Anticoagulation in the Cardiac Catheterization Laboratory

Jonathan D. Marmur, MD, FACC
Professor of Medicine
Director, Cardiac Catheterization and Interventional Cardiology
Health Science Center at Brooklyn
State University of New York
## Limitations of Heparin

<table>
<thead>
<tr>
<th>Limitation</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-specific binding to plasma proteins and endothelial cells</td>
<td>Variability in anticoagulant effect, especially in seriously ill patients</td>
</tr>
<tr>
<td>Release of Platelet factor 4 and vWF from platelets during clotting</td>
<td>Results in heparin resistance and a need for higher levels of heparin</td>
</tr>
<tr>
<td>Inability of heparin to inactivate fibrin-bound thrombin</td>
<td>Thrombin remains active when bound to fibrin and continues to activate platelets</td>
</tr>
<tr>
<td><strong>Heparin induces platelet activation</strong></td>
<td><strong>Further activates the clotting cascade and release of heparin-binding proteins</strong></td>
</tr>
<tr>
<td>Forms heparin antibodies</td>
<td>Can result in heparin-induced thrombocytopenia and thrombosis syndrome</td>
</tr>
<tr>
<td>Dose-dependent half-life</td>
<td>Non-linear increase in half-life as dose increases</td>
</tr>
</tbody>
</table>
SE (4,000X) Micrographs of Platelet Morphology

- **Normal resting platelet**
- **12 µg/mL of bivalirudin**
- **Platelets treated with UFH**
- **Release of platelet microparticles (arrows)**

Loss of the normal discoid shape and formation of distinct pseudopodia.
Enhanced Platelet Activation on UFH

- Unstable angina patients
- Samples drawn before and after heparin infusion
- Light transmission aggregometry

- Maximum (max) platelet aggregation in PRP from volunteers after adding saline, UFH, enoxaparin, or argatroban

Xiao and Theroux *Circulation* 1998;97:251-256
n~10,000 hi-risk ACS committed to an invasive strategy

Enoxaparin

UF heparin

TIMI major bleeding (non-CABG)

<table>
<thead>
<tr>
<th></th>
<th>Enox</th>
<th>UFH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.4</td>
<td>1.8</td>
</tr>
</tbody>
</table>

p=0.025

14.5%

14.0%

p=NS

Proportion with death or myocardial infarction

Hazard Ratio, 0.96 (95% CI, 0.86-1.06)

Days From Randomization

JAMA 2004;292:45-54
Pre-randomization Tx | Randomization | Crossover (n=798)
--- | --- | ---
No Prerandom. Tx (n=2440) | 24% | UFH → Enox → UFH → Enox → UFH → Enox → UFH → Enox
UFH (n=2939) | 29% | UFH → Enox → UFH → Enox → UFH → Enox → UFH → Enox
Enox (n=4293) | 43% | UFH → Enox → UFH → Enox → UFH → Enox → UFH → Enox
Both (n~300) | 3% | UFH → Enox → UFH → Enox → UFH → Enox → UFH → Enox

16% RR↓ in death/MI at 30 days
Meta-analysis of Enoxaparin vs UFH in ACS

N ~ 22,000 patients from 6 randomized controlled trials comparing Enox vs UFH in ACS

Petersen JL et al JAMA 2004;292:89-96
Lesson of SYNERGY: Avoid Switching

SYNERGY: Enoxaparin as effective as heparin but bleeding may be an issue
Mar 10, 2004 / Updated with interviews / with slides /
While experts are arguing over the clinical implications of the data, they agree on one clear message--that switching antithrombotic therapy worsens outcome and patients should remain on the first drug started whether they go to the cath lab or not. (American College of Cardiology 2004 Scientific Sessions.)
[ HeartWire > News ]
**Enoxaparin’s Major Problem in the Cath Lab: Timing-Based Dosing**

<table>
<thead>
<tr>
<th>TIME of PCI</th>
<th>Enoxaparin</th>
<th>UFH</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 8 hrs since last dose</td>
<td>No IV dose needed</td>
<td>Target ACT ~250 sec</td>
</tr>
<tr>
<td>8-12 hrs since last dose</td>
<td>0.3mg/ kg IV</td>
<td>Target ACT ~250 sec</td>
</tr>
<tr>
<td>&gt;12 hrs since last dose</td>
<td>Nobody knows</td>
<td>Target ACT ~250 sec</td>
</tr>
</tbody>
</table>
The Activated Clotting Time Can Be Used to Monitor the Low Molecular Weight Heparin Dalteparin After Intravenous Administration

Jonathan D. Marmur, MD, FACC,* Sunil X. Anand, BA,† Ramanjit S. Bagga, MD,† Jawed Fareed, PhD,‡ Chi-Miau Pan, PhD,§ Samin K. Sharma, MD, FACC,† Merwin F. Richard, MD†

Marmur et al J Am Coll Cardiol 2003;41:394-402
Both IV dalteparin and enoxaparin can be monitored with the ACT.

Cavusoglu, Lakhani, and Marmur (Journal of Invasive Cardiol 2005;17:416-421)

Target ACT for LMWH: >175 sec
Conversion of UFH targets of 200 and 300 sec (with and without adjunctive IIb/IIIa) to theoretic values for enoxaparin or dalteparin. Assuming similar levels of drug concentration, the intersection of a vertical line drawn from the 300 (or 200) sec UFH-intercept will yield a corresponding target LMWH ACT on the y-axis. Based on these observations, we propose a minimum LMWH target ACT of 175 (or 200) in the presence (or absence) of GP IIb/IIIa inhibition.
Protamine Can Neutralize LMWH (at least partially)

<table>
<thead>
<tr>
<th>Time</th>
<th>ACT</th>
<th>aPTT</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>121</td>
<td>31.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dalteparin 80 U/kg</td>
</tr>
<tr>
<td>40 min</td>
<td>172</td>
<td>77.3</td>
<td></td>
</tr>
<tr>
<td>Perforation</td>
<td></td>
<td></td>
<td>Protamine 10 mg</td>
</tr>
<tr>
<td>45 min</td>
<td>119</td>
<td>32.4</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LMWH</th>
<th>% Anti-Xa Neutralized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tinzaparin</td>
<td>86</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>74</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>54</td>
</tr>
</tbody>
</table>

STEEPLE randomized 3528 patients from 124 sites to one of two doses of IV enoxaparin or IV unfractionated heparin, with GP IIb/IIIa inhibition use at the discretion of the operator. The primary end point of the study was non-CABG major and minor bleeding out to 48 hours.

The primary end point of major bleeding was 57% lower in the enoxaparin arms, compared with the UFH arm. There were no significant differences in rates of death; nonfatal MI, death, or MI; or death, MI, and urgent target vessel revascularization.
Inhibition of one molecule of Xa can inhibit the generation of 50 molecules of thrombin.
OASIS-5 Study Design: Randomized, Double Blind

Patients with NSTE ACS, Chest discomfort < 24 hours
2 of 3: Age>60, ST Segment Δ, ↑ cardiac markers

Randomize

**Fondaparinux**
2.5 mg sc once daily

**Enoxaparin**
1 mg/kg sc twice daily

 PCI < 6 h: IV Fonda 2.5 mg without IIb/IIIa, 0 with IIb/IIIa
PCI > 6 h: IV Fonda 2.5 mg with and 5.0 mg without IIb/IIIa

ASA, Clop, GP IIb/IIIa, planned Cath/PCI as per local practice
(mean days to cath: 5±2)

Outcomes

**Primary:** Efficacy: Death, MI, refractory ischemia at 9 days
Safety: Major bleeding at 9 days
Risk benefit: Death, MI, refractory ischemia, major bleeds 9 days

**Secondary:** Above & each component separately at day 30 & 6 months

**Hypothesis:** First test non-inferiority, then test superiority

Exclude
Age < 21
Any contra-ind to Enox
Hem stroke < 12 mo.
Creat> 3 mg/dL/265 umol/L

N=20,000
Primary Efficacy Outcome
Death/MI/RI at Day 9

HR 1.01
95% CI 0.90-1.13

Days
Cumulative Hazard
0.0 0.01 0.02 0.03 0.04 0.05 0.06
0.0 1.0 2.0 3.0 4.0 5.0 6.0 7.0 8.0 9.0

- Enoxaparin
- Fondaparinux

Primary Efficacy Outcome
Death/MI/RI at Day 9

HR 1.01
95% CI 0.90-1.13
Major Bleeding: 9 Days

Cumulative Hazard

HR 0.53
95% CI 0.45-0.62
P<<0.00001

Enoxaparin

Fondaparinux
Mortality: Day 30

Enoxaparin

Fondaparinux

HR 0.83
95% CI 0.71-0.97
P=0.022
Mortality at 6 Months

Enoxaparin

Fondaparinux

HR 0.89
95% CI 0.79-0.99
P=0.037
# PCI During Study Treatment Period

## Procedural Complications

<table>
<thead>
<tr>
<th>Events at 30 days</th>
<th>Enox (%)</th>
<th>Fonda (%)</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Rand.</td>
<td>3089</td>
<td>3118</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any UFH during PCI</td>
<td>53.8</td>
<td>18.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary--Any Complication</td>
<td>8.6</td>
<td>9.6</td>
<td>1.11 (0.95-1.30)</td>
<td>0.18</td>
</tr>
<tr>
<td>Abrupt Closure</td>
<td>1.1</td>
<td>1.5</td>
<td>1.33 (0.86-2.06)</td>
<td>0.20</td>
</tr>
<tr>
<td>Vasc. Access Site</td>
<td>8.1</td>
<td>3.3</td>
<td>0.40 (0.32-0.50)</td>
<td>&lt;&lt;0.0001</td>
</tr>
<tr>
<td>Pseudo-aneurysm</td>
<td>1.6</td>
<td>1.0</td>
<td>0.63 (0.40-0.98)</td>
<td>0.039</td>
</tr>
<tr>
<td>Large Hematoma</td>
<td>4.4</td>
<td>1.6</td>
<td>0.35 (0.26-0.49)</td>
<td>&lt;&lt;0.0001</td>
</tr>
<tr>
<td>Catheter thrombus*</td>
<td>0.5</td>
<td>1.3*</td>
<td>2.76 (1.50-5.07)</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

*Following institution of routine UFH prior to PCI, only one case of cath thrombus in 330 patients given fonda.
PCI During Study Treatment Period: Events Before and After Amendment

Amendment
1. Small dose UFH option
2. Flush IV line after fonda admin.
3. Push syringe down completely
4. Do not expel air bubble

Before Amendment
- Death/MI: 7.1%
- Major Bleeds: 5.5%

After Amendment
- Death/MI: 6.7%
- Major Bleeds: 2.8%

Death or MI at 30 days (%)
OASIS – 6 Trial: Study Design

12,092 patients presenting with STEMI within 24 hours of symptom onset (shortened to 12 hours of symptom onset midway through trial)
Randomized. Blinded. Factorial.
28% female, mean age 62 years, mean follow-up 3-6 months

- Stratum 1 (No UFH)
  - Fondaparinux 2.5mg/day for up to 8 days or hospital discharge
  - Placebo

- Stratum 2 (UFH)
  - Fondaparinux 2.5mg/day for up to 8 days or hospital discharge
  - UFH

- Primary Endpoint: Composite of death or reinfarction at 30 days
- Secondary Endpoint: Composite of death or reinfarction at 9 days and at final follow-up

Presented at ACC 2006
The primary endpoint was lower in the fondaparinux group compared with the control group (9.7% vs. 11.2%, HR 0.86, p=0.008).

The results were similar at 9 days (HR 0.83, p=0.003) and at study end (HR 0.88, p=0.008).

Presented at ACC 2006
There was no difference in the primary endpoint for patients who were managed with primary PCI (6.1% vs 5.1%, p=0.19).

Guiding catheter thrombosis in the primary PCI cohort occurred more often with fondaparinux compared with control (n=22 vs. n=0, p<0.001)

Presented at ACC 2006
• There was a higher instance of guiding catheter thrombosis in the PCI cohort treated with fondaparinux compared to control (n=22 vs. n=0, p<0.001)

Presented at ACC 2006
OASIS- 5 and 6 Trials

- Fondaparinux appears superior to enoxaparin and UFH *as administered in the trials* and within the context of medically managed patients.

- Its benefit appears to be related to reduced bleeding.

- Fondaparinux appears to be associated with a hazard of guiding catheter thrombosis, which may be corrected by administration of UFH.
Direct versus Indirect Thrombin Inhibition

Indirect Inhibition

- Anti-Xa:Anti-IIa ratio
- Cheap, familiar
- Reversible with protamine

Direct Inhibition

- Bivalent versus univalent
- Inhibits clot-bound thrombin
- No platelet activation; no HIT
Reduced Bleeding with Bivalirudin: Potential Mechanism

Non-competitive inhibition (high affinity state)

Competitive inhibition (low affinity state)
Bivalirudin Pharmacokinetic Profile

Bolus 1 mg/kg

Infusion 2.5 mg/kg/h

Plasma half life 25 min

Complete inhibition of thrombin-induced platelet activation at 1/500th the concentration achieved with clinical doses.
**Trial Design**

N = 6010 “elective or urgent” PCI patients

Randomization - double blind, triple dummy

- **Heparin**
  - 65 U/kg initial bolus
  - Planned GP IIb/IIIa (abciximab or eptifibatide)
  - Target ACT > 225 sec

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

- **Low-moderate risk population**
  - No acute MI
  - No UFH within 6 hrs
  - No LMWH within 8 hrs
  - No IIb/IIIa within 12 hrs

- “Quadruple Endpoint” at 30 Days
Primary Quadruple Endpoint

Heparin + GP IIb/IIIa non-inferiority boundary = 0.92

Heparin Better

Odds Ratio & 95% CI

Bivalirudin Better

Death, MI, URev, Maj Bld (%)

Odds Ratio = 0.917 (0.772 - 1.089)

p = 0.32

Lincoff et al *JAMA* 2003;289:853-863
Quadruple Endpoint

30 Day Primary Endpoint Components

% of Patients

- Composite: 10.0% Heparin + GP IIb/IIIa (n = 3008), 9.2% Bivalirudin (n = 2994)
- Death: 0.4% Heparin + GP IIb/IIIa, 0.2% Bivalirudin
- MI: 6.2% Heparin + GP IIb/IIIa, 7.0% Bivalirudin
- Urgent Revasc: 1.4% Heparin + GP IIb/IIIa, 1.2% Bivalirudin
- Major Bleeding: 4.1% Heparin + GP IIb/IIIa, 2.4% Bivalirudin

p <0.001

Lincoff et al. JAMA 2003;289:853-863
Multi-Year Follow-up of Abciximab Therapy in Three Randomized, Placebo-Controlled Trials of Percutaneous Coronary Revascularization*

Eric I. Topol, MD, A. Michael Lincoff, MD, Dean J. Kereiakes, MD, Neal S. Kleiman, MD, Eric A. Cohen, MD, James J. Ferguson, MD, James E. Tcheng, MD, Shelly Sapp, MS, Robert M. Califf, MD

n=5,799 pts in 3 randomized, double-blind placebo-controlled trials of abciximab in PCI

Am J Med 2002;113:1–6
REPLACE-2: 1 year mortality

Mortality (% of Patients)

- Heparin + GP IIb/IIIa
- Bivalirudin

Days from Randomization

- p-value = 0.16

Lincoff MA et al. *JAMA* 2004;292:696-703
# 1-year mortality - high risk pts

Death rates among elderly, diabetics, renal impairment

<table>
<thead>
<tr>
<th>Condition</th>
<th>Group Description</th>
<th>Death Rate</th>
<th>Heparin + GPIIb/IIIa inhibitor</th>
<th>Bivalirudin</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;75 (N=795)</td>
<td></td>
<td>6.9%</td>
<td>48%</td>
<td>3.6%</td>
<td>0.039</td>
</tr>
<tr>
<td>Diabetes (N=1606)</td>
<td></td>
<td>3.9%</td>
<td></td>
<td>2.3%</td>
<td>0.068</td>
</tr>
<tr>
<td>Creat clear. &lt;60 (N=908)</td>
<td></td>
<td>7.1%</td>
<td></td>
<td>4.5%</td>
<td>0.091</td>
</tr>
</tbody>
</table>
## 1-Year Mortality

### Multivariate Logistic Model

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl &lt;30 mL/min</td>
<td>7.9</td>
<td>2.7-22.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CrCl 30-60 mL/min</td>
<td>3.8</td>
<td>2.2-6.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CrCl 60-90 mL/min</td>
<td>1.7</td>
<td>1.0-2.7</td>
<td></td>
</tr>
<tr>
<td>Major Bleed</td>
<td>3.67</td>
<td>2.1-6.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-Q MI</td>
<td>2.58</td>
<td>1.5-4.4</td>
<td>0.004</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.74</td>
<td>1.3-2.6</td>
<td>0.005</td>
</tr>
<tr>
<td>Prior angina</td>
<td>1.97</td>
<td>1.3-3.4</td>
<td>0.017</td>
</tr>
</tbody>
</table>
Bleeding and primary endpoint components - 30 days

Patients with major bleeding had higher ischemic event rates

<table>
<thead>
<tr>
<th></th>
<th>No Major Bleed</th>
<th>Major Bleed</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=5807</td>
<td>N=194</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>9 (0.2%)</td>
<td>10 (5.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MI</td>
<td>354 (6.1%)</td>
<td>3 (1.6%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Urgent TVR</td>
<td>50 (0.9%)</td>
<td>6 (3.1%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Urgent PCI</td>
<td>43 (0.7%)</td>
<td>2 (1.0%)</td>
<td>ns</td>
</tr>
<tr>
<td>Urgent CABG</td>
<td>9 (0.2%)</td>
<td>4 (2.1%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Death/MI/TVR</td>
<td>397 (6.9%)</td>
<td>4 (10.9%)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
Anti-thrombin therapy in the cath lab

- Heparin is obsolete by virtue of a variety of disadvantages, most significant of which is the propensity to activate platelets.

- LMWH has the advantage of demonstrated improved outcomes in ACS, but transition to PCI requires clarification, particularly with respect to the issue of bedside monitoring. At the very least, check the ACT (minimum 180 sec).

- For PCI, the data in favor of bivalirudin over heparin alone is incontrovertible. No one should be doing PCI with regular heparin alone.

- The real question is whether to stick with heparin plus IIb/IIIa. Previously, the answer was: use bivalirudin for low to moderate risk and IIb/IIIa for high risk. Based on the REPLACE-2 mortality data, the answer today is: use bivalirudin.

  Caveat: you can use IIb/IIIa only if you have a way of keeping your bleeding complications as low as those demonstrated with bivalirudin.
Abciximab in Patients With Acute Coronary Syndromes Undergoing Percutaneous Coronary Intervention After Clopidogrel Pretreatment
The ISAR-REACT 2 Randomized Trial

N=2,022 high risk ACS patients (unstable angina with EKG abnormalities or troponin elevation)

The primary end point was a composite of death, myocardial infarction, or urgent target vessel revascularization
## EPIC trial: Bleeding Complications

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (N = 696)</th>
<th>c7E3 Fab Bolus (N = 695)</th>
<th>c7E3 Fab Bolus and Infusion (N = 708)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding — no. (%)</td>
<td>46 (7)*</td>
<td>76 (11)</td>
<td>99 (14)</td>
</tr>
<tr>
<td>Site of major bleeding — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Groin</td>
<td>20</td>
<td>49</td>
<td>58</td>
</tr>
<tr>
<td>Need for surgical repair</td>
<td>7 (1.0)</td>
<td>16 (2.3)</td>
<td>6 (0.8)</td>
</tr>
<tr>
<td>Retroperitoneal</td>
<td>3</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Coronary artery†</td>
<td>23</td>
<td>21</td>
<td>26</td>
</tr>
<tr>
<td>Intracranial</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Hematemesis</td>
<td>0</td>
<td>5</td>
<td>11</td>
</tr>
</tbody>
</table>
EPI C Outcomes: Bolus-Only Effective at 6hrs

30-day Death/MI/Urgent Revx

- Placebo: 12.8%
- Bolus: 11.4%
- Bolus + infusion: 8.3%

24-hour Death/MI/Urgent Revx

- Placebo
- Bolus Only
- Bolus + Infusion

\[ p = 0.022 \]


Marmur JD et al (AHJ in press)
Intention to Treat

EPI C: 7 Year Mortality Follow-Up

Mortality (%)

years

0 1 2 3 4 5 6 7

Intention to Treat

Placebo

Bolus

Bolus + Infusion

20.1%
17.3%
16.1%
Bolus-Only at SUNY Downstate

- N=1001 consecutive pts from Jan 2003 to Aug 2004
- Single center retrospective registry
- 58% eptifibatide; 37% abciximab; 5% tirofiban

Marmur JD et al JIC 2006
Platelet function post tirofiban bolus-only

PAU timecourse

PAU

Time (min)

% platelet inhibition

Baseline 4 8 10 15 20 25 30 45 60 90 120 150 180
Predictors of Subacute Stent Thrombosis
Results of a Systematic Intravascular Ultrasound Study

Edouard Cheneau, MD; Laurent Leborgne, MD; Gary S. Mintz, MD; Jun-ichi Kotani, MD; Augusto D. Pichard, MD; Lowell F. Satler, MD; Daniel Canos, MPH; Marco Castagna, MD; Neil J. Weissman, MD

- **N = 7,484** consecutive patients undergoing IVUS-guided stenting
- **N = 27** (0.4%) had angiographic stent thrombosis <1 week post-PCI
- Presumed causes included
  - Inadequate lumen (MUSIC*) - 78%
  - Malapposition - 9%
  - Dissection - 17%
  - Thrombus - 4%
  - Tissue protrusion through struts leading to lumen compromise - 4%

*final lumen CSA <90% of the reference, or <80% if minimal lumen CSA was >9 mm²

**NO relation to IIb/IIIa use**
Predictors and outcomes of stent thrombosis

An intravascular ultrasound registry

N. G. Uren, S. P. Schwarzacher, J. A. Metz, D. P. Lee, Y. Honda, A. C. Yeung, P. J. Fitzgerald and P. G. Yock, on behalf of the POST Registry investigators

- POST Registry collected IVUS examinations of patients who developed subsequent stent thrombosis within 4 weeks
- Multicenter, international, retrospective registry of cases from 1991-96 (period of evolution of implantation techniques)
- N= 53 cases identified

**Results**
- Under-expansion- 49%
- Malapposition- 49%
- Edge tear/dissection- 26%
- In-stent thrombus- 23%

**NO relation to IIb/IIIa use**

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Underexpansion of Sirolimus-Eluting Stents: Incidence and Relationship to Delivery Pressure

Edouard Cheneau, MD, Lowell F. Satler, MD, Esteban Escolar, MD, William O. Suddath, MD, Kenneth M. Kent, MD, Neil J. Weissman, MD, Ron Waksman, MD, and Augusto D. Pichard, MD

We aimed to assess the incidence of underexpansion and the relationship between delivery pressure and expansion with sirolimus-eluting stents. Adequate stent expansion contributes to early and late improved outcomes. In 51 patients (53 lesions) with native coronary artery narrowing, balloon-expandable sirolimus-eluting stents (Cypher) were serially expanded with gradual balloon inflations [14 atm, 20 atm, and in case of minimal stent cross-sectional area (CSA)/reference lumen CSA < 50% at 20 atm, post-dilation with 0.5 mm larger balloon]. Intravascular ultrasound (IVUS) imaging was performed before intervention and after each gradual balloon inflation. Stent expansion (minimal stent CSA/reference lumen CSA) was measured. Stent expansion was 72% ± 16% after 14 atm balloon inflation, 90% ± 18% after 20 atm balloon inflation (P < 0.001 vs. 14 atm), and 90% ± 18% at the end of the procedure (including optional postdilatations with 0.5 mm larger balloon; P = NS vs. 20 atm). Stent expansion addressed by MUSIC criteria (all struts apposed, no tissue protrusion, and final lumen CSA > 80% of the reference or > 90% if minimal lumen CSA was < 9 mm²) was adequate in 15% of the cases after 14 atm balloon inflation, in 80% after 20 atm balloon inflation (P < 0.001 vs. 14 atm), and in 60% at the end of the procedure (P = NS vs. 20 atm). Sirolimus-eluting stent underexpansion is common when deployed at conventional pressures. Increasing balloon delivery pressure or assessing stent expansion with IVUS seems warranted in order to ensure adequate sirolimus-eluting stent deployment.

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Conclusions

- Stent thrombosis has everything to do with operator technique and nothing to do with IIb/IIIa inhibitors. Better you should focus on hi-pressure stent deployment and clopidogrel compliance pre and post procedure.

- There is nothing magical about the low bleeding rates associated with bivalirudin in REPLACE-2. Lack of prolonged infusion, with rapid return to hemostatic competence is the key.

- Preventing bleeds is probably more important than preventing CK-MB release, but preventing both is the ideal.

- This ideal can be achieved with a bolus-only IIb/IIIa strategy (and at a lower cost). The mortality data of REPLACE-2 mandates a response from the IIb/IIIa users. Either you switch to bivalirudin, or you convert to a IIb/IIIa bolus-only strategy.

- Either way, the era of conventional bolus plus infusion of IIb/IIIa is over.