Antiplatelet drugs are the cornerstone in prevention and treatment of atherothrombotic vessel occlusions, i.e., myocardial infarction and stroke. The introduction of clopidogrel and its use in dual antiplatelet treatment (DAPT) has substantially reduced both the incidence and mortality of acute coronary syndromes (ACS) and has improved the efficacy of percutaneous coronary interventions (PCI) (1). The development of further, more potent antiplatelet drugs, such as the newer generation ADP-receptor antagonists prasugrel and ticagrelor has further added to improved clinical outcome (2). The price to be paid was an increased risk of bleeding, because the targeted clotting factors in physiological haemostasis and pathological thrombosis are largely the same. Thus, the question came up, whether even more potent antiplatelet drugs, such as the direct thrombin inhibitors vorapaxar or atopaxar will further reduce the thrombotic risk or merely increase the risk of bleeding without enlarging the therapeutic window between prevention of thrombosis and inhibition of haemostasis.

In this context, the concept of “High on-treatment platelet reactivity (HTPR)” – for definition and measurement see the overview of Cattaneo in this issue (3) - has attracted much attention (4-9). Indeed, HTPR is a quite frequent event in clinical practice, i.e. DAPT in ACS and/or percutaneous (PCI), and a key variable for the patients’ outcome. Its’ possible reasons, determination, clinical significance and possible ways to deal with it are the topics to be discussed in more detail in various ‘state of the art’ articles in this theme issue of Thrombosis and Haemostasis (3, 10-14). Recently, the measurement of reticulated platelets has also attracted the interest of researchers, as outlined also by Cesari et al. in this issue who found an association between an increase of reticulated platelets and CV mortality in patients with acute coronary syndromes (15).

For several reasons, HTPR has been mostly studied with clopidogrel (16), the best studied ADP-antagonist. Specifically, the variable, and in general moderate antiplatelet efficacy of the compound has raised concerns, since high on-clopidogrel platelet reactivity has consistently been associated with increased risk for ischaemic events in PCI patients (17). As also discussed by Trenk et al. in this issue (14), the individual response variability could be linked to both genetic and clinical factors (18, 19). However, the impact on activity of cytochrome P450 enzymes, which are influenced by both genetic and environmental factors, the factors identified so far could only explain up to about 12% of clopidogrel variability in terms of inhibition of ADP-induced platelet aggregation ex vivo (20). Thus, additional and possibly disease- or alternative treatment-related variables need also to be considered. This includes stimulation of platelets by agents, such as collagen, thrombin or thromboxane in ACS, which are not sensitive to ADP-antagonists. Alternatively, proton-pump inhibitors (PPIs) or statins can at least pharmacologically modify the antiplatelet effect of clopidogrel and ticagrelor, respectively (21, 22). Diabetes is another clinical condition with reduced antiplatelet effects of clopidogrel and there are certainly more (19, 23).

Another possibility to deal with HTPR is the choice of drug alternatives (24, 25). Despite DAPT with the more effective P2Y12-inhibitors, the one-year event rate after ACS varies from 9-12%. Accordingly, the addition of an anticoagulant or a third antiplatelet agent to DAPT has been discussed and investigated. As pointed out by Brouwer and colleagues in this issue (10), among the new oral anticoagulants (NOACs), only rivaroxaban has been demonstrated to improve outcome in secondary prevention after ACS, including cardiovascular and all-cause mortality, albeit at the cost of bleeding, and this only as adjunctive therapy to DAPT (26). In addition, in patients on DAPT who require additional anticoagulation, e.g. patients with atrial fibrillation and increased atherothrombotic risk, adjunctive therapy (“triple therapy”) with dose adjusted vitamin-K antagonists (INR 2.0-2.5) has to be considered as well (27-29). Whether vitamin-K antagonists could be replaced by (lower-dose) NOACs is still matter of discussion. Alternatively, as shown in the WOEST trial, a combination of an oral anticoagulant with only one antiplatelet drug, such as clopidogrel, might cause less bleeding at no excess of thrombotic events and reduced all-cause mortality (30). In contrast, the use of the thrombin receptor antagonist voraxapar as a third antiplatelet agent in ACS and/or in secondary prevention after ACS did not fulfill its expectations because of higher bleeding complications despite a better efficacy as compared to DAPT alone (31, 32). There might be a potential of this strategy for specific subgroups with high thrombotic but low bleeding risk that have to be better defined before this strategy might become clinical routine (33). Importantly, the impact of prolonged anticoagulation (low-dose rivaroxaban, vitamin-K antagonists) as adjunctive to DAPT after ACS has not been addressed with the most potent antiplatelet agents (prasugrel, ticagrelor) and this merits further study.

As demonstrated by Dahlen et al. in this issue (11), one of the most heavily discussed issues in this context is how to measure platelet function and what is the predictive value of standard laboratory measurements.
for the clinical outcome of patients (34, 35). Two contributions to this theme issue exclusively deal with the topic of personalised antiplatelet treatment and its clinical value (12, 14). Although not routinely undertaken and still a scientific tool, platelet function testing is a promising approach to personalise and to tailor antiplatelet therapy for the individual patients. Studies of patients treated with clopidogrel, which is associated with wide inter-individual variation in antiplatelet effect as noted above, suggest that platelet function testing may also predict bleeding risk related to coronary artery bypass grafting (CABG) surgery and potentially guide the timing of surgery following discontinuation of clopidogrel. A recent meta-analysis, including more than 4,000 patients (36), has shown that in patients with HTPR-guided antiplatelet therapy compared to standard antiplatelet therapy with clopidogrel, the rate of thrombotic events was markedly reduced without increasing the risk of major bleeding, eventually resulting in a significantly reduced cardiovascular mortality: OR 0.38 (95% CI: 0.18-0.78). In addition, the net benefit obtained by intensified antiplatelet regimens in patients with HTPR might be greater in those at higher risk of stent thrombosis. Future randomised trials are warranted to optimise the risk-benefit ratio of intensified antiplatelet therapy, specifically by looking at the therapeutic window with respect to bleeding.

Uncertainties also remain regarding the way platelet function testing is performed. Indeed, many laboratory tests suffer from major inter- and intra-assay reproducibility problems, as well as defining lower limits of detection. As pointed out by M. Cattaneo in this issue (3), laboratory tests of platelet function that specifically explore the platelet activation pathway, which is targeted by the drug, should be utilised in order to answer the question whether the pharmacodynamic antiplatelet effect is associated with a reduction in the rate of thrombosis. Despite a clear association between the two, enthusiasm for the clinical usefulness of platelet function testing has been tempered based on observed sensitivity, specificity, and positive predictive value for the detection of future thrombotic events. Dahlén et al. make a clear statement in this context: Platelet function tests are able to confirm the pharmacodynamic effect of a drug but are not appropriate to diagnose which patient will have events (11). With other words, platelet function tests are a useful support to assist in risk stratification – but not more. Prognostic performance of HTPR should be evaluated using clinical measures such as hazard ratios and net reclassification improvement, i.e. procedures similar to risk definition by other well-established risk factors for cardiovascular events. Unfortunately, universal cut-off values for HTPR have not been clearly established yet. In addition, the concordance among different tests in the identification of patients at risk is poor.

Another key aspect to be considered when discussing all the pros and cons in pharmacology of the newer antiplatelet agents is the fact that platelets themselves, as well as their natural ways of stimulation in vivo, are a most relevant variable that ultimately determines the clinical efficacy of any antiplatelet drug treatment, including aspirin and ADP-antagonists (13, 37). In addition to “high reactivity” of circulating platelets, enhanced thrombin formation, in particular in acute emergency conditions, such as rupture of an atherosclerotic plaque in ACS and thrombin-induced translocation and exposition of GP IIb/IIIa receptors at the platelet membrane might cause a variable but transient HTPR in response to DAPT (38), because neither of these anti-platelet compounds antagonises thrombin-induced platelet aggregation. In addition, this might also markedly influence the long-term clinical outcome and this in both direction, i.e. antithrombotic efficacy and risk of bleeding (8, 39).

In addition to platelet-drug-, drug-drug interactions need also to be considered as another factor, eventually resulting in HTPR specifically in clopidogrel-treated patients (19, 21). However, in DAPT, this might also be true for the aspirin component, though frequently not sufficiently appreciated, since the irreversible acetylation of cyclooxygenase (COX)-1 in platelets – its mode of antiplatelet action – is apparently complete in about 99% of patients (40). As discussed by Hohlfeld et al. in this issue (13), there are clinically relevant interactions between this compound and other COX-1 inhibitors, namely non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, eventually resulting in a marked reduction or even loss of its antiplatelet effect. This type of interaction is also seen with non-anti-inflammatory analgesics, such as dipyrene (metamizole), but not with others, such as acetaminophen (paracetamol). Hence, this interaction is not a class effect of NSAIDs and/or non-steroidal analgesics, but rather due to specific structural requirements, which still remain to be defined. This NSAID-induced HTPR may increase the cardiovascular risk in long-term treatment for primary and secondary cardiovascular prevention but also be involved in treatment failure of DAPT. Thus not only the ADP-receptor antagonist variability but also a HTPR to the aspirin component might result in treatment failure (13).

In conclusion, the introduction of more powerful antiplatelet agents has clearly improved the clinical outcome of patients suffering from ischaemic heart disease and its acute complications. However, this has also uncovered the large inter-individual variability in response to antiplatelet drugs, eventually associated with HTPR. Personalised treatment, while being an obvious option to deal with this issue, is not yet possible and platelet function tests, though providing important information about pharmacodynamics of the respective antiplatelet drug, might not reflect sufficiently the much more complex in vivo situation of the individual patient. Thus, HTPR is still an issue for both, the thrombotic risk and the problem of bleeding and more work is clearly needed to deal with it in both diagnostic and therapeutic sense.

Conflicts of interest
K. Huber has received lecture fees from Astrazeneca, Eli Lilly, Daiichi Sankyo, Boehringer Ingelheim, Bayer, Sanofi-Aventis, The Medicines Company. K. Schröer has been consultant and advisory board member for Bayer, Daiichi Sankyo and Eli Lilly.

References
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