Anthithrombotics and Anticoagulants

Keywords
- Platelets
- Aspirin resistance
- Aggregation
- Thienopyridines
- IIb/IIIa
- Clopidogrel resistance
- Heparin
- LMWH

David Hasdai, MD

Platelet adhesion, activation, and aggregation

Antiplatelet agents

Aspirin

Therapeutic interventions against platelet activation and aggregation
History of Aspirin

- 1948 Dr. Lawrence Craven notes 400 pts taking aspirin (aspergum) had not had heart attacks (Mississippi Valley Medical Journal)
- 1967 Weiss and Aledort discover aspirin inhibits platelets
- 1982 Sir John Vane awarded Nobel Prize for finding mechanism of dose-dependent inhibition of PG formation
- 1988 FDA approved ASA for reducing risk of recurrent MI, preventing first MI, and preventing recurrent TIA

Potential Mechanisms of Aspirin Resistance

- Noncompliance
- Insufficient dose
- Alternative pathway
- Genetic predisposition
- Increased prothrombotic milieu
- Drug interactions

Aspirin Resistance

- Definition – clinical vs. biochemical vs. functional
- Clinical significance – diagnosis and prognosis

Effect of Aspirin Dose

<table>
<thead>
<tr>
<th>Aspirin Dose (mg/d)</th>
<th>Trials, No.</th>
<th>Patients, No.</th>
<th>Odds Reduction, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>500–1,500</td>
<td>30</td>
<td>18,471</td>
<td>21 ± 4</td>
</tr>
<tr>
<td>100–325</td>
<td>12</td>
<td>23,670</td>
<td>28 ± 3</td>
</tr>
<tr>
<td>75</td>
<td>4</td>
<td>5,012</td>
<td>20 ± 7</td>
</tr>
</tbody>
</table>

*Data from Antiplatelet Trialists’ Collaboration.*

- Higher doses may inhibit endothelial prostacyclin production
- No dose-response effect for thrombosis, but there is a dose-response relation for GI side effects

Alternative Pathways: Contribution of COX$_2$

- COX$_1$ is the major isoform constitutively expressed in mature human platelets
- COX$_2$ can also contribute to production of TXA$_2$
- COX$_2$ upregulation and overexpression could contribute to aspirin resistance as a result of incomplete TXA$_2$ suppression
Aspirin Resistance and NSAIDS

Any CK-MB or troponin I elevation in aspirin-resistant and aspirin-sensitive patients

<table>
<thead>
<tr>
<th>Marker</th>
<th>Aspirin resistant (%)</th>
<th>Aspirin sensitive (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK-MB</td>
<td>51.7</td>
<td>24.6</td>
<td>0.006</td>
</tr>
<tr>
<td>Troponin I</td>
<td>65.5</td>
<td>38.5</td>
<td>0.012</td>
</tr>
</tbody>
</table>


ASA Responsiveness Varies Over Time

Prospective, blinded
- 326 stable patients with CAD who were taking ASA for \( \geq 7 \)d, not taking other antiplt drugs
- 17 (5.2%) had ASA resistance by optical aggregation at baseline
  - Female
  - Lower Hb
- 24% of resistant pts suffered MI, CVA or death vs 10% of responders (p=0.03)


Natural History of Aspirin Resistance

Prospective, blinded
- 326 stable patients with CAD who were taking ASA for \( \geq 7 \)d, not taking other antiplt drugs
- 17 (5.2%) had ASA resistance by optical aggregation at baseline
  - Female
  - Lower Hb
- 24% of resistant pts suffered MI, CVA or death vs 10% of responders (p=0.03)


Parenteral inhibitors of GP IIb-IIIa

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Abciximab (ReoPro®, Centocor/Lilly)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclic peptide</td>
<td>Eptifibatide (INTEGRILIN®, COR/Key)</td>
</tr>
<tr>
<td>Nonpeptide</td>
<td>Tirofiban HCI (Aggrastat®, Merck)</td>
</tr>
</tbody>
</table>

Glycoprotein IIb/IIIa Inhibitors
Pharmacokinetics and Monitoring
GP IIb/IIIa Receptor

- Upon activation of the platelet (by one of numerous possible routes) conformational change of the receptor occurs → high affinity ligand binding state
- All ligands (fibrinogen, vWF, fibronectin) are characterized by the arginine-glycine-aspartate (RGD) sequence which has been implicated as the binding site to the GP IIb/IIIa receptor
- Fibrinogen is a divalent ligand – each molecule can bind simultaneously to two GP IIb/IIIa receptors on adjacent platelets resulting in cross-linking

Platelet Glycoprotein IIb/IIIa Inhibitors

<table>
<thead>
<tr>
<th>Specificity</th>
<th>Abciximab</th>
<th>Eptifibatide</th>
<th>Tirofiban</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIb/IIIa</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>αβ3</td>
<td>+++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MAC-1</td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>↓ thrombin generation</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Activated clotting time (sec)</td>
<td>30</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>Drug:receptor ratio</td>
<td>2</td>
<td>&gt;250</td>
<td>&gt;250</td>
</tr>
<tr>
<td>Plasma T1/2</td>
<td>Min</td>
<td>2-3 hr</td>
<td>2 hr</td>
</tr>
<tr>
<td>Platelet-bound T1/2</td>
<td>Hr</td>
<td>Sec</td>
<td>Sec</td>
</tr>
<tr>
<td>Reversibility (hr)</td>
<td>12-24</td>
<td>4-6</td>
<td>4-6</td>
</tr>
<tr>
<td>Renal adjustment</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

COMPARE Study – early platelet aggregation

- 73 ACS pts planned for PCI
- Samples drawn in PPACK
- Batchelor WB et al Circulation 2002

Proportion of patients (%), in whom >80% inhibition of 20 µmol/L ADP-induced PA was achieved

Platelet Glycoprotein IIb/IIIa Inhibitors

<table>
<thead>
<tr>
<th>Treatment of bleeding</th>
<th>Abciximab</th>
<th>Eptifibatide</th>
<th>Tirofiban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet transfusion (8-10 units)*</td>
<td>Fibrinogen Cryoprecipitate (8-10 units) or fresh frozen plasma (16-20 units)</td>
<td>Platelets (16-20 units)*</td>
<td></td>
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<td>Cryoprecipitate (8-10 units) or fresh frozen plasma (16-20 units)</td>
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*Random donor
Why is Monitoring of GP IIb/IIIa Inhibitor Therapy Necessary?

1. Significant variability in the individual response to GP IIb/IIIa inhibitors
2. Clinical effect dependent on factors such as renal function (for the small molecule inhibitors) and platelet count (mainly for abciximab)
3. Need to evaluate platelet function after the GP IIb/IIIa is withdrawn, for instance before CABG

GOLD Study

- 485 patients undergoing a PCI with planned use of 1 of the 3 approved GP IIb/IIIa inhibitors
- Platelet function evaluated at various time points by RPFA correlated to clinical endpoints – MACE at 30 days
- Platelet inhibition at 10 min and MACE:
  - ≥ 95% inhibition ⇒ 6.4% MACE
  - < 95% inhibition ⇒ 14.4% MACE (p=0.006)
- Platelet inhibition at 8 hrs and MACE:
  - ≥ 70% inhibition ⇒ 8.1% MACE
  - < 70% inhibition ⇒ 25% MACE (p=0.009)
  
Steinhubl et al, Circulation 2001; 103: 2572-2578

Optical Platelet Aggregation

- Most common assay, employs platelet rich plasma (PRP), or less frequently whole blood
- The assay measures light passing through a sample of PRP after stimulation with a platelet agonist
- Advantages: wide use, correlates highly with bleeding time and with clinical efficacy of anti-platelet agents
- Disadvantages: time consuming, requires technical proficiency, high degree of intra-test and inter-laboratory variation, not sensitive at receptor occupancy levels of <30% and >80%

Monitoring of GP IIb/IIIa Inhibitor Therapy – cont.

4. Narrow therapeutic window – low dosages result in higher rates of ischemic complications (e.g. IMPACT II), overdosage increases risk of bleeding

Moderate levels of platelet inhibition (especially for prolonged periods) may also induce prothrombotic + proinflammatory effects!

At high levels of GP IIb/IIIa receptor occupancy → inhibitory effect on inflammatory markers, whereas at low levels increase in platelet-monocyte complexes and CD40L. (Li et al ATVJ 2006; Nannizzi-Alaimo et al Circ. 2001)

Monitoring of GP IIb/IIIa Therapy

Platelet function assessment:

standard laboratory methods

vs. bedside rapid assays
**Perfusion Chamber**
- Evaluates total blood thrombogenicity, not just platelet function.
- Venous blood is pumped directly from the patient into the chamber which contains 3 cylindrical flow channels with thrombogenic surfaces.
- Porcine aortic tunica media prepared by peeling off the intima serves as a model of severe arterial injury (Badimon J, ATVB 1991).
- Rheologic conditions mimic those typical of a patent artery and mild-moderate coronary stenosis.

**Flow Cytometry**
- Becoming the gold standard for platelet function evaluation.
- FACS measures the specific characteristics of a large number of cells after fluorescent labeling (typically fluorescent conjugated MoAbs).
- Mainly used for evaluation of platelet activation, for instance with FITC-labeled anti-fibrinogen MoAb (measures fibrinogen binding), PAC-1, P-Selectin or platelet-monocyte complexes.
- Can also be used for evaluation of GP IIb/IIIa receptor occupancy (MoAbs for the binding sites).
- Advantages: accurate, measures many aspects of platelet function, low variability in results.
- Disadvantages: Time consuming, requires very high technical proficiency, expensive.

**Perfusion Chamber**
- Evaluates total blood thrombogenicity, not just platelet function.
- Venous blood is pumped directly from the patient into the chamber which contains 3 cylindrical flow channels with thrombogenic surfaces.
- Porcine aortic tunica media prepared by peeling off the intima serves as a model of severe arterial injury (Badimon J, ATVB 1991).
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**Accumetrics’ Ultegra® System**
- Ultegra Rapid Platelet Function Assay (RPFA) is a cartridge-based, automated rapid assay that is based on the interaction between platelet GP IIb/IIIa receptors and fibrinogen-coated beads leading to the agglutination of the beads.
- The assay incorporates anticoagulated whole blood, fibrinogen beads, buffers and modified TRAP. Results expressed as percentage of baseline.
- High correlation to aggregation and FACS (r>0.8).
- Disadvantage: price, requires baseline sample.

**Monitoring of GP IIb/IIIa Therapy**
- Platelet function assessment:
  - standard laboratory methods
  - vs. bedside rapid assays
Cone and Plate(let) Analyzer CPA

- Measures platelet deposition under high shear rate flow conditions.
- Whole blood is placed on wells. Shear force is applied, using a rotating cone (1300 sec⁻¹, for 2 min). Samples washed and stained.
- Surface platelet deposition is evaluated using an image analyzer.
- 4 samples can be analyzed during less than 10 min. A fully automatic version of the CPA is currently being developed.
- High correlation to aggregation and FACS (r>0.8).

Varon et al. Thromb Res 1997;85:283-294

Accumetrics’ Ultegra® System

- Insert cartilage
- Insert whole blood sample
- Results within 60 sec

CLOPIDOGREL

Pharmacokinetcis, Response and Variability

Pharmacokinetic properties

- Requires metabolism by the hepatic cytochrome P450-1A enzyme system to acquire activity.
- Peak plasma concentrations of the main circulating metabolite, an inactive carboxylic acid derivative occur at 1 hour.
- Active metabolite identified in vitro by incubation of human liver microsomes (Pereillo JM et al Drug Metabol and Disp 2002).
- Contrary to ticlopidine, its bioavailability is unaffected by food.

Oral IIb/IIIa inhibitors

CLOPIGOGREL

- A thienopyridine, inhibits ADP induced platelet aggregation.
- The specific target of inhibition appears to be the P2Y₁₂ receptor.
- Fewer side effects than ticlopidine.
Pharmacodynamic properties

- Dose dependent inhibition of platelet aggregation can be seen 2 hours after a single dose
- Inhibition of ADP induced platelet aggregation reaches a maximum of 40% to 60% after 3 to 5 days. Similarly, recovery of platelet function is delayed after discontinuation, occurring slowly over 3 to 5 days.

P2Y Receptors

- The effect of ADP on platelets is mediated by two P2Y receptors - P2Y<sub>1</sub> and P2Y<sub>12</sub>.
- Activation of the P2Y<sub>1</sub> receptor leads to platelet shape changes and a rapid reversible wave of platelet aggregation.
- Activation of the G-coupled P2Y<sub>12</sub> receptor leads to a progressive and sustained wave of platelet aggregation (mediated by inhibition of adenylate cyclase) as well as activation of GP IIb/IIIa by another pathway.
- The P2Y<sub>12</sub> receptor is the target of clopidogrel (metabolite).
- Clopidogrel also inhibits platelet aggregation induced by other agonists, by inhibiting the effects of ADP released from platelet dense granules (in activated platelets).

Response to Clopidogrel

- Marked interindividual variability in response to clopidogrel as measured by inhibition of aggregation.
- “Resistance”, defined as baseline aggregation minus post-treatment aggregation ≤10% by 5 µmol/L ADP, was present in 31% and 15% of patients at 5 and 30 days. Gurbel P et al. Circulation 2003; 110:7: 2908-13.
- 5-11% non responders (≤10% delta in ADP aggregation) and 9-26% semi-responders (10-29% delta) in the study of Muller et al. Throm Haemost 2003.

Possible Reasons for Low Response

- Mutations in the ADP receptor P2Y<sub>12</sub> 5 frequent polymorphisms identified in the gene for the P2Y<sub>12</sub> receptor. Among healthy volunteers, two groups of subjects with low and high responsiveness to ADP aggreg. were identified and associated to one of the polymorphisms. Fontana et al. Circulation 2003; 108: 989-95
- Interaction with other drugs – mainly drugs metabolized by cytochrome P450-1A (CYP3A4).
- Differences in the rate of conversion of clopidogrel to its active metabolite.
Cardiovascular events according to antiplatelet effect of clopidogrel

<table>
<thead>
<tr>
<th>Quartile according to % reduction of ADP-induced platelet aggregation</th>
<th>Platelet aggregation at day 6 (as % of baseline)</th>
<th>% of patients with a CV event at 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>103</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>69</td>
<td>6.7</td>
</tr>
<tr>
<td>3</td>
<td>58</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>33</td>
<td>0</td>
</tr>
</tbody>
</table>

(Matetzky S et al. Circulation 2004)

Endpoints:
- Primary: 30 day death / MI / urgent target vessel revascularization
- Secondary: 30 day bleeding complications

Acute coronary syndrome with ST-segment depression
Positive biomarkers
Insulin-dependent diabetes
Chronic total occlusions
EF <=30%
Thrombus presence
Lesions in bypass grafts

Clopidogrel (600 mg loading dose, 2 x 75 mg/d through discharge, 75 mg/d for 4 weeks)

ISAR-REACT Trial: 30 Day Endpoints

Anticoagulants
Catalysis of Antithrombin-Mediated Inactivation of Thrombin or Factor Xa by Unfractionated Heparin or Low-Molecular-Weight Heparins

**TABLE 1. COMPARISON OF LOW-MOLECULAR-WEIGHT HEPARIN PREPARATIONS.**

<table>
<thead>
<tr>
<th>PREPARATION</th>
<th>METHOD OF PURIFICATION</th>
<th>MW (KDa)</th>
<th>Antithrombin Activity (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fragmin (Merieux)</td>
<td>Direct heparinization</td>
<td>6000</td>
<td>3.7</td>
</tr>
<tr>
<td>Dalteparin (Reguin)</td>
<td>Direct heparinization</td>
<td>6000</td>
<td>3.7</td>
</tr>
<tr>
<td>Enoxaparin (Lovenia)</td>
<td>Sodium salting out and DEAE depolymerization</td>
<td>4500</td>
<td>3.8</td>
</tr>
<tr>
<td>Nadoparin (Novapar)</td>
<td>Sodium salting out and DEAE depolymerization</td>
<td>4500</td>
<td>3.6</td>
</tr>
<tr>
<td>Benagin (Bek_page)</td>
<td>Sodium salting out, chromatographic purification</td>
<td>6000</td>
<td>3.5</td>
</tr>
<tr>
<td>Lantoparin (Tavaria)</td>
<td>Heparin digestin</td>
<td>4500</td>
<td>1.9</td>
</tr>
</tbody>
</table>

*The ratios were calculated by dividing the activity of Xa (anti-Xa) activity by the antithrombin (anti-thrombin) activity. The ratios are based on information provided by the manufacturer.*

**Thrombotic Process – Pathophysiology**

**Thrombin**

Promotes:
- Tissue factors
- Adhesive molecules
- Smooth muscle
- Leukocyte activation
- Platelet aggregation
- Release reaction

**Anticoagulants**

**Direct Thrombin Inhibitors**

**Hirudin-**

**Thrombin Binding**

**Mechanisms of Thrombin Inhibition**

**TABLE 2. MECHANISMS RESPONSIBLE FOR THE PHARMACODYNAMIC ADVANTAGES OF LOW-MOLECULAR-WEIGHT HEPARINS OVER UNFRAGMENTED HEPARIN.**

<table>
<thead>
<tr>
<th>ADVANTAGE</th>
<th>MECHANISM</th>
</tr>
</thead>
<tbody>
<tr>
<td>More predictable anticoagulant response</td>
<td>Low binding to plasma proteins and to proteins released from activated platelets and endothelial cells</td>
</tr>
<tr>
<td>Better bioavailability allows dosing</td>
<td>Less binding to endothelium</td>
</tr>
<tr>
<td>Dose-independent clearance mechanisms</td>
<td>Less binding to macrophages</td>
</tr>
<tr>
<td>Longer half-life</td>
<td>Less binding to macrophages</td>
</tr>
</tbody>
</table>

**Anticoagulants**

**Direct Thrombin Inhibitors**

- **Hirudin**
  - 65 amino acid protein
  - Originally identified in saliva of medicinal leech (Hirudo medicinalis)
  - Now available through recombinant DNA technology (lepirudin and desirudin)
Anticoagulants

Direct Thrombin Inhibitors

Hirudin Monitoring

**ECT**

- Sensitive, rapid
- Linear correlation – hirudin/time
- No heparin/warfarin interaction

**Ecarin Clotting Time (ECT)**

- **ECT**
- **Hirudin**

**Clinical RCTs**

**Hirudin vs UFH**

**OASIS-1, OASIS-2, TIMI-2, GUSTO-2B Combined Analysis**

**Proportion of Patients with Event (%)**

- **< 72hr**
- **< 7d**
- **< 35d**

**Clinical RCTs**

**Bivalirudin vs Heparin + GP IIb/IIIa During PCI**

**Randomization - double blind, triple dummy**

- **Heparin**
  - 65 U/kg initial bolus
  - Planned GP IIb/IIIa (abciximab or eptifibatide)
- **Bivalirudin**
  - 0.75 mg/kg initial bolus, 1.75 mg/kg-hr during PCI
  - Provisional GP IIb/IIIa (abciximab or eptifibatide)

**abciximab**: 0.25 mg/kg bolus, 0.125 µg/kg-min (max 10 µg/min) x 12 hrs
eptifibatide: 180 µg/kg double bolus, 2.0 µg/kg-min x 18-24 hrs

- "Quadruple Endpoint" at 30 Days

**Statistical Methods - 1**

**Imputed Comparison**

- **O.R. (Biv-Hep)**
- **Heparin**
- **Heparin + GP IIb/IIIa**
- **Bivalirudin**

**1st Hypothesis**: Bivalirudin superior to Heparin:

- **O.R. (Biv-Hep)** = 0.68 (0.55 - 0.84)

**2nd Hypothesis**: Bivalirudin not inferior to GP IIb/IIIa + Heparin:

- **O.R. (Biv-Hep) preserves half benefit of O.R. (Hep-GP)**

**Study Flow**

**Screen and consent**

**Interventionalist’s choice of abciximab vs eptifibatide**

**Telephone randomization**

**Bivalirudin**

- Heparin placebo
- GP IIb/IIIa placebo

- Aspirin Clopidogrel prescribed

**Bivalirudin + GP IIb/IIIa**

- blinded ACT and 2nd bolus (active drug if ACT < 225s)

**PCI**

- If provisional GP IIb/IIIa

- **Heparin**

- **Heparin + GP IIb/IIIa**

- **Heparin + GP IIb/IIIa placebo**
**Activated Clotting Times**

- **Heparin + GP IIb/IIIa**
  - Planned: 0.07%
  - Provisional: 7.2%
- **Bivalirudin**
  - Planned: 0.07%
  - Provisional: 7.2%

**Triple Ischemic Endpoint**

- **Heparin + GP IIb/IIIa**
  - Odds Ratio: 1.088 (95% CI: 0.895 - 1.322)
  - Placebo: 7.1%
- **Bivalirudin**
  - Odds Ratio: 0.917 (95% CI: 0.772 - 1.089)
  - Placebo: 7.6%

**Primary Quadruple Endpoint**

- **Heparin + GP IIb/IIIa**
  - Odds Ratio: 0.82
  - Placebo: 10.0%
- **Bivalirudin**
  - Odds Ratio: 0.83
  - Placebo: 9.2%

**Quadruple Endpoint**

- **Composite**
  - Heparin + GP IIb/IIIa (n=3008): 10.0%
  - Bivalirudin (n=2994): 9.2%
- **Death**
  - Heparin + GP IIb/IIIa (n=3008): 6.2%
  - Bivalirudin (n=2994): 7.0%
- **MI**
  - Heparin + GP IIb/IIIa (n=3008): 4.3%
  - Bivalirudin (n=2994): 4.7%
- **Urgent Revasc**
  - Heparin + GP IIb/IIIa (n=3008): 2.4%
  - Bivalirudin (n=2994): 2.4%
- **Major Bleeding**
  - Heparin + GP IIb/IIIa (n=3008): 1.4%
  - Bivalirudin (n=2994): 1.2%

*p = 0.002*
### ESTEEM: Post-hoc analysis

<table>
<thead>
<tr>
<th>End point</th>
<th>Placebo (%)</th>
<th>Combined ximelagatran groups (%)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality, nonfatal MI, nonfatal stroke</td>
<td>11.1</td>
<td>7.4</td>
<td>0.66 (0.48-0.90)</td>
</tr>
</tbody>
</table>

### ESTEEM: Primary end point

<table>
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<tr>
<th>End point</th>
<th>Placebo (%)</th>
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</thead>
<tbody>
<tr>
<td>All-cause mortality, nonfatal MI, severe recurrent ischemia</td>
<td>16.3</td>
<td>12.7</td>
<td>0.76 (0.59-0.98)</td>
</tr>
</tbody>
</table>

### ESTEEM: Bleeding complications

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Warfarin (%/yr)</th>
<th>Ximelagran (%/yr)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolic events (n)</td>
<td>93</td>
<td>91</td>
<td>0.94</td>
</tr>
<tr>
<td>Primary event rates (all strokes plus SAEs)</td>
<td>1.7</td>
<td>1.6</td>
<td>0.941</td>
</tr>
<tr>
<td>Secondary event rates (%/yr)</td>
<td>3.3</td>
<td>2.8</td>
<td>0.625</td>
</tr>
<tr>
<td>Major bleeding rates (%/yr)</td>
<td>2.5</td>
<td>1.9</td>
<td>0.054</td>
</tr>
<tr>
<td>Combined minor and major bleeding rates</td>
<td>39</td>
<td>32</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>aLAT levels &gt;3 times normal (%)</td>
<td>0.8</td>
<td>6.1</td>
<td>HS*</td>
</tr>
</tbody>
</table>

SEE = systemic embolic events  
*Highly significant

### SPORTIV III/V combined analysis

<table>
<thead>
<tr>
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<td>aLAT levels &gt;3 times normal (%)</td>
<td>0.8</td>
<td>6.1</td>
<td>HS*</td>
</tr>
</tbody>
</table>

SEE = systemic embolic events  
*Highly significant

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**Thromboembolic events**:  
- **Primary event rates (all strokes plus SAEs)**: 1.7 vs. 1.6 (%/yr)  
- **Secondary event rates**: 3.3 vs. 2.8 (%/yr)  
- **Major bleeding rates**: 2.5 vs. 1.9 (%/yr)  
- **Combined minor and major bleeding rates**: 39 vs. 32 (%/yr)  
- **aLAT levels >3 times normal (%)**: 0.8 vs. 6.1

**Bleeding complications**:
- **Major bleeding**: 1 vs. 2 (%/yr)  
- **Total bleeding (major or minor)**: 13 vs. 22 (%/yr)