Predictive power

Multiplate® analyzer
Multiplate® analyzer
Strengthening Roche’s hemostasis portfolio

With a series of industry firsts and innovative applications for early disease detection and monitoring, Roche is introducing yet another novel product to its hemostasis portfolio.

Whilst Roche’s responsive laboratory coagulation roadmap is going to deliver platforms with outstanding productivity, the Multiplate® system focuses on addressing a significant unmet medical need. Improving the assessment of a patient’s platelet function status is key for hematologists, cardiologists and anesthetists in order to support clinical decisions in cardiology, surgery and intensive care.

With the acquisition of Verum Diagnostica GmbH Roche gains an innovative and unique platelet function testing solution. Carried by a strong medical momentum its best in class predictivity of thrombotic and bleeding risk allows to tailor anti-platelet therapy and stratify patients at risk for bleeding.

Supported by a highly standardized testing technology the Multiplate® system has the potential to set new standards in patient care. Therefore Multiplate® is a perfect complement to Roche’s ambition to combine true innovation with proved medical and diagnostic expertise into a new hemostasis portfolio.
**Predictive power**

**Multiplate® analyzer**

**Medical momentum**
- > 200 Medline-listed publications with Multiplate®
- Consensus paper of “Working Group on High-On-Treatment-Platelet-Reactivity” featuring Multiplate®
- Guidelines introducing recommendations for platelet function testing in CABG and PCI for patients treated with clopidogrel

**Consistent results**
- Standardised and fast test procedure utilizing whole blood, easy to use, low blood volume/test
- Broad menu of CE marked tests for various applications
- 5 channel analyzer with high throughput
- High sensitivity and dynamic range
- Twin sensors for quality control

**Best predictivity – for tailored anti-platelet therapy**
- Approx. 20% of patients do not respond adequately to clopidogrel
- Other potent drugs have been introduced, which have advantages and disadvantages compared to clopidogrel and which are up to 10-15 fold more expensive compared to clopidogrel
- Patients showing a “low-response” to clopidogrel in Multiplate® analysis have shown a 5-10 fold risk for ischemic complications
- Patients with a “high response” to clopidogrel have shown a 2.6 fold risk for major bleeding
- Successful experiences using the tailoring of anti-platelet therapy aided by Multiplate® analysis have been reported by several groups

**Best predictivity – for stratification of bleeding risk**
- Patients with impaired platelet function according to Multiplate® analysis have an increased risk for intra- and post-operative bleeding complications and/or transfusion requirements
- Multiplate® can contribute to an improved management of bleeding complications in surgical procedures
Platelet function testing

**Overview**

Blood platelets play a pivotal role in physiological hemostasis, but also in the development of arterial thrombosis (myocardial infarction and stroke). Platelet function testing is utilized in the analysis of inherited and acquired platelet function disorders, in the analysis of platelet function in anesthesia and intensive care, and for monitoring of platelet function antagonists.

**Analysis of platelet disorders**
Various drugs and diseases, as well as genetic factors can lead to platelet dysfunction, which may cause a transient or permanent bleeding tendency. The Multiplate® analyzer can detect platelet dysfunction and thus aid in the therapeutic management of such patients.

**Platelet function in anesthesia and intensive care**
Platelet dysfunction can lead to severe bleeding complications. The detection or exclusion of platelet dysfunction before invasive procedures or in bleeding patients can support the risk stratification and management in these situations.

**Monitoring of anti-platelet therapy**
Anti-platelet drugs are among the most frequently administered drugs in modern medicine. A combination of aspirin with an ADP receptor antagonist (clopidogrel, prasugrel or ticagrelor) is the mainstay antiplatelet therapy for patients with acute coronary syndromes (ACS) and/or coronary interventions with stent placement.

**The challenge of compliance and low response**
In the increasingly elderly and multimorbid patient population the issue of adherence to prescribed medications is of crucial importance. Through the ability to monitor and thus control anti-platelet therapy the Multiplate® system can support the management of these patients. In addition anti-platelet drugs do not always act properly, even when taken appropriately by the patient. Reduced absorption, as frequently witnessed in patients suffering from cardiac shock, as well as an impaired metabolism of the drug (especially clopidogrel) due to genetic factors, comediations or other confounders can lead to a diminished anti-platelet response to the medication ("low response"). In large prospective evaluations it was shown with Multiplate® results that up to 20% of patients do not respond adequately to clopidogrel treatment. These patients have a 5-10 fold increased risk for stent thrombosis, stroke and q-wave myocardial infarction following percutaneous coronary interventions (PCI).

**Novel ADP P2Y12 receptor antagonists**
Prasugrel and ticagrelor are novel P2Y12 receptor antagonists that act more potently and more consistently than clopidogrel. This includes an enhanced risk of fatal bleedings (prasugrel) and higher risk for non-CABG related major bleedings and dyspnea (ticagrelor). At the expense of a higher rate of bleeding or undesired side effects not all patients are likely to benefit from the use of these drugs compared to the standard therapy with clopidogrel. In addition prasugrel and ticagrelor are up to 10-15 times more expensive than clopidogrel. In summary, the question of which ADP receptor inhibitor to use has pharmacological as well as socio-economic implications with advantages and disadvantages for all three available drugs.
Best predictivity – for tailored anti-platelet therapy

Evidence is available confirming that low-response to clopidogrel is a modifiable risk factor and Multiplate® guided antiplatelet therapy has the potential to improve patient outcome:

“Routine PF testing [with Multiplate®] is useful for guidance of tailored antiplatelet treatment and switching to prasugrel markedly reduces stent thrombosis risk in high platelet reactivity patients on clopidogrel.”

“Routine tailoring of antiplatelet therapy with MEA [Multiplate®] …is capable of eradicating early definite stent thrombosis”

 “…tailoring the dose of clopidogrel with the Multiplate® analyzer significantly reduced the risk of ischemic complications as compared to a uniform dosing strategy of 75 mg clopidogrel in an all-comer cohort of patients after PCI.”

Recent PCI guidelines are supporting PFT with a class IIb recommendation:

“In patients treated with clopidogrel with high platelet reactivity, alternative agents, such as prasugrel or ticagrelor, might be considered (Level of evidence: C)”
Best predictivity – for stratification of bleeding risk

Blood platelet function plays a pivotal role in hemostasis during surgery and following traumatic injuries. Platelet dysfunction can lead to bleeding complications, increased transfusion of blood products and occasionally the need for surgical re-exploration. Therefore, in patients undergoing surgery the ability to assess platelet function before, during and after the intervention is desirable.

Causes of platelet dysfunction
Platelet dysfunction may be caused by the ingestion or administration of anti-platelet drugs, concomitant medications such as antibiotics or anti-rheumatics, or by patient comorbidities.

Stratification of bleeding risk
Several studies have shown the ability of the Multiplate® analyzer to detect patients with an increased risk for bleeding complications and/or transfusion requirements during surgery.16-20

Testing the effects of anti-platelet drugs
Aspirin® and ADP receptor antagonists can be sensitively assessed using the Multiplate® analyzer. Patients undergoing cardiac surgery who demonstrate a strong anti-platelet effect of clopidogrel have a significantly higher risk to experience major bleeding compared to individuals who express a weak or lack of anti-platelet effect.18 Several studies have shown that Multiplate® analysis can effectively determine the recovery from the effects of anti-platelet drugs such as aspirin21,22 clopidogrel and prasugrel.23

Reduced need for preoperative waiting periods
Clopidogrel should normally be discontinued for 5 days before a surgical procedure. According to the 2011 blood conservation clinical practice guidelines platelet function testing may be used to detect clopidogrel non-responders who may not require a preoperative waiting period after clopidogrel discontinuation.24 This can lead to reduced hospitalization times and considerable cost savings.

Citations from studies using the Multiplate® analyzer:
“The multiple electrode aggregometry ADP test in patients under thienopyridine treatment and undergoing cardiac surgery is associated with postoperative bleeding and platelet transfusion and provides an accurate preoperative prediction of postoperative bleeding risk.”

“The inclusion of MEA in our POC supported algorithm allowed for timely and specific detection of platelet dysfunction.”

“POC-guided therapy was associated with lower Fresh Frozen Plasma and Platelet Concentrates usage and costs as well as an improved clinical outcome in this prospective randomized single-center study.”
Weber CF et al. Anesthesiology in press
Consistent results

The Multiplate® analyzer is an easy to use, compact system. It deploys a Windows® based interface programmed with a comprehensive menu of whole blood platelet function assays. Its flexible design allows for a fast turn around time of 10 minutes per test a period. Combined with its 5 channels, this permits the processing of up to 30 tests per hour that require only 300 µl blood per analysis.

Broad menu of tests for a wide spectrum of applications
With its menu of six CE marked procedures (ADPtest, ASPtest, TRAPtest, COLtest, RISTOtest, ADPtest HS) the Multiplate® system
• is sensitive for the monitoring of platelet function inhibitors
• determines platelet dysfunction before invasive procedures and in bleeding patients
• is suitable for the detection of hereditary or acquired platelet function disorders25
• is sensitive for von Willebrand Disease (comparable to optical aggregometry)26
• is used in various research models, the functional determination of Heparin induced thrombocytopenia in whole blood27-30 and various animal models31-35

Patented Detection Technology
The signal reaction in the Multiplate® analyzer is triggered by the adhesion of activated platelets to the surfaces of the sensor electrodes that induces an increase of electrical resistance. Each test cell incorporates two pairs of sensors (multiple electrode aggregometry = MEA), serving as a built-in quality control.

Citations from studies using the Multiplate® analyzer:
“MEA is a fast and standardized method to individually assess platelet function prior to and after clopidogrel treatment.”

“As a whole blood method, Multiplate® avoids the handling of blood samples, with the advantage that the cellular environment remains unchanged, and allows rapid evaluation of platelet aggregation by ready-to-use test cuvettes with 2 independent sensor units. In addition, the use of whole blood tests platelet function under more physiologic conditions.”

“The effect size by use of multiple electrode aggregometry (MEA) was consistently greater for clopidogrel and aspirin as compared to other methods.”

“MEA accurately detected the time-dependent antiplatelet effect of aspirin and provided reproducible platelet aggregation results.”

“A further advantage of this method [Multiplate®] allows the clinician to use small amounts of whole blood.”
With its introduction to the market in 2005, the Multiplate® analyzer has witnessed great momentum in terms of adoption and medical consensus on its value. Since that time over 200 medline listed publications have been generated with the Multiplate® system, validating the growing interest and adoption of the Multiplate® analyzer in clinical practice.

The MEA principle of the Multiplate® analyzer has been incorporated into the 2008 revision of the Clinical and Laboratory Standards Institute (CLSI) approved guideline on platelet function testing.36

Large prospective studies such as that performed by the ISAR group in a cohort of 1608 patients associated Multiplate® results with risk for stent thrombosis and other ischemic events in PCI patients.1 The JACC consensus paper of the “high on treatment platelet reactivity” working group made reference to the Multiplate® analyzer with unmatched odds ratios to determine patients at enhanced thrombotic risk.19

Platelet function testing is further supported by guidelines. The 2011 American College of Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography and Interventions Guideline for Percutaneous Coronary Intervention15 includes platelet function testing for anti-platelet drug selection with a class IIb recommendation:

“Platelet function testing may be considered in patients at high risk for poor clinical outcomes. (Level of Evidence: C). In patients treated with clopidogrel with high platelet reactivity, alternative agents, such as prasugrel or ticagrelor, might be considered. (Level of Evidence: C)”

Platelet function testing has also received a Class IIb recommendation by the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists in their 2011 blood conservation clinical practice guidelines.24

“Point-of-care testing for platelet ADP responsiveness might be reasonable to identify clopidogrel nonresponders who are candidates for early operative coronary revascularization and who may not require a preoperative waiting period after clopidogrel discontinuation. (Level of evidence C).”

As more evidence is gathered to demonstrate the benefits of anti-platelet therapy aided by the use of the Multiplate® analyzer, there is further room for guidelines’ recommendations to become stronger.
Multiplate® analyzer

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