intermediate metabolisers: clopidogrel; Intervention group: CYP2C19 intermediate metabolisers: prasugrel; observational group: no Intervention</td>
<td>Composite of non-fatal myocardial infarction, non-fatal stroke, definite or probable stent thrombosis and death secondary to any cardiovascular cause at 1 year</td>
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<tr>
<td>NCT01097343</td>
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<td>Clopidogrel Pharmacogenomics Project</td>
<td>clopidogrel intake</td>
<td>CYP2C19*2</td>
<td>200</td>
<td>Active Comparator: clopidogrel 150 mg/day; Control Comparator: clopidogrel 75 mg/day</td>
<td>Level of platelet inhibition</td>
</tr>
<tr>
<td>NCT01134380</td>
<td>GIANT</td>
<td>Genotyping Infarct Patients to Adjust and Normalize Thienopyridine Treatment</td>
<td>STEMI+primary PCI</td>
<td>CYP2C19*2</td>
<td>1,500</td>
<td>Increase of the clopidogrel dosage, prasugrel or clopidogrel</td>
<td>Composite of death, MI and stent thrombosis at 12 months</td>
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<tr>
<td>NCT01538446</td>
<td>ANTARC-TIC</td>
<td>Tailored Antiplatelet Therapy Versus Recommended Dose of Prasugrel</td>
<td>ACS</td>
<td>VerifyNow</td>
<td>962</td>
<td>Down-adjustment of the dose of prasugrel in high responders and up-adjustment of the dose of prasugrel in low responders as compared to a fixed dose of 5 mg to every patient without monitoring</td>
<td>Composite of cardiovascular death, MI, stroke, ST, urgent revascularisation or bleeding</td>
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<tr>
<td>NCT01643031</td>
<td>MATTIS-D</td>
<td>Effect of Modifying Anti-platelet Treatment to Ticagrelor in Patients With Diabetes and Low Response to Clopidogrel</td>
<td>Diabetes with elective PCI</td>
<td>VerifyNow</td>
<td>500</td>
<td>Switch to ticagrelor in patients with HTPR to clopidogrel for 30 days (followed by continued clopidogrel therapy) versus clopidogrel</td>
<td>Elevation of troponin or CK-MB (above the upper limit of normal, and above 3 times the upper limit of normal) measured 20–24 hours after the PCI</td>
</tr>
<tr>
<td>NCT01742117</td>
<td>TAILOR-PCI</td>
<td>Tailored Antiplatelet Therapy Following PCI</td>
<td>PCI</td>
<td>CYP2C19*2 or *3</td>
<td>5,945</td>
<td>Patients with the wild type CYP2C19 allele will be assigned to receive clopidogrel 75 mg. Patients with the CYP2C19*2 and *3 will be assigned to receive ticagrelor 90 mg.</td>
<td>Composite of non-fatal MI, non-fatal stroke, cardiovascular mortality, severe recurrent ischaemia, and stent thrombosis</td>
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<tr>
<td>NCT01959451</td>
<td>TROPICAL-ACS</td>
<td>Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment For Acute Coronary Syndromes Trial</td>
<td>ACS with PCI</td>
<td>MEA</td>
<td>2,600</td>
<td>1 week prasugrel treatment and switch over to clopidogrel treatment in adequate responders to clopidogrel versus standard treatment with prasugrel</td>
<td>The combined incidence of bleeding and thrombotic complications during 12 months</td>
</tr>
</tbody>
</table>
(78). A registry data suggested that prasugrel use in patients with HTPR resulted in a better outcome compared to use of high-dose clopidogrel (91). Therefore, the accumulating evidence suggests that when intensified antiplatelet treatment is tested, the more potent drugs prasugrel or ticagrelor should be preferred over doubling the maintenance dose of clopidogrel or use of repeated loading doses of clopidogrel. Importantly, repeated testing after switch to a more potent drug might be crucial in order to ensure sufficient level of platelet inhibition, as it has been performed in a small scale MADONNA [Multiple electrode Aggregometry in patients receiving Dual antiplatelet therapy to guide treatment with Novel platelet Antagonists] study (71).

Reasons related to the definition of the primary endpoint

The primary endpoint in the ARTIC trial was mainly based on the incidence of peri-procedural myocardial infarction (MI), which was defined as a documented rise in cardiac biomarkers (cardiac troponins or CK-MB measured 6 h after PCI higher than threefold the upper reference limit). Indeed, the primary endpoint (34.6%) was driven by the occurrence of MI (30.3%) and the visual inspection of the survival analyses confirms that the peri-procedural MI was the major driver of the primary endpoint (as suggested by the vast majority of events occurring immediately after inclusion). Therefore, it might well be that the inclusion of cardiac biomarker rise in the definition of MI in the ARCTIC study explains the difference in the incidence of MI between the trials: ARCTIC (30.2%), GRAVITAS (1.8%) and TRIGGER-PCI (0%) (78, 79, 82, 92).

As some studies proposed the concept of a therapeutic window for P2Y₁₂ receptor inhibition, which shows that a moderate level of platelet reactivity corresponds best with a net clinical benefit (20, 25, 26, 93), it might be an option to target a moderate level of platelet inhibition. This hypothesis is based on a rationale that patients with ACS treated with prasugrel or ticagrelor have a benefit in terms of a reduction of ischaemic events, but, for both drugs, at the cost of an increased rate of spontaneous bleeding events. Thus there might still be room for optimisation of antiplatelet therapy. Tempered against this hypothesis is the uncertainty about the mechanisms by which ticagrelor reduces mortality compared to clopidogrel therapy and the possibility that pleiotropic effects unrelated to platelet inhibition may be contributory (94).

Reasons related to the time point of participants inclusion

Inhibition of platelet function might depend on the time from drug intake to blood sampling and on the time between ACS/PCI and blood sampling (95–97). One must be aware of the circumstance that randomisation was performed 12–24 h after PCI in the GRAVITAS trial and 2–7 h after the first clopidogrel maintenance dose intake the day after successful PCI in the TRIGGER-PCI trial. Therefore, patients experiencing peri-procedural events, early after PCI or those with unsuccessful or complicated PCI procedures were not eligible for GRAVITAS or TRIGGER-PCI. In the TRILOGY ACS platelet substudy, post-ACS patients were treated up to seven days after the index event with non-study clopidogrel and then randomised to either clopidogrel or prasugrel (80). Therefore, it seems that timing of testing and eventual switching to more potent drugs should be set before or at least very early after stenting, as HTPR seems to play the most important role in the early phase.

Reasons related to the statistical power of the studies

Inappropriate power of the studies might be another reason why testing and adjustment was not effective. As mentioned the TRIGGER-PCI trial was stopped prematurely for futility after randomisation of 423 patients because an interim analysis indicated a lower than expected incidence of the primary endpoint (assumed: 4.7%, occurred: 0.4% after inclusion of only 20% of planned study population) (79). Concordantly, the event rates for the composite endpoint in GRAVITAS trial were also substantially lower than expected (assumed: 5%, observed: 2.3%) (78). It has also been suggested that the ARCTIC trial was not properly powered. If the traditional composite end point (death, MI, or stroke) had been selected, the investigators would have needed to enroll 17,540 patients with non-ST-elevation ACS in each study group (98).

Proposed algorithm for future personalised antiplatelet treatment

In general, current guidelines recommend a “one-size-fits-all” approach for antiplatelet agents due to lack of prospective double-blind randomised studies demonstrating an improvement in clinical outcome by personalised antiplatelet therapy. P2Y₁₂ receptor inhibitors are recommended on top of aspirin. The ACCF/AHA/SCAI and ESC guidelines issue a Class IIb recommendation for platelet function testing to facilitate the choice of P2Y₁₂ inhibitor in selected patients with high risk for thrombotic events following PCI, whereas routine testing is not recommended (Class III) (99–101). In patients presenting with an ACS, the novel platelet inhibitors prasugrel and ticagrelor provide superior inhibition of platelet reactivity and a reduction of thrombotic events, although at costs of increased spontaneous bleeding risk (102, 103). Indeed, it could be a valuable approach to use these potent drugs in almost all ACS patients as it was demonstrated for both compounds in high-risk patients, and as it is recommended by the current ESC guidelines (recommendation: prasugrel IB or ticagrelor IB over clopidogrel IC) (100, 104). In contrast, the ACC/AHA guidelines recommend either clopidogrel or ticagrelor or prasugrel in interventionally managed ACS (recommendation IB for all three agents) (105). As different guidelines exist world-wide and the American guidelines do not prefer one antiplatelet agent over other for ACS with stenting (106), it is possible that personalised antiplatelet treatment would be of interest at least in countries following the ACC/AHA guidelines. Moreover, there are several other reasons, which might
sion of an algorithm for personalised antiplatelet therapy, also in Europe:

- A therapeutic window for P2Y12 receptor inhibitors has been proposed, which indicates that more likely a moderate level of platelet inhibition correlates best with the net benefit (20, 25, 26, 93).

- Clopidogrel is still the only P2Y12 receptor blocker used in elective patients (107).

- Clopidogrel is currently recommended in ACS patients with a need for oral anticoagulation.

- Clopidogrel is also the P2Y12 receptor blocker of choice in patients with a high bleeding risk (104).

- Clopidogrel is the P2Y12 receptor blocker of choice in patients with contraindications to the novel antiplatelet drugs (up to 40% of patients) (100, 104, 108).

- Clopidogrel is already available as a generic. Several countries have financial constraints and the authorities start to discuss the need of new antiplatelet agents, especially with respect to the long-term use.

- Many countries in the world have currently no access to ticagrelor or prasugrel at all. Therefore, a personalised approach to antiplatelet treatment strategy might be a strategy in ACS patients in these countries considering the costs of novel antiplatelet drugs.

Based on these considerations and until ongoing trials (e.g. ANTARCTIC [Tailored Antiplatelet Therapy Versus Recommended Dose of Prasugrel], MATTIS-D [Effect of Modifying Anti-platelet Treatment to Ticagrelor in Patients With Diabetes and Low Response to Clopidogrel], TAILOR-PCI; Table 3) will show whether patients benefit from personalised antiplatelet therapy, we propose an algorithm that might be appropriate for design of future clinical trials. It is important to emphasise that the proposed algorithm is hypothetical. Additionally, although platelet function testing with the available test systems should not be recommended routinely, it might be considered as valuable diagnostic tool on a case-by-case basis, especially in patients who are at high thrombotic risk (e.g. diabetics), eventually also in patients scheduled for high-risk PCI (e.g. left main stenting or stenting of proximal bifur-
cations in elective cases), and specifically in those experiencing recurrent ischaemic events including stent thrombosis. However, randomised double-blinded clinical studies demonstrating a clinical benefit for this approach are lacking so far.

Patients might benefit from a global risk algorithm based on clinical (PREDICT score), biological (platelet function) and genetic (CYP2C19*2 carrier status) information (Figure 2). However, complementary information received from phenotyping and genotyping would provide a reassurance mainly about the clopidogrel response status and such an approach is time consuming and costly. Whereas platelet function testing identifies patients who do not respond sufficiently to clopidogrel, pharmacogenetic testing provides only a risk marker for HTPR. Genotyping alone may help guiding antiplatelet treatment in some specific clinical scenarios, e.g. for planned stenting of complex lesions or of the left main before intake of clopidogrel, especially when the patient is homozygous for the CYP2C19*2 allele, as those patients have a high probability for HTPR under clopidogrel treatment. Nevertheless, the major shortcoming of genotyping is the uncertainty in the prediction of the phenotype of clopidogrel response. Moreover, the response to clopidogrel is even less predictable in individuals with a wild type or heterozygous for CYP2C19*2. Based on these considerations, homozygote carriers of CYP2C19*2 may benefit by treatment with the more potent antiplatelet agents prasugrel or ticagrelor, while in wild type or heterozygous carriers of CYP2C19*2 platelet function testing might provide an adjunctive information.

Platelet function testing provides more comprehensive information than genotyping, as it reflects the influence of intrinsic (co-morbidities, genetic polymorphisms) and extrinsic factors (cigarette smoking, drug-drug interactions) on platelet reactivity. However, it is still a matter of ongoing investigations to define those patient cohorts, in whom ADP-related platelet function testing is of clinical importance. As platelet function testing has been shown to be a good risk stratifier for adverse events, phenotyping takes a central position in the algorithm (Figure 4). Judgment whether to perform platelet function testing might be based on the scores predicting the individual risk for nonresponsiveness to antiplatelet drugs. For example, the PREDICT score offers a tool to individualise antiplatelet therapy (32). Several clinical variables are included into the score: age >65 years, ACS at admission, diabetes mellitus, renal dysfunction (serum creatinine >1.5 mg dL−1), and reduced left ventricular function (LVF; ejection fraction [EF]<50%). Although reduced LVF has been indicated as a predictor of HTPR in a minority of studies (32, 33, 109), three points are assigned to the reduced LVF in the PREDICT score (32). Platelet function testing might be also taken into consideration in patients scheduled for high risk PCI and in those experiencing recurrent ischaemic events despite good compliance. If the test identifies a patient with HTPR, and known drug-drug interactions could be excluded, other therapies, particularly novel platelet inhibitors as prasugrel or ticagrelor might be considered. Repeated loading with clopidogrel and double maintenance dose might be considered in patients with high bleeding risk or when novel antiplatelet drugs are unavailable. One must be aware, however, of the circumstance that the latter strategy might not achieve the required level of platelet inhibition and up to four repeated loadings with clopidogrel could be necessary in some patients (67, 68, 73) thus delaying the time until optimal platelet function inhibition. Importantly, repeated testing after switching to a more potent drug might be crucial in order to ensure sufficient level of platelet inhibition and to prevent LTPR. In patients who develop life-threatening bleeding because of treatment with prasugrel or ticagrelor, the switch to clopidogrel might be an option. Another option would be to reduce the dose of ticagrelor or prasugrel. However, this approach has not been tested elsewhere. In summary, phenotyping of the response to antiplatelet agents with a subsequent modification of therapy in patients with coronary artery disease treated with P2Y12 receptor antagonists might be considered.

The next question to be addressed is to define the optimal platelet assay for use in a daily clinical practice beyond the different platelet function tests that can be used (Table 3). Unfortunately, cross validation of the assays is limited. Only two bigger studies compared different methods for prediction of events: in the PEGASUS-PCI (Phenotyping versus Genotyping for prediction of cardiac Adverse events in patients Undergoing Percutaneous Coronary Intervention) study multiple electrode aggregometry (MEA) was most predictive for stent thrombosis and MACE whereas in the POPULAR (Do Platelet Function Assays Predict Clinical Outcomes in Clopidogrel-Pretreated Patients Undergoing Elective PCI) study LTA, Plateletworks and VerifyNow were shown to have the best predictive values for ischaemic events (15, 110). In a small single centre study it was shown that the VASP assay exhibited a good prediction of future ischaemic events (111). Nevertheless, a good prediction of future ischaemic events by the VASP assay may be related to the low cut-off value of HTPR (platelet reactivity index [PRI] <50%) based on the small number of initial clinical data, and might therefore overestimate the patients risk for HTPR (5, 112). Reflecting the growing body of evidence, the test should be judged based on the following properties: predictive value for clinical outcome, reliability and reproducibility of results, known threshold with the best predictive value, operator skills for running tests and time necessary for testing. A fundamental patient care issue remains that the cost for these tests are typically not reimbursed. The above aspects require careful consideration. In regards to feasibility of the most frequently used tests, light transmission aggregometry and the VASP assay seem to be too labour-intensive to be performed on a daily basis. In contrast, the results of VerifyNow and MEA are available within a few minutes. The major shortcoming of VerifyNow, however, is the cost of a single measurement. Moreover, the additional limitation of VerifyNow is the poor correlation with the P2Y12 receptor occupancy, where the sensitivity of the VerifyNow P2Y12 assay decreased at higher clopidogrel responses (113). MEA, on the other side, is not strictly speaking point of care test, as the test is relatively labour-intensive (reagent preparation, blood dilution, multiple pipetting steps). MEA has also been reported to show a relatively high value of coefficient of variation (11%) (114). As none of the currently available tests have yet been evaluated in a randomised trial for superiority over another test, no special recommendation concerning the type of assay can be given at the present time.
Figure 4: A proposed algorithm for personalised antiplatelet treatment with P2Y12 receptor blockers. *The PREDICT score might be used when ticagrelor or prasugrel are not available or contraindicated. Acute coronary syndrome (ACS), calcium channel blocker (CCB), left ventricular function (LVF), percutaneous coronary intervention (PCI), proton pump inhibitor (PPI).
As stated before, it is necessary to confirm the usefulness of our algorithm in prospective trials. Whether use of a blinded design will be feasible remains unclear at the moment. This possible difficulty is based on the observation of the TRIGGER trial, in which one third of patients declined participation after being identified as having HTPR (79). This underlines on the other hand the consideration whether it is ethically correct to randomise patients with HTPR to clopidogrel. A possible solution would be to perform non-inferiority trials, comparing e.g. novel platelet inhibitors versus personalised treatment with the net clinical benefit as outcome variable.

Conflicts of interest
Jolanta M. Siller-Matula has received lecture or consultant fees from AstraZeneca, Daiichi Sankyo and Eli Lilly. Dietmar Trenk has received consulting fees or paid advisory board fees and lecture fees from Eli Lilly, Daiichi Sankyo, AstraZeneca, and Bayer and lecture fees from Boehringer-Ingelheim KG, Bristol Myers Squibb, and Merck Sharp & Dohme. Karsten Schröer has received lecture or consulting fees from AstraZeneca, Bayer, Eli Lilly/Daiichi-Sankyo, IROKO. Meinrad Gawaz has received lecture or consulting fees from AstraZeneca, Boehringer-Ingelheim, Bayer, Eli Lilly/Daiichi-Sankyo. Steen Kristensen has received lecture fees from AZ, Bristol Myers Squibb, BAYER, Boehringer-Ingelheim, Eli-Lilly, IROKO, Merck, Pfizer, Sanofi, The Medicines Company. Robert Storey has received honoraria, consultancies fees and/or institutional grants from AstraZeneca, Merck, Accutemics, Eli Lilly, Daiichi Sankyo, Sanofi Aventis, Regeneron, Bristol Myers Squibb, Iroko, Medscape, Novartis and Roche. Kurt Huber has received lecture and consultant fees from AstraZeneca, Daiichi Sankyo, Eli Lilly, Sanofi Aventis, Bristol Myers Squibb, Pfizer, Iroko, and The Medicines Company.

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