Point-of-Care Platelet Function Testing with the ROTEM® *platelet* Module

1. Limitations of Viscoelastic Testing

A major limitation of standard viscoelastic testing is its insensitivity to the effects of antiplatelet drugs (e.g., cyclooxygenase-1 (COX-1) inhibitors, and ADP ($P2Y_{12}$)-receptor antagonists [1-4]. This limitation is caused by the generation of high amounts of thrombin in viscoelastic test systems which mask the effects of antiplatelet drugs by stimulating the platelets via the thrombin-receptor pathway (protease-activated receptor (PAR) 1 and 4). Since thrombin is the strongest activator of platelets, the inhibition of other pathways (e.g., arachidonic acid or ADP pathway) does not affect viscoelastic test results in the presence of high amounts of thrombin.

2. ROTEM® *platelet* Module

To overcome this limitation, **ROTEM® *delta*** can be combined with the **ROTEM® *platelet*** module, which is CE-marked in Europe since November 2013. It provides two channels for whole blood impedance aggregometry in addition to the four viscoelastic channels of ROTEM® *delta* (**figure 1 A-D**). Arachidonic acid (**ARATEM**), adenosine di-phosphate (**ADPTEM**) and thrombin receptor-activating peptide-6 (**TRAPTEM**) can be used as activators in ROTEM® *platelet*. The corresponding reagents are designed as user-friendly lyophilized single use reagents. The main parameters of ROTEM® *platelet* are the area under the aggregation curve (AUC in Ω·min), the amplitude at 6 minutes (A6 in Ω), and the maximum slope (MS in Ω/min). AUC is the clinically most important parameter and reflects the overall platelet aggregation (**figure 1 D**).

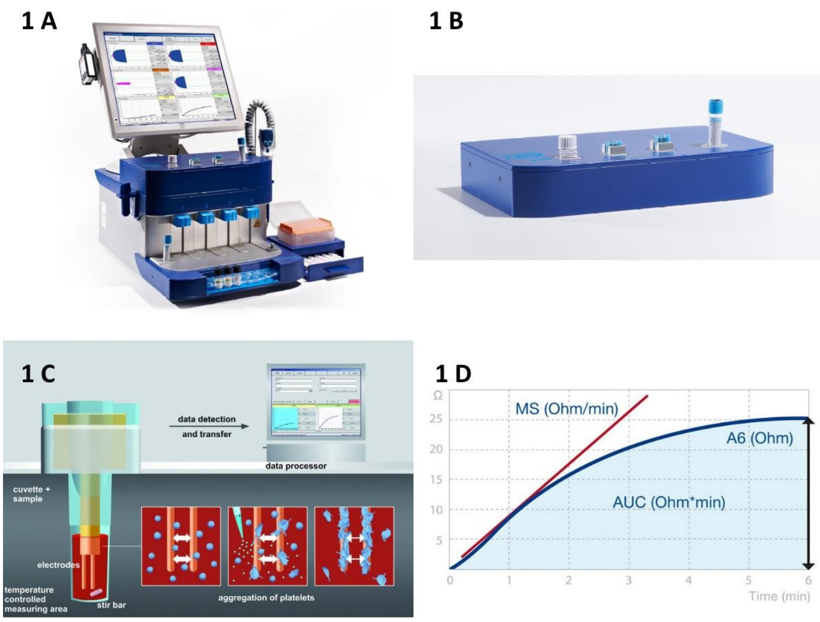

Figure 1 A-D: A. ROTEM® delta device (thromboelastometry) plus ROTEM® platelet module (whole blood impedance aggregometry); B. ROTEM® platelet module; C. ROTEM® platelet measuring principle; D: ROTEM® platelet measuring curve and parameters (AUC = area under the aggregation curve in Ω·min; A6 = amplitude after 6 min in Ω; MS = maximum slope in Ω/min).

Platelet function analysis is much more susceptible to pre-analytic factors such as the anticoagulant used (citrate, Lithium-heparin or hirudin), the size of the blood sampling vial, transportation with a pneumatic system, and resting time of the blood sample before analysis [5-8]. Therefore, these pre-analytic factors have to be standardized and validated, and hospital-specific reference ranges and cut-off values for therapeutic interventions should be established. In contrast to citrated blood samples which need a resting time of 20-30 minutes between blood sampling and analysis, heparin and hirudin blood samples can be analysed immediately after blood sampling with stable results over at least 120 minutes. This is crucial if timely decisions have to be made based on the results, e.g., in severe bleeding during and after cardiac surgery. Furthermore, the effect of ADP-receptor antagonists can be detected most reliably in hirudinized blood samples.

If the ROTEM® device is not used at the point-of-care, the screen with the viscoelastic and platelet function testing results, can be transmitted in real-time to the attending physician at the point-of-care, to a haematology/haemostaseology consultant and/or to the blood bank by remote viewing.

Whole blood impedance aggregometry has been shown to detect the effect of COX-1 inhibitors and ADP-receptor antagonists, reliably (**figure 2 A-D**), and to predict stent thrombosis/ischemic events and bleeding/platelet transfusion in interventional cardiology and cardiac surgery, as well as mortality in severe trauma and sepsis [9-22]. Furthermore, the effects of drugs, such as desmopressin and tranexamic acid, on platelet function can be monitored by whole blood impedance aggregometry [23-24]. However, it is not clear whether platelet transfusion is beneficial or even harmful in patients with early platelet dysfunction in severe trauma and sepsis.

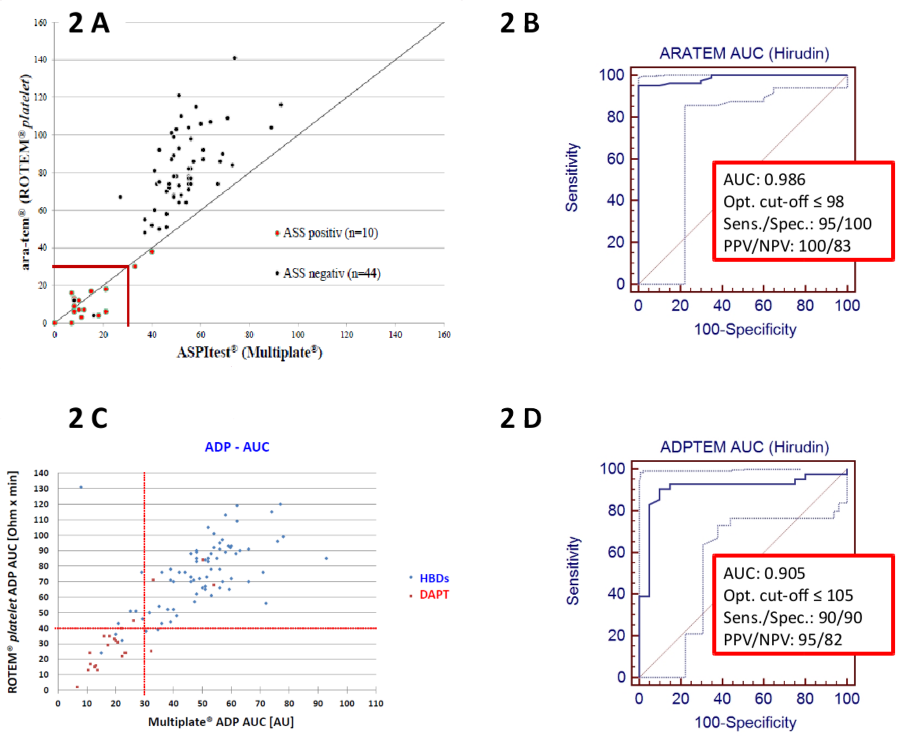

Figure 2 A-D: Diagnostic performance of ROTEM® platelet. A. Correlation between ROTEM® platelet (AUC in Ω·min) and Multiplate® (AUC in AU) in patients with and without Aspirin; n = 54 [10]; B. ROC analysis for ARATEM AUC (hirudin) to detect patients on Aspirin; n = 101 [unpublished data]; C. Correlation between ROTEM® platelet (AUC in Ω·min) and Multiplate® (AU) in patients with or without dual antiplatelet therapy; n = 100 [11]; D. ROC analysis for ADPTEM AUC (hirudin) to detect patients with dual antiplatelet therapy; n = 101 [unpublished data].

Notably, in liver transplantation, platelet transfusion is associated with increased mortality, independent from the platelet count prior to transfusion [25]. Therefore, decision-making for platelet transfusion should be done carefully and alternatives (e.g., desmopressin, tranexamic acid or fibrinogen) may be considered [23-24, 26-28].

Recent publications demonstrated that prophylactic platelet transfusion may even be more harmful than beneficial in the perioperative setting as well as in patients with acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH Trial) [29-31]. Again, this supports a targeted rather than a prophylactic administration of platelets in bleeding patients.

3. Predictive Value of Whole Blood Impedance Aggregometry for Bleeding, Throm bosis, and Mortality

The positive predictive value of thromboelastometry and impedance aggregometry to predict bleeding in elective surgery is low but the negative predictive value is very high (up to 100%) [12-14]. Therefore, presenting pathologic thromboelastometry or impedance aggregometry results does not mean that the patient has to bleed. Accordingly, pathologic thromboelastometry or impedance aggregometry results should only be treated in the presence of significant bleeding requiring a haemostatic intervention. In contrast to patients scheduled for elective surgery, in patients with pre-existing haemostatic disorders, such as cirrhosis, trauma, sepsis, or specific drug effects, thromboelastometry and impedance aggregometry provides a positive predictive value, too [12-13, 18, 20-21, 32].

However, it is rather the question 'Why does this patient bleed?' than 'Will this patient bleed?' which can be answered by thromboelastometry and impedance aggregometry in the perioperative setting. Accordingly, the main advantage of thromboelastometry and impedance aggregometry is to identify or exclude a specific haemostatic disorder as the reason for bleeding in a timely manner. Here, POC thromboelastometry and whole blood impedance aggregometry provides rapid and reliable data within 10-12 minutes. If both, thromboelastometry and impedance aggregometry, show normal results, the probability of coagulopathic bleeding is very low and the patient should be re-checked for surgical bleeding (**figure 3.**).

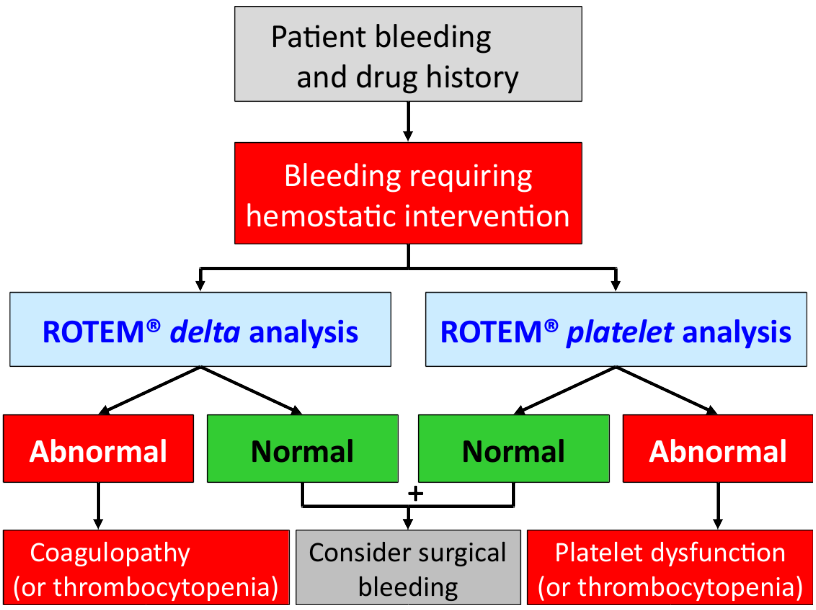

Figure 3: ROTEM® diagnostics flowchart (improved diagnostic performance by combining thromboelastometry (ROTEM® delta) with whole blood impedance aggregometry (ROTEM® platelet)).

Besides pre-existing platelet dysfunction due to antiplatelet drugs and other drugs which might deplete platelet function (e.g., analgetics, antidepressants, antibiotics, cardiovascular drugs), platelet function can be impaired by cardiopulmonary bypass (CPB) itsels as well as by protamine administration – in particular in protamine overdose [33-35]. In contrast, increased platelet aggregability can be an early sign of preeclampsia [36]. Characteristic ROTEM® *platelet* traces are displayed in **figure 4 A-F**. Accordingly, blood samples taken after weaning from CPB and heparin-reversal by protamine show the best predictive value for bleeding in cardiac surgery. A comparative

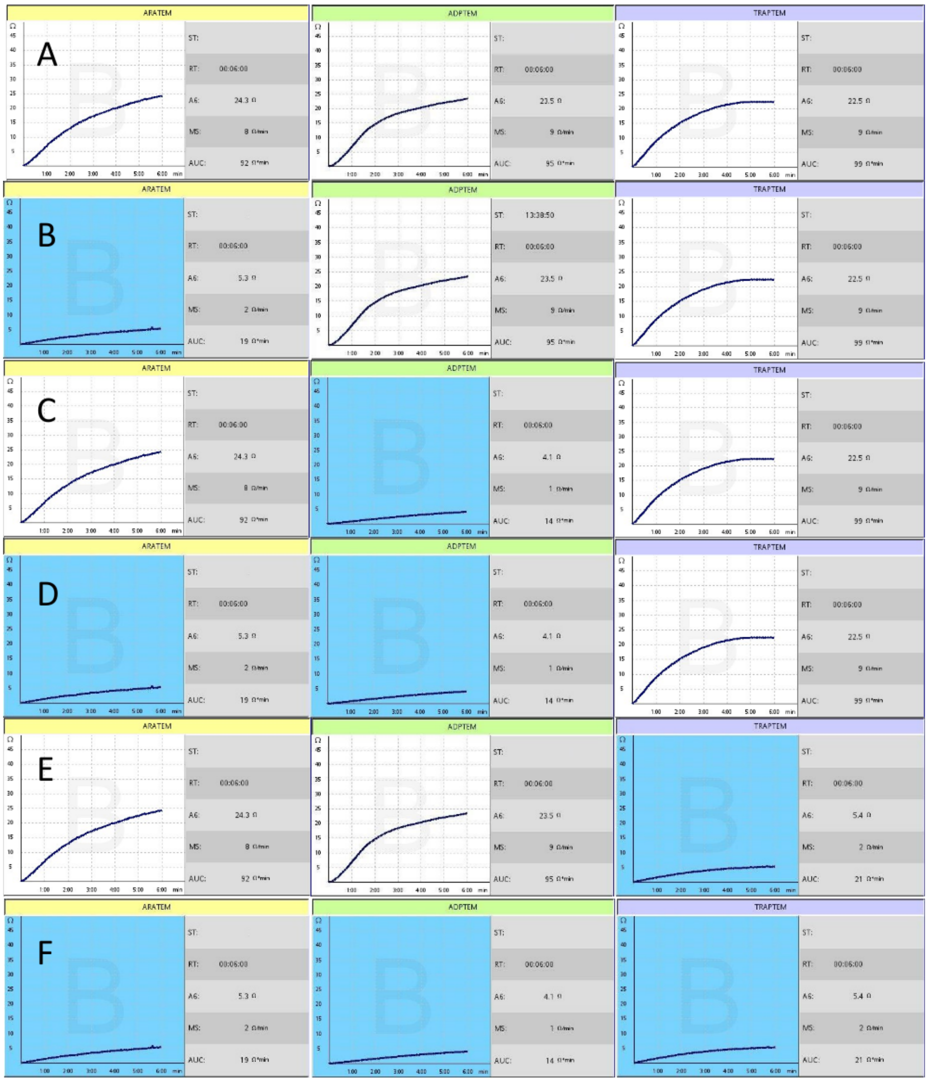

Figure 4: Characteristic whole blood impedance aggregometry traces (ROTEM® platelet) achieved by activation with arachidonic acid (AA) (ARATEM; left column), ADP (ADPTEM; middle column), and TRAP-6 (TRAPTEM; right column). A. Normal platelet function; B. Selective inhibition of the AA pathway (e.g., by aspirin); C. Selective inhibition of the ADP-receptor pathway (e.g., by clopidogrel or prasugrel); D. Inhibition of the AA and ADP-receptor pathway (e.g., dual antiplatelet therapy with aspirin and clopidogrel); E. Selective inhibition of the thrombin-receptor pathway (e.g., by vorapaxar); F. General platelet dysfunction due to triple antiplatelet therapy, GPIIb/IIIa-receptor antagonists (e.g., abciximab, eptifibatide, or tirofiban), platelet receptor destruction (e.g., due to cardiopulmonary bypass, severe trauma, or sepsis), or severe thrombocytopenia.

study between the two impedance aggregometry devices Multiplate® and ROTEM® *platelet* using Li-heparin blood samples identified the best cut-off value to predict severe bleeding at 5-10 min after heparin reversal with protamine as ASPItest ≤ 26 U, ARATEM ≤ 13 Ω·min, ADPtest ≤ 27 U, ADPTEM ≤ 36 Ω·min, TRAPtest ≤ 77 U, and TRAPTEM ≤ 46 Ω·min. Notably, RBC and platelet transfusion requirements correlated significantly with the number of platelet activation pathways inhibited [17]. This is in-line with the results of other authors [12-15]. Chapman et al. could identify an optimum threshold for TRAPTEM < 53 Ω·min (ROC AUC, 0.97) and for ADPTEM of < 43 Ω·min (ROC AUC, 0.95) in citrated blood samples taken at hospital admission for prediction of massive transfusion by impedance aggregometry using ROTEM® *platelet* [20].

4. The 'Therapeutic Window Concept', Development of POC-guided Bleeding Management Algorithms, and its Impact on Patient Outcomes

Efficacy of viscoelastic testing can be increased by a combination with POC platelet function analysis such as whole blood impedance aggregometry (e.g., ROTEM® *platelet* or Multiplate®) [18]. The algorithm presented in **figure 5** [37] is based on the 'therapeutic window concept'. This concept has been developed for guiding antiplatelet therapy in patients undergoing percutaneous coronary

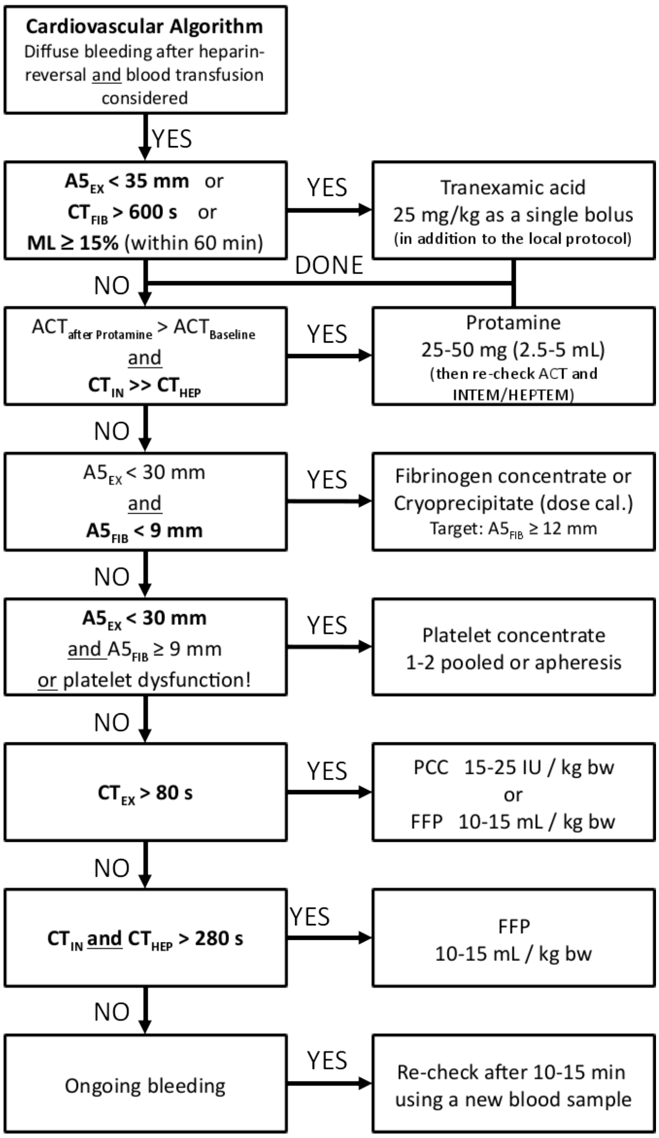

Figure 5: Cardiac Surgery ROTEM® A5 Bleeding Management Algorithm [37]

interventions (PCIs) in order to minimize the risk of ischemia (stent thrombosis) and bleeding [16, 19, 38-40]. Accordingly, bleeding management algorithms guided by thromboelastometry and whole blood impedance aggregometry are designed to minimize the risk of both, bleeding and thrombosis, by an individualized therapy. Here, the right therapeutic intervention, in the right dose and the right sequence is defining the framework of the therapeutic window, e.g.:

- EXTEM A5: 30-50 mm
- FIBTEM A5: 8-16 mm
- EXTEM CT: 60-80 s
- ARATEM AUC: 20-80 Ω·min (Li-heparin blood samples; after weaning from CPB and protamine administration)
- ADPTEM AUC: 35-70 Ω·min (Li-heparin blood samples; after weaning from CPB and protamine administration)
- TRAPTEM AUC: 45-90 Ω·min (Li-heparin blood samples; after weaning from CPB and protamine administration)

Using this concept in cardiovascular surgery, it was possible to reduce RBC, FFP and platelet transfusion requirements, surgical re-exploration, postoperative acute kidney injury, thromboembolic events, and nosocomial infection rates, significantly [41-48]. Furthermore, hospital costs could be reduced significantly, first by reduction of transfusion-associated costs, and second – and may be even more important – by reduction of complication-related costs, reduced ICU and hospital length of stay, and increased number of cases performed in the study period [41-50].

5. References

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