Acute Coronary Syndrome (ACS)

Understanding the need for fast and potent antithrombotic agents through thrombus analysis

Johanne Silvain, MD-PhD
Pitié-Salpêtrière Hospital
Paris - France

http://www.action-coeur.org/

Disclosures

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Johanne SILVAIIN MD, PhD

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## ACS Guidelines 2010/2011

### 1- Aspirin LD 150-300mg (MD 75-100mg)

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin should be given to all patients without contraindications at an initial loading dose of 150–300 mg, and at a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy.</td>
<td>I</td>
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### 2- P2Y₁₂ Inhibitor ASAP

A P2Y₁₂ inhibitor should be added to aspirin as soon as possible and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.

### NSTE-ACS

<table>
<thead>
<tr>
<th>Low life-threatening bleeding risk = Prasugrel 60/10mg</th>
<th>TRITON</th>
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</thead>
<tbody>
<tr>
<td>Prasugrel (60-mg loading dose, 10-mg daily dose) is recommended for P2Y₁₂-inhibitor-naïve patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of life-threatening bleeding or other contraindications.</td>
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<table>
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<tr>
<th>STEMI</th>
<th>Antiplatelet therapy = Prasugrel 60/10mg</th>
<th>TRITON STEMI</th>
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Montalescot G. Lancet 2009

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1- Is coronary thrombus frequent in STEMI ?

2- Is distal embolization important ?

3- What about thrombus in NSTE-ACS ?

4- What do we know about thrombus formation and which are the therapeutic targets ?

5- Does time play a role ?

6- How to interpret clinical trials ?

7- Which drug should you choose ?
Thrombus in STEMI

Visible prePCI thrombus in 46.3% of patients

Aspirated thrombus in 74.6% of patients

Svilaas, T. et al. NEJM 2008

1,342 (80.5%) angiograms of STEMI patients enrolled in ASSENT-4 PCI.

**Residual TIMI thrombus grade 2 and/or distal embolization and/or slow flow**

**post-PCI THROMBUS BURDEN**

OR 2.43 for 90-day mortality (95% CI 1.3-4.51, p=0.0052)

**Thrombus in STEMI**

**Avoid**
- Fibrinolytic therapy

**Use**
- LD of thienopyridine
- PCI + Stent

**Neutral**
- Gp IIb/IIIa inhibitors

"longer time interval from SO to PCI (ischemic time) is independently associated with a larger residual thrombus"

Zalewsky K. et al. JACC 2011
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**Distal embolization in STEMI**

883 patients with STEMI undergoing pPCI

- **6.3% of angiographic visible distal embolization**
  - (Thrombus fragment)
  - Platelet poor/Fibrin rich thrombus = More distal embolization

- Lower MBG and ST-segment resolution
- Higher enzyme level
- Higher risk of re-MI
- Higher mortality (ns)

Fokkema M. et al. EJH 2009
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Thrombus in NSTE-ACS

Goto K. et al. JACC Cardiovasc Intervention 2011

3,627 patients with NSTE-ACS (moderate to high-risk) undergoing PCI

Pre-PCI THROMBUS
530 (15%) patients

Impact on prognosis?
Predictors of Thrombus?
Adapted from Goto K. et al. JACC Cardiovasc Intervention 2011

### Thrombus in NSTE-ACS

#### Angiographic Endpoints
- **Blush <3 prePCI:**
  - Thrombus +: 63.1%
  - Thrombus -: 37.2%
  - **p<0.0001 for all**
- **Blush <3 postPCI:**
  - Thrombus +: 21.6%
  - Thrombus -: 13.5%
- **DVE / no-reflow:**
  - Thrombus +: 5.5%
  - Thrombus -: 0.6%

#### Ischemic Endpoints
- **MACE ST:**
  - Thrombus +: 13.0%
  - Thrombus -: 37.2%
  - **p=0.0023**

- **ST:**
  - Thrombus +: 9.4%
  - Thrombus -: 2.8%
  - **p=0.0023**

### Protectors of thrombus formation
- **Thienopyridines on admission**
  - OR 0.77 [95% CI: 0.59 to 0.99], p=0.04
- **Planned GPI use**
  - OR 0.80 [95% CI: 0.65 to 0.98], p=0.03

1. optimal anticoagulation
2. optimal antiplatelet therapy

Adapted from Goto K. et al. JACC Cardiovasc Intervention 2011
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Key elements of thrombus formation

Therapeutic targets?

Thrombus in STEMI patients.

1- Tissue Factor  
2- Platelets  
3- Thrombin  
4- Fibrin mesh

Weisel JW et al. Science 2009

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Generation of the Hypothesis ... “Time make the difference”

Beygui et al. Circulation 2006;113;e21-e23

Question?

How time affects the dynamic process of thrombus formation in patients presenting an ST-elevation Myocardial Infarction (STEMI)?

Mouse Models of In Vivo Thrombosis.

Unique opportunity to study thrombus composition, dynamic formation and architecture in vivo.
Microscope Analysis

Random assignation of 10+ areas to control for heterogenity

Image Analysis

n=10+ frames per thrombus; n = 408 "boxes" in each grid

Silvain et al. J Am Coll Cardiol 2011
Results (1)

Thrombus Composition

Identification of crystal like structure – potentially cholesterol plaque debris

Platelet rich Thrombus <3 hours
Thrombus with identification of a) White Cell b) platelets c) Fibrin fibers d) Red Cell

**Mixed Thrombus 3-6 hours**

**Fibrin rich Thrombus >6 hours**
Results (2)

Influence of Time
Dynamic thrombus formation

Every additional hour of Ischemic time
- X2 rate of fibrin rich thrombus adjOR 2 [1.03-3.7], p=0.001
- 50% reduction in platelet content adjOR 0.5 [0.27-0.94], p=0.001

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A crucial timing for anti-thrombotic treatment

Platelet and thrombin inhibition with fast acting and potent drugs ++

Silvain et al. J Am Coll Cardiol 2011

New P2Y<sub>12</sub> Inhibitor

4 hours after administration

Guidelines 2010 – ACS

New P2Y<sub>12</sub> inhibitors

Silvain et al. Circulation CVI 2010
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**FAST AND POTENT DRUGS +++**

**ANTICOAGULANTS**
- Full dose
- Enoxaparin IV
- Bivalirudin IV
- Fondaparinux
- HNF

**PLATELET INHIBITORS**
- Aspirin
- Abciximab
- Clopidogrel
- Tirofiban
- Prasugrel
- Eptifibatide
- Ticagrelor
- Cangrelor
- Voraxapar
- Elinogrel

**FIBRINOLYTICS**
- « Golden Hour »

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**Conclusion**

- Formation of a coronary thrombus is a fast evolving process with 3 major therapeutical target (thrombin, platelet and fibrin).

- Thrombus burden impacts myocardial reperfusion, patients prognosis and increases mortality.

- Thrombus is present in STEMI and NSTE-ACS and needs to be treated by PCI with an optimal timing and an optimal antithrombotic therapy.

- Thrombus studies highlight the crucial role of pharmacodynamic of fast-acting antiplatelet agent using a triple antiplatelet therapy (aspirin + new P2Y12 inhibitor + GIIbIIa inhibitors) and potent thrombin inhibitor especially in early STEMI presenters.