Introduction to Antithrombotic Monitoring
Topics

• What is thrombosis, and why is it significant?
• Coagulation Cascade
  – Pathways of coagulation, anticoagulation, and fibrinolysis
• Thrombophilia screening
  – Hereditary & Acquired Risk Factors
  – Laboratory Evaluation of Thrombotic Risk
• Monitoring anticoagulation and anti platelet therapy
  – Heparin Monitoring (UFH & LMWH)
  – Oral Anticoagulant Monitoring (Warfarin, Dabigatran, Rivaroxaban)
  – Antiplatelet drugs monitoring
Hemostasis

- **Hemostasis**: The balance between clotting and bleeding

- Components of Hemostasis:
  - Vasculature
  - Coagulation proteins
  - Platelets
Venous Thromboembolism – Incidence & Significance

- Complications from DVT kill up to 500,000 people per year in the E.U.
  - More than AIDS and breast cancer combined!
- Third most common vascular disease
- Pulmonary Embolism (PE) leading preventable cause of death
- Incidence of DVT about 135 per 100,000 annually
- Incidence of PE about 69 per 100,000 annually
Complications of DVT

- Permanent vascular damage
- Post-phlebitic syndrome
- Pulmonary embolism (PE)
- Pulmonary hypertension
VENOUS THROMBOEMBOLISM

Virchow’s triad for venous thromboembolism:

- Reduced Blood Flow
- Vessel Damage
- Change in Blood Components
Venous Thromboembolism

• Complex, multi-causal disease
  – Physiological factors
    • Age, hormonal influence (i.e. pregnancy)
  – Acquired risk factors
    • Cancer, surgery, O.C., obesity, trauma, immobility, antiphospholipid syndrome (SLE)
  – Hereditary (genetic) risk factors
    • Deficiencies in anticoagulation proteins (AT,PC,PS)
    • Elevated coagulation proteins (FVIII)
    • Gene mutations – FII, F V Leiden
Coagulation Cascade

- Vascular damage initiates the coagulation cascade.
- Results in the generation of thrombin at the site of injury.
- Thrombin catalyzes the conversion of fibrinogen to an insoluble fibrin (clot) matrix.
Coagulation Cascade

Intrinsic Pathway

“Contact Activation”

XI

XIIa

XIIa

Prekallikrein
HMW
Kininogen

Xla

Extrinsic Pathway

“TF Pathway”

TF-VIIa

PL

Ca$^{2+}$

IX

IXa

“TF Pathway”

Tissue Factor + VII

X

Xa

Common Pathway

Prothrombin

Pl, Ca$^{2+}$ (Tenase)

VIIIa

XIII

XIIIa

XL-Fibrin Polymer

Anticoagulation proteins:
Protein C, Protein S,
Antithrombin III, TFPI

Thrombin

Fibrin Monomer

Fibrinogen

Polymer

((Prothrombinase))
Intrinsic Pathway

“Contact Activation”: Initiated by the activation of FXII involving contact factors on negatively-charged phospholipid surfaces (glass or kaolin in vitro)

- Factors XII, XI, IX, VIII, prekallikrein, HMW kininogen
- Measured with aPTT clotting assay
Intrinsic Pathway - APTT

• The Activated Partial Thromboplastin Time (APTT): The clotting time in seconds of a mixture of citrated plasma, Ca\(^{2+}\), contact activator, and phospholipid – norm 35 sec

• Tests for deficiencies of pro-coagulant factors in the INTRINSIC and COMMON pathways – FXII, XI, IX, VIII

• Heparin, dabigatran (Pradaxa), Factor Inhibitors, Lupus Anticoagulant can prolong the APTT
Extrinsic Pathway

“TF Pathway”

Initiated when blood is exposed to TF released from damaged endothelium

- Measured with PT clotting assay (INR 0.8-1.2)
Extrinsic Pathway - PT

- **Prothrombin Time (PT):** clotting time in seconds or in INR.

- Tests for deficiencies of pro-coagulant factors of the EXTRINSIC and COMMON pathways- FVII, FX, FII, **warfarin (INR!),** rivaroxaban(Xarelto), apixaban(Eliquis)
Anticoagulation Pathways -

Antithrombin

• Antithrombin is the major inhibitor of thrombin, accounting for approximately 80% of thrombin inhibitory activity in plasma

• Antithrombin primarily inhibits Thrombin and FXa
Anticoagulation Pathways - Antithrombin

- **TF** → **FVIIa**
- **TFPI**
- **Heparin** (cofactor)
- **Antithrombin III**
- **FXa** → **Thrombin**
- **Prothrombin**

**Pathways and Reactions**

- FX (Fletcher X) converts to FXa with help from factor VIIa (FVIIa) and tissue factor (TF).
- FXa then activates prothrombin to thrombin with the help of factor V (FV) and platelet (PL) components.
- Antithrombin III (AT III) inhibits thrombin.
- Heparin acts as a cofactor in the anticoagulation process, enhancing AT III's ability to inhibit thrombin.
- TFPI (tissue factor pathway inhibitor) regulates the TF-FVIIa complex, preventing uncontrolled FX activation.

These pathways are crucial in balancing the clotting process to prevent clot formation and thrombosis.
Activated Protein C (APC) + cofactors

APC has two known cofactors: Protein S and Factor V.

Protein S:
Protein S enhances binding of APC to the phospholipid of platelets and endothelial cells.
Only free protein S has a APC cofactor function. 60% of protein S is bound to C4bBP.

Factor V:
Factor V together with Protein S makes APC degrade FVIIIa and FVa more effectively.
Fibrinolytic Pathway

Fibrinolysis is initiated when fibrin is formed and eventually dissolves the clot.
Fibrinolytic Pathway

- Plasminogen
- Tissue Plasminogen Activator (t-PA)
- Urokinase (uPA)
- Exogenous: streptokinase
- Plasmin Inhibitor
- PAI-1
- XL-Fibrin, fibrinogen
- XL- fibrin degradation products (FDP)
Laboratory Tests to Diagnose thrombophilia and VTE

– Due to the high prevalence of DVT and PE, and in order to prevent the morbidity and mortality associated with such diseases, a reliable and rapid diagnosis of thrombophilia state is required.
Laboratory Tests to Diagnose VTE

- The current standard methods for the diagnosis of
  
  DVT : doppler ultrasound
  
  PE : pulmonary angiography

- Both DVT and PE : D-dimer
D-Dimer

- D-Dimer, a measure of fibrin degradation products.

- Utility is in its Negative Predictive Value = none DVT or PE

- Elevated levels of D-Dimer:
  
  • Found in pathological conditions such as deep vein thrombosis (DVT) ++++, more than 500 ng/l
  
  • pulmonary embolism (PE) ++++++, more than 1000 ng/l
Hereditary & Acquired Risk Factors

• There are several well-established risk factors and corresponding assays to test for them
  
  – Most of these risk factors can be hereditary or acquired
Hereditary & Acquired Risk Factors

**Inherited Risk Factors**
- APC resistance-Factor V Leiden
- AT deficiency
- Protein C deficiency
- Protein S deficiency
- Prothrombin Mutation
- Dysfibrinogenemia (rare)

**Acquired Risk Factors**
- Age
- Malignancy
- Immobilization
- Trauma, Post-op
- Pregnancy
- Estrogen use
- Antiphospholipid Antibodies
- Long distance flights
- Hematologic Diseases

**Inherited or Acquired Risk Factors:**
- Hyperhomocysteinemia
- Elevated levels of FVIII, IX, XI
# Laboratory Evaluation of Thrombotic Risk

## Risk Factor
<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Laboratory Assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombin Deficiency</td>
<td>AT activity</td>
</tr>
<tr>
<td>Protein C Deficiency</td>
<td>Protein C Deficiency PC activity (clotting or chromogenic)</td>
</tr>
<tr>
<td>Protein S Deficiency</td>
<td>Protein S Free Antigen (ELISA, LIA)</td>
</tr>
<tr>
<td>APC Resistance / Factor V Leiden Mutation</td>
<td>APC Resistance (aPTT); FV Leiden genetic test if abnormal</td>
</tr>
<tr>
<td>Prothrombin Mutation G20210A</td>
<td>Genetic Test</td>
</tr>
<tr>
<td>Hyperhomocysteinemia (elevated homocysteine)</td>
<td>EIA, Mass Spec, HPLC</td>
</tr>
<tr>
<td>Elevated Factor VIII Activity</td>
<td>Factor VIII activity (clotting or chromogenic)</td>
</tr>
<tr>
<td>Lupus Anticoagulant</td>
<td>Russel viper diluted Clotting Assay</td>
</tr>
<tr>
<td>Anticardiolipin Antibody, IgG / IgM</td>
<td>aCL IgG/IgM Antigen ELISA (cardiolipins)</td>
</tr>
</tbody>
</table>
Antithrombin, Protein C, Protein S Deficiencies

- Loss-of-Function Abnormalities
- Deficiencies of AT, PC, and PS are most commonly seen in the heterozygous state
- Levels are about 30 – 60% of normal
- Risk potential of each of these deficiencies is 10 – 25 fold
- Individuals with AT, PC, or PS deficiencies typically have a thrombotic event at a fairly young age
APC Resistance

- Common in the general population (8%)
- Most common cause of hereditary thrombophilia - F V Leiden

- APC Resistance alone is not a significant risk factor (HR 2-3x). Having FVL combined with other risk factors, however, greatly increases risk of thrombosis - i.e. FVL heterozyg. + O.C. = HR 30 x
INACTIVATION OF NORMAL FVα

Activated PC

FVα heavy chain

Ca^{2+}

FVα light chain

306 506 679
INACTIVATION OF MUTANT FVa:Q^{506}

FV Leiden Mutation
- Accounts for approx. 90% of APC Resistance
- Prevalent in about 2 – 13% of general population
- Accounts for about 20 – 60% of VTE cases
- Heterozygotes for FV Leiden have 2 – 5 fold increased thrombotic risk

**APC cleavage sites**

- 306
- 679

**FVa heavy chain**

**FVa light chain**

**Ca^{2+}

- Mutant

Mutation results in a 10-fold lower inactivation rate of FVa
Detection by PCR: FV Leiden (Arg506Gln)
Now: real time – PCR Light typer (Roche)

- Reaction volumes of 10 – 100 µl.
- Software automates genotype assignments.
- Data captured directly from its CCD camera.
- Melting curve analysis enables the rapid, straight-forward, and reliable genotyping of wild-type sequence, heterozygotes, and homozygous SNPs.

Duration of PCR 40 minutes
APC RESISTANCE test: INTERPRETATION OF RESULTS

- APC-ratio = \( \frac{\text{Clot time APC/CaCl}_2}{\text{Clot time CaCl}_2} \)

- APC Resistance is when the APC ratio is below or equal to 2,0.
Prothrombin G20210A mutation

- Prevalence in normal population approximately 3%
- G → A translation at nucleotide 20210 in prothrombin gene
  - Leads to an increase in Factor II (prothrombin) levels more than 130%
- Increased risk of venous thrombosis
- Detection by PCR
Hyperhomocysteinemia

- Homocysteine: an amino acid metabolite – toxic for endothel
- Conversion of homocysteine to either metabolite dependent on a number of enzymes (MTHFR) with cofactors: folic acid, vitamins B12 and B6
  - Elevated homocysteine (>$15 \mu\text{mol/l}$) is a risk factor for AIM, stroke and recurrent VTE
Elevated Factor VIII

- FVIII activity > 1.5 IU/mL results in 5-6-fold higher risk for DVT, especially recurrent DVT, than FVIII activity ≤ 1.0 IU/mL

- Confirmation of risk not associated with acute phase response

- Elevated FVIII persistent over time

- Familial trait observed – no explanation so far
Lupus Anticoagulant / Anti-Phospholipid Syndrome (APS)

- Auto-antibodies against phospholipids or phospholipid-binding proteins
- Also known as Lupus Anticoagulant
- Major risk for recurrent miscarriage
- Major risk factor for venous thrombosis
  - Presence of antiphospholipid antibodies increases risk 9-fold
  - Thrombotic event in about 30% of patients with aPS
Anti-Phospholipid Syndrome - Laboratory Assays

Diagnosis of a definite syndrome: meet at least one clinical and one laboratory criteria.

- **Clinical criteria:**
  - Occurrence of thrombotic event – venous or arterial
  - Recurrent miscarriage, fetal death, or premature birth

- **Laboratory criteria:**
  - Lupus anticoagulant
    - Prolonged APTT, DRVVT assays
  - Anti-cardiolipin Antibodies IgG or IgM
    - Perform testing on two or more occasions, 6 weeks apart
    - Can also perform panel including anti-β2-GPI & anti-Prothrombin
Treatment of DVT

• Once DVT is diagnosed, Unfractionated Heparin or Low Molecular Weight Heparin is administered, followed by an oral anticoagulant drug such as warfarin.

• Or – Rivaroxaban (Xarelto) – direct inhibitor of FXa.
Heparin Monitoring – Unfractionated Heparin (UFH)

- UFH is typically monitored with an APTT test
- Ideally, the therapeutic range of APTTs for each reagent (~1.5 – 2.5) should correspond to anti-Xa activity of 0.3 – 0.7 U/ml
LMWH Monitoring

- Low Molecular Weight Heparin (LMWH) has been shown as effective in preventing recurrent VTE and cause less bleeding
- Generally LMWH does not need monitoring
- When monitoring is required, a chromogenic anti-Xa assay is required:
  - Therapy: 0.6 - 1.2 IU/ml anti FXa
  - Prophylaxis: 0.2 - 0.4 IU/ml anti F Xa
Long Term Therapy

• Warfarin is the most commonly used oral anticoagulant (OAC)
• Warfarin is a vitamin K antagonist - Impairs the generation of active vitamin K, decreasing the amounts of vitamin K dependent coagulation factors (FII, FVII, FIX, FX)
• Treatment time:
  • DVT and PE: 3 months, 6 months, 12 months, lifetime
  • Atrial fibrillation: lifetime?
Monitoring Warfarin Therapy is a Balancing Act!
Warfarin Monitoring

Why monitor? Need to balance proper anticoagulation without bleeding risk.
Monitored with PT, expressed as INR:

\[ INR = \left[ \frac{\text{Patient PT}}{\text{Mean Normal PT}} \right]^{\text{ISI}} \]

– Where ISI = international sensitivity index, assigned by each thromboplastin manufacturer

Warfarin is given orally and titrated to achieve an INR of typically 2.0 – 3.0
INR

\[ INR = \left( \frac{PT_{test}}{PT_{normal}} \right)_{ISI} \]

- ISI: International Sensitivity Index
- Compares local reagent with international reference preparation
Warfarin and bleeding

![Graph showing the relationship between INR midpoint and event rate for thromboembolic and hemorrhagic events. The graph indicates a decrease in thromboembolic events and an increase in hemorrhagic events as the INR midpoint increases.]

New oral anticoagulants

N.O.A.C.
Illustration showing the sites of action of new anticoagulants in the coagulation cascade.

<table>
<thead>
<tr>
<th>Steps in coagulation</th>
<th>Coagulation pathway</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiation</td>
<td>TF/Vlla</td>
<td></td>
</tr>
<tr>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IX</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VIIa</td>
<td>Rivaroxaban</td>
</tr>
<tr>
<td></td>
<td>IXa</td>
<td>Apixaban</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Edoxaban</td>
</tr>
<tr>
<td></td>
<td></td>
<td>YM150</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Betrixaban</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TAK-442</td>
</tr>
<tr>
<td>Propagation</td>
<td>Xa</td>
<td>Dabigatran etexilate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AZD0837</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ila</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrin formation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fibrinogen</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fibrin</td>
<td></td>
</tr>
</tbody>
</table>
Use of NOAC (2012)

- Thromboprophylaxis in Patients Undergoing Major Orthopedic Surgery (all: 14 - 35 days)
- DVT and PE: rivaroxaban –
  2x15 mg / 3 weeks, after 20mg
- Atrial fibrillation (prevention of stroke):
  dabigatran, 2 x 150 mg,
  2 x 110 mg
  rivaroxaban 20 mg
How do we determine stroke risk?

- **CHADS2** (Gage, et al.: JAMA 2001)
  - Congestive heart failure - 1 pt
  - Hypertension - 1 pt
  - Age > 75 - 1 pt
  - Diabetes - 1 pt
  - Stroke or TIA - 2 pts

- 0 points – **low risk** (1.2-3.0 strokes per 100 patient years)
- 1-2 points – **moderate risk** (2.8-4.0 strokes per 100 patient years)
- > 3 points – **high risk** (5.9-18.2 strokes per 100 patient years)
A. Dabigatran 75, 110 and 150 mg capsule.
Dabigatran and bleeding

- No reversal agent or antidote currently
- Supportive care and control of bleeding
- Eliminate by natural excretion through kidney unless renal impairment
- Plasma half life: 12 – 17 hrs
Laboratory monitoring of dabigatran

- APTT – 2x
- Specific test using a snake venom called Ecarin (Not widely available)
- Thrombin time – more 150 sec
- Thrombin dilute test
  HEMOCLOT > 220 ng/l
Rivaroxaban

- Once daily
- As effective or better than warfarin
- Less hemorrhagic stroke than warfarin
- Similar reduction in ischemic stroke
- Less bleeding than warfarin
- No routine lab testing
- No reversal
  - Half life 5-9 hours
Laboratory monitoring of rivaroxaban

- Coagulation testing: aPTT no !,
- only PT ( sec ),
- best test - inhibition of F Xa
Guide to the management of bleeding in patients taking NOAC.

Patient with bleeding on dabigatran therapy

Mild bleeding
- Delay next dose or discontinue treatment as appropriate

Moderate-Severe bleeding
- Symptomatic treatment
- Mechanical compression
- Surgical intervention
- Fluid replacement and hemodynamic support
- Blood product transfusion
- Oral charcoal application* (if dabigatran etexilate ingestion <2 hours before)
- Hemodialysis

Life-threatening bleeding
- Consideration of rFVIIa or PCC*
- Charcoal filtration*

Hankey G J, Eikelboom J W Circulation
2011;123:14361450
Anti platelet therapy
Platelet function
Mechanisms

1. Adhesion
   - Thrombin
   - PAR1, PAR4
   - GPVI
   - CD36
   - GPIb/IX/V
   - vWF
   - PGI₂, NO, EctoADPase

2. Activation
   - Shape Change
   - Granule Secretion
   - "Paracrine Effect"

3. Aggregation
   - ADP
   - TxA₂
   - "Autocrine and Paracrine Effect"
   - P2Y₁, P2Y₁₂
   - Activated GPIIb/IIIa
   - Fibrinogen vWF

### Anti-platelet drugs

#### Main classes

<table>
<thead>
<tr>
<th>Cyclooxygenase Inhibitors</th>
<th>Antagonists of ADP receptor</th>
<th>Antagonists of GP IIb/IIIa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Ticlopidin</td>
<td>Abciximab (Reopro)</td>
</tr>
<tr>
<td></td>
<td>Clopidogrel</td>
<td>Tirofiban (Aggrastat)</td>
</tr>
<tr>
<td></td>
<td>Prasugrel (Efient)</td>
<td>Ticagrelor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eptifibatide (Integrisin)</td>
</tr>
</tbody>
</table>

![Aspirin image](image1)

![Plavix image](image2)

![Efient image](image3)
Clopidogrel Response variability - resistance to therapy


Resistance = 28% (300 mg)
Resistance = 8%   (600 mg)

Δ Aggregation (5 µM ADP-induced Aggregation) at 24 Hr

Clopidogrel vs. Prasugrel: Anti-platelet effects of the loading doses

P<0.0001 for each

Clopidogrel 600 mg

Prasugrel 60 mg

PRINCIPLE TIMI 44
Clopidogrel vs. Prasugrel: Phase III study results-ACsy

- **Endpoint (%):**
  - Clopidogrel: 12.1
  - Prasugrel: 9.9
  - **HR 0.81 (0.73-0.90)**
  - **P=0.0004**

- **CV Death / MI / Stroke (138 events):**
  - Clopidogrel: 12.1
  - Prasugrel: 9.9
  - **HR 0.81 (0.73-0.90)**
  - **P=0.0004**

- **All Cause mortality (35 events):**
  - Clopidogrel: 3.2%
  - Prasugrel: 3.0%
  - **P=0.64**

- **TIMI Major NonCABG Bleeds:**
  - Clopidogrel: 2.4
  - Prasugrel: 2.4
  - **HR 1.32 (1.03-1.68)**
  - **P=0.03**
### ADP receptor antagonists

**Comparison**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Administration</th>
<th>Prodrug</th>
<th>ttPeak plt inhibition</th>
<th>Reversibility (half-life)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Route</td>
<td>Frequency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Oral</td>
<td>Once daily</td>
<td>yes</td>
<td>2-6h (after 600 mg loading dose)</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>Oral</td>
<td>Once daily</td>
<td>yes</td>
<td>2h</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>Oral</td>
<td>Twice daily</td>
<td>No</td>
<td>2h</td>
</tr>
</tbody>
</table>
partial stent thrombosis in clopidogrel non-responder

resolved clot after 30 min tirofiban
aggregometry

Platelet function testing
Platelet function testing

- VerifyNow
- VASP
- LTA
- Multiplate

→ highest relative risk for clopidogrel „resistant“ patients using the Multiplate analyzer
Multiplate tracings
Examples

- no platelet inhibition
  - TRAPtest: 113 U
  - ASPItest: 102 U
  - ADPtest: 89 U

- 100 mg aspirin qd
  - TRAPtest: 139 U
  - ASPItest: 17 U
  - ADPtest: 134 U

- 75 mg clopidogrel qd
  - TRAPtest: 98 U
  - ASPItest: 89 U
  - ADPtest: 31 U

- 100 mg aspirin + 75 mg clopidogrel qd
  - TRAPtest: 88 U
  - ASPItest: 8 U
  - ADPtest: 17 U

- tirofiban (Aggrastat® i.v.)
  - TRAPtest: 7 U
  - ASPItest: 3 U
  - ADPtest: 3 U
### Interpretation of MEA results for patients on dual anti-platelet therapy (analysis of hirudin blood)

<table>
<thead>
<tr>
<th>ADPtest</th>
<th>ASPItest</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 45 U</td>
<td>≤ 50 U</td>
</tr>
<tr>
<td>Aggregation is higher than expected for a clopidogrel-treated individual.</td>
<td>Aggregation is higher than expected for an aspirin-treated individual.</td>
</tr>
<tr>
<td>Check compliance. If patient is treated with Clopidogrel 75 mg or Clopidogrel 150 mg / d consider switching to Prasugrel 10 mg / d (as long as there is no contraindication to Prasugrel treatment).</td>
<td>Check compliance. If the patient is treated with &lt; 100 mg Aspirin / d or with coated aspirin, consider switching to Aspirin 100 mg / d uncoated.</td>
</tr>
<tr>
<td>Reduced platelet aggregation compared to average non-clopidogrel treated individuals. Result is in accordance with sufficient P2Y12 blockade.</td>
<td>Reduced platelet aggregation compared to average non-aspirin treated individuals. Result is in accordance with a regular COX blockade.</td>
</tr>
</tbody>
</table>

**NB:** The antiplatelet treatment of the patient should always be acceptable regarding the clinical status of the patient in the light of current recommendations by the clinical societies, also without reference to the Multiplate result. Intensifying anti-platelet therapy can increase bleeding.
51 clopidogrel low responders to 75 mg qd
→ 150mg Clopidogrel qd

15 patients: Adequate response
→ 225mg Clopidogrel qd

8 patients: Inadequate response
→ 5mg Prasugrel qd

4 patients: Inadequate response
→ 5mg Prasugrel qd

2 patients: Inadequate response
→ 10mg Prasugrel qd

14 (+5) patients: Adequate response
→ 10mg Prasugrel qd

9 Patients: No adjustment of therapy