STEMI and NSTEMI Pharmacology
Confusion: How to Choose and Use Antithrombins (Unfractionated and Low Molecular Heparins, Bivalirudin, Fondaparinux) and Antiplatelet Agents (Aspirin, Clopidogrel and Prasugrel)

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Columbia University Medical Center
Cardiovascular Research Foundation
Disclosures

- Gregg W. Stone
  - Research support from The Medicines Company
My Dilemma

How to Cover 25 Years of Data and >350 Randomized Trials in 20 minutes?

• The Drugs
  - Antiplatelet agents
    - Aspirin
    - Thienopyridines
    - GP IIb/IIIa inhibitors
  - Antithrombins
    - Unfractionated heparin
    - LMWH (enoxaparin)
    - Bivalirudin
    - Fondaparinux

• The Settings
  - PCI in...
    - ACS
    - AMI
      - Primary PCI
      - Rescue PCI
    - Acute use vs.
    - Chronic use

XXX00XXX
PCI Pharmacology

Aspirin
Aspirin
(From the German acetylspirsaure + chemical suffix – in)

First synthesized in pure form by Felix Hoffman of Friedr. Bayer & Co. in 1897.
# Aspirin in ACS (n=54,089)

<table>
<thead>
<tr>
<th>Category of trial</th>
<th>N of trials</th>
<th>MI, Stroke, or Vascular Death</th>
<th>Odds ratio &amp; CI (Antiplatelet: Control)</th>
<th>% odds reduction (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior MI</td>
<td>11</td>
<td>1330/9677 (13.7%) 1693/9914 (17.1%)</td>
<td>0.50 1.0 1.5 2.0</td>
<td>25%</td>
</tr>
<tr>
<td>Acute MI</td>
<td>9</td>
<td>992/9388 (10.6%) 1348/9385 (14.4%)</td>
<td>0.50 1.0 1.5 2.0</td>
<td>29%</td>
</tr>
<tr>
<td>Prior Stroke/TIA</td>
<td>18</td>
<td>1076/5837 (18.4%) 1301/5870 (22.2%)</td>
<td>0.50 1.0 1.5 2.0</td>
<td>22%</td>
</tr>
<tr>
<td>Unstable Angina</td>
<td>7</td>
<td>182/1991 (9.1%) 285/2027 (14.1%)</td>
<td>0.50 1.0 1.5 2.0</td>
<td>45%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Thienopyridines</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticlopidine (Ticlid)</td>
<td>Clopidogrel (Plavix)</td>
<td>Prasugrel (Effient)</td>
</tr>
<tr>
<td>300 mg pill also approved</td>
<td>60 mg load 10 mg QD Approved in EU</td>
<td></td>
</tr>
</tbody>
</table>
CURE

12,562 pts with ACS were treated with aspirin and randomized to clopidogrel vs. placebo and followed for up to 12 months

Primary endpoint = CV Death, MI, or Stroke

Placebo + Aspirin*
(n = 6303)

Clopidogrel + Aspirin*
(n = 6259)

11.4%  9.3%

20% ↓
P<0.001

* In combination with standard therapy

12,562 pts with ACS were treated with aspirin and randomized to clopidogrel vs. placebo and followed for up to 12 months

Primary endpoint = CV Death, MI, or Stroke

<table>
<thead>
<tr>
<th></th>
<th>ASA + Clopidogrel</th>
<th>ASA + Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, MI, stroke</td>
<td>9.3%</td>
<td>11.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CV death, MI, stroke, refractory ischemia</td>
<td>16.5%</td>
<td>18.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- CV death</td>
<td>5.1%</td>
<td>5.5%</td>
<td>NS</td>
</tr>
<tr>
<td>- MI</td>
<td>5.2%</td>
<td>6.7%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>- Stroke</td>
<td>1.2%</td>
<td>1.4%</td>
<td>NS</td>
</tr>
<tr>
<td>- Refractory ischemia</td>
<td>8.7%</td>
<td>9.3%</td>
<td>NS</td>
</tr>
<tr>
<td>Non CV death</td>
<td>0.7%</td>
<td>0.7%</td>
<td>NS</td>
</tr>
<tr>
<td>Bleeding events, any</td>
<td>8.5%</td>
<td>5.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Major</td>
<td>3.7%</td>
<td>2.7%</td>
<td>0.001</td>
</tr>
<tr>
<td>- Minor</td>
<td>5.1%</td>
<td>2.4%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
PCI was performed in 2658 pts (21%): 1 Yr CV Death or MI

A = median time to PCI; B = open label clopidogrel for 30 d after PCI

PCI-CURE

CV Death or MI at Various Intervals

<table>
<thead>
<tr>
<th>RRR</th>
<th>Overall</th>
<th>Before PCI</th>
<th>PCI to 30 d</th>
<th>30 d to 1 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>31%</td>
<td>12.6</td>
<td>5.1</td>
<td>4.4</td>
<td>3.9</td>
</tr>
<tr>
<td>32%</td>
<td>8.8</td>
<td>3.6</td>
<td>2.9</td>
<td>3.1</td>
</tr>
<tr>
<td>34%</td>
<td>15.1</td>
<td>8.8</td>
<td>4.4</td>
<td>3.9</td>
</tr>
<tr>
<td>21%</td>
<td>15.1</td>
<td>8.8</td>
<td>4.4</td>
<td>3.9</td>
</tr>
</tbody>
</table>

P=0.002

# Clopidogrel Pretreatment Prior to Elective CABG

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel (n=59)</th>
<th>No Clopidogrel (n=165)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT output 1st 24º</td>
<td>1224</td>
<td>840</td>
<td>0.001</td>
</tr>
<tr>
<td>Transfusions any</td>
<td>85%</td>
<td>61%</td>
<td>0.001</td>
</tr>
<tr>
<td>- RBC any</td>
<td>79%</td>
<td>58%</td>
<td>0.004</td>
</tr>
<tr>
<td>- RBC mean U</td>
<td>2.51</td>
<td>1.74</td>
<td>0.036</td>
</tr>
<tr>
<td>- Platelet any</td>
<td>51%</td>
<td>18%</td>
<td>0.001</td>
</tr>
<tr>
<td>- Plat mean U</td>
<td>0.86</td>
<td>0.24</td>
<td>0.001</td>
</tr>
<tr>
<td>Reop for bleed</td>
<td>6.8%</td>
<td>0.6%</td>
<td>0.02</td>
</tr>
<tr>
<td>Extubate &lt;8º</td>
<td>54%</td>
<td>76%</td>
<td>0.002</td>
</tr>
<tr>
<td>LOS ≤5 days</td>
<td>34%</td>
<td>47%</td>
<td>0.09</td>
</tr>
</tbody>
</table>

ACUITY: Impact of Thienopyridine Exposure Prior to CABG (n=1,539 pts)

- Thieno (+) (N=806)
- Thieno (−) (N=733)

- Net clinical outcome: 15.5% vs 19.4% (P=0.05)
- Composite ischemia: 12.8% vs 17.3% (P=0.01)
- Major bleeding (non-CABG): 3.5% vs 3.1% (P=0.71)
- All Major Bleeding: 54.2% vs 54.3% (P=0.98)

Ebrahimi et al, In press
Healthy Volunteer Crossover Study

 IPA at 24 hours (%)

N=66

Interpatient Variability

Response to Clopidogrel 300 mg

Response to Prasugrel 60 mg

Clopidogrel Responder

Clopidogrel Non-responder

From Brandt JT et al. AHJ 2007;153:66.e9-66.e16
13,608 pts with ACS (unstable angina, NSTEMI, acute STEMI, or recent STEMI) undergoing PCI with known coronary anatomy (except for primary PCI pts) were treated with aspirin and randomized to clopidogrel 300 mg load + 75 mg qd vs. prasugrel 60 mg load + 10 mg qd and followed for 6-15 mos (median 12 mos).

Wiviott SD et al. NEJM 2007;357:2001-15

![Graph showing primary endpoint: CV death, MI, or stroke (%) vs. days. Clopidogrel: 12.1%, HR 0.80, P=0.0003; Prasugrel: 9.9%, HR 0.77, P=0.0001.](image.png)
Definite or probable stent thrombosis in 12,844 pts receiving any stent

- **CLOPIDOGREL**
  - Definite ST: 0.9% vs. 2.0%
  - HR 0.42 [0.31, 0.59]
  - P<0.0001

- **PRASUGREL**
  - Definite ST: 1.1%
  - HR 0.48 [0.36-0.64]
  - P<0.0001

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Wiviott SD et al. Lancet. 2008;371:1353-63
### TRITON-TIMI-38

<table>
<thead>
<tr>
<th>Event</th>
<th>Prasugrel (n=6813)</th>
<th>Clopidogrel (n=6795)</th>
<th>HR [95%CI]</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CV death, MI, stroke</strong></td>
<td>9.9%</td>
<td>12.1%</td>
<td>0.81 [0.73, 0.90]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- CV death</td>
<td>2.1%</td>
<td>2.4%</td>
<td>0.89 [0.70, 1.12]</td>
<td>0.31</td>
</tr>
<tr>
<td>- Nonfatal MI</td>
<td>7.3%</td>
<td>9.5%</td>
<td>0.76 [0.67, 0.85]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Non fatal stroke</td>
<td>1.0%</td>
<td>1.0%</td>
<td>1.02 [0.71, 1.45]</td>
<td>0.93</td>
</tr>
<tr>
<td><strong>Urgent TVR</strong></td>
<td>2.5%</td>
<td>3.7%</td>
<td>0.66 [0.54, 0.81]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Death, all-cause</strong></td>
<td>3.0%</td>
<td>3.2%</td>
<td>0.95 [0.78, 1.16]</td>
<td>0.64</td>
</tr>
<tr>
<td><strong>TIMI bleed, major or minor</strong></td>
<td>5.0%</td>
<td>3.8%</td>
<td>1.31 [1.11, 1.56]</td>
<td>0.002</td>
</tr>
<tr>
<td>- Major, CABG related</td>
<td>13.4%</td>
<td>3.2%</td>
<td>4.73 [1.90, 11.82]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Major, non CABG related</td>
<td>2.4%</td>
<td>1.8%</td>
<td>1.32 [1.03, 1.68]</td>
<td>0.03</td>
</tr>
<tr>
<td>- Life-threatening</td>
<td>1.4%</td>
<td>0.9%</td>
<td>1.52 [1.08, 2.13]</td>
<td>0.01</td>
</tr>
<tr>
<td>- Fatal</td>
<td>0.4%</td>
<td>0.1%</td>
<td>4.19 [1.58, 11.11]</td>
<td>0.002</td>
</tr>
<tr>
<td>- Requiring transfusion</td>
<td>4.0%</td>
<td>3.0%</td>
<td>1.34 [1.11, 1.63]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Wiviott SD et al. NEJM 2007;357:2001-15
PCI Pharmacology

Antithrombins I: Unfractionated Heparin and Enoxaparin
Unfractionated Heparin in ACS (N=1353)

RR: Death/MI

Summary Relative Risk
0.67 (0.44–1.02)

Heparin + ASA
55/698 = 7.9%

ASA Alone
68/655 = 10.4%

Theroux
RISC
Cohen ’90
ATACS
Holdright
Gurfinkel

Oler et al. JAMA 1996;276:811–6
Antithrombin Choices for PCI, ACS and AMI

LMW Heparin

Unfractionated heparin

Fondaparinux

Bivalirudin
Invasive Management Strategy

High-risk ACS patients

Enoxaparin
1 mg/kg SQ

UF heparin
60 U/kg

2/3 of:
• Age > 60
• (+) ST ↓
• (+) biomarkers

n = 10,027
467 sites
12 countries

Primary Endpoint:
Death / MI at 30 days

2/3 of:
• Age > 60
• (+) ST ↓
• (+) biomarkers

Ferguson JJ et al. JAMA. 2004;292:45–54
SYNERGY
Enoxaparin vs. Heparin in 10,027 High Risk ACS Pts
Inclusion: 2/3 age ≥60, EKGΔ or troponin/CKMB+ (85%)
Early invasive strategy (92% cath, 46% PCI, 19% CABG)

30 day primary endpoint (%)

- Death or MI: Heparin (n=4982) 14.5%, Enoxaparin (n = 4992) 14.0%, p = 0.40
- Death: Heparin 3.1%, Enoxaparin 3.2%, p = 0.11
- MI: Heparin 12.7%, Enoxaparin 11.7%, p = 0.008

Major bleeding (%)

- GUSTO Severe: Heparin 2.4%, Enoxaparin 2.9%, p = 0.16
- TIMI Major: Heparin 7.6%, Enoxaparin 9.1%, p = 0.008
- Transfusion: Heparin 16.0%, Enoxaparin 17.0%, p = 0.40

Ferguson JJ et al. JAMA. 2004;292:45–54
PCI Pharmacology

Antithrombins II: Fondaparinux
Fondaparinux: An Indirect Synthetic Factor Xa Inhibitor – Activates ATIII

Adapted from Turpie AGG et al. NEJM 2001;344:619.

T1/2 = 15–18 hrs
OASIS-5
Fondaparinux vs Enoxaparin in ACS

20,078 pts with unstable angina or NSTEMI; 70% troponin +

Yusuf S et al. NEJM 2006;354:1464–76
# OASIS 5: Select Features

<table>
<thead>
<tr>
<th></th>
<th>Enoxaparin (n=10,021)</th>
<th>Fondaparinux (n=10,057)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N days on drug</strong></td>
<td>5.2 ± 2.3</td>
<td>5.4 ± 2.4</td>
</tr>
<tr>
<td><strong>Hospital meds and procedures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiography</td>
<td>63.1%</td>
<td>63.5%</td>
</tr>
<tr>
<td>PCI</td>
<td>34.3%</td>
<td>34.3%</td>
</tr>
<tr>
<td>CABG</td>
<td>9.0%</td>
<td>9.6%</td>
</tr>
<tr>
<td>Clopidogrel/ticlopidine</td>
<td>67.2%</td>
<td>67.6%</td>
</tr>
<tr>
<td>GP IIb/IIIa</td>
<td>17.6%</td>
<td>18.6%</td>
</tr>
<tr>
<td>- during PCI</td>
<td>41.0%</td>
<td>41.7%</td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>31.2%</td>
<td>22.0%</td>
</tr>
</tbody>
</table>

Yusuf S et al. *NEJM* 2006;354:1464–76
## OASIS-5

### Fondaparinux vs. Enoxaparin in ACS

Outcome in pts undergoing PCI within first 8 days (N=6239)

<table>
<thead>
<tr>
<th>Event</th>
<th>Enoxaparin (n = 3104)</th>
<th>Fondaparinux (n = 3135)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfractionated heparin</td>
<td>55.5</td>
<td>20.8</td>
</tr>
<tr>
<td>GP IIb/IIIa inhibitor</td>
<td>41.0</td>
<td>41.7</td>
</tr>
<tr>
<td>Thienopyridine</td>
<td>74.6</td>
<td>74.9</td>
</tr>
<tr>
<td>Acute closure, new thrombus, dissection or no reflow</td>
<td>5.2</td>
<td>6.0</td>
</tr>
<tr>
<td>Catheter-related thrombi (CEC)</td>
<td>0.4</td>
<td><strong>P=0.008</strong> 0.9</td>
</tr>
<tr>
<td>Death, MI or stroke (30 days)</td>
<td>7.3</td>
<td>7.4</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>5.4</td>
<td>2.8</td>
</tr>
</tbody>
</table>

Yusuf S et al. *NEJM* 2006;354:1464–76
### OASIS 6: Fondaparinux During Primary PCI

3,788 pts with STEMI undergoing primary PCI were randomized to UFH for 4-48 hrs vs. fondaparinux 2.5 mg SQ QD for up to 8 days in a placebo-controlled double-blind trial.

<table>
<thead>
<tr>
<th>30 day events</th>
<th>UFH (n=1,898)</th>
<th>Fonda (n=1,890)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catheter thrombus</td>
<td>0%</td>
<td>1.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary complications*</td>
<td>11.9%</td>
<td>14.3%</td>
<td>0.04</td>
</tr>
<tr>
<td>Death or MI</td>
<td>4.9%</td>
<td>6.0%</td>
<td>0.13</td>
</tr>
<tr>
<td>Severe bleed</td>
<td>0.5%</td>
<td>0.8%</td>
<td>0.16</td>
</tr>
</tbody>
</table>

* Abrupt coronary closure, new angio thrombus, catheter thrombus, no reflow, dissection, or perforation.

Yusuf S et al. JAMA 2006;295:1519–30
PCI Pharmacology

Antithrombins III: Bivalirudin
Bivalirudin
Bivalent Synthetic Direct Thrombin Inhibitor

- Specifically inhibits
  - Fluid phase thrombin
  - Clot-bound thrombin
  - Thrombin-mediated
  - Platelet aggregation

- Reversible

- $T_{0.5}$ 25 minutes
**ACUITY: First Randomization**

Moderate and high risk unstable angina or NSTEMI undergoing an invasive strategy (N = 13,819)

Aspirin in all Clopidogrel dosing and timing per local practice

Moderate and high risk ACS (n=13,819)

- UFH/Enox + GP IIb/IIIa (n=4,603)
- Bivalirudin + GP IIb/IIIa (n=4,604)
- Bivalirudin Alone (n=4,612)

Angiography 19.6° median

- Medical management 33%
- PCI 56%
- CABG 11%

*Stratified by pre-angiography thienopyridine use or administration

Stone GW et al. NEJM 2006;355:2203-16
Ischemic Composite Endpoint

UFH/Enoxaparin + GPI vs. Bivalirudin + GPI vs. Bivalirudin Alone

Estimate P
(log rank)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH/Enoxaparin + IIb/IIIa (N=4603)</td>
<td>7.4%</td>
<td>0.37</td>
</tr>
<tr>
<td>Bivalirudin + IIb/IIIa (N=4604)</td>
<td>7.9%</td>
<td></td>
</tr>
<tr>
<td>Bivalirudin alone (N=4612)</td>
<td>8.0%</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Stone GW et al. NEJM 2006;355:2203-16
Major Bleeding Endpoint

UFH/Enoxaparin + GPI vs. Bivalirudin + GPI vs. Bivalirudin Alone

Estimate P
(log rank)

UFH/Enoxaparin + IIb/IIla (N=4603) 5.7%
Bivalirudin + IIb/IIla (N=4604) 5.3% 0.41
Bivalirudin alone (N=4612) 3.1% <0.0001

Stone GW et al. NEJM 2006;355:2203-16
## Bleeding Endpoints

<table>
<thead>
<tr>
<th></th>
<th>UFH/Enoxaparin + GP IIb/IIIa (N=4,603)</th>
<th>Bivalirudin + GP IIb/IIIa (N=4,604)</th>
<th>Bivalirudin alone (N=4,612)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACUITY Scale</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Major Bleed, all</td>
<td>11.8%</td>
<td>11.1%</td>
<td>9.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Major, non-CABG</td>
<td>5.7%</td>
<td>5.3%</td>
<td>3.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Minor, non-CABG</td>
<td>21.6%</td>
<td>21.7%</td>
<td>12.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>TIMI Scale</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Any</td>
<td>6.6%</td>
<td>6.5%</td>
<td>4.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Major</td>
<td>1.9%</td>
<td>1.7%</td>
<td>0.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Minor</td>
<td>6.4%</td>
<td>6.1%</td>
<td>3.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Blood transfusion</strong></td>
<td>2.7%</td>
<td>2.6%</td>
<td>1.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td>11.1%</td>
<td>10.8%</td>
<td>9.9%</td>
<td>0.01*</td>
</tr>
</tbody>
</table>

*P value for Bivalirudin alone vs. GP IIb/IIIa inhibitor based regimen
Impact of Thienopyridine Pre-Administration

UFH/Enoxaparin + GPI vs. Bivalirudin Alone

Thienopyridine pre angio/interv (n=5,753)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>UFH/Enox+GPI</th>
<th>Bivalirudin alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Net benefit</td>
<td>11.7%</td>
<td>9.5%</td>
</tr>
<tr>
<td>Ischemic composite</td>
<td>7.3%</td>
<td>7.0%</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>5.9%</td>
<td>3.1%</td>
</tr>
</tbody>
</table>

RR [95%CI] = 0.81 [0.70-0.94]

No thienopyridine pre angio/interv (n=3,304)

<table>
<thead>
<tr>
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</tr>
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<tr>
<td>Net benefit</td>
<td>11.0%</td>
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</tr>
<tr>
<td>Ischemic composite</td>
<td>7.1%</td>
<td>9.1%</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>4.8%</td>
<td>2.9%</td>
</tr>
</tbody>
</table>

RR [95%CI] = 1.01 [0.83-1.23]

Net benefit $P_{int}=0.08$; Ischemic composite $P_{int}=0.054$; Major bleed $P_{int}=0.53$
Harmonizing Outcomes with Revascularization and Stents in AMI

3602 pts with STEMI with symptom onset ≤12 hours

Aspirin, thienopyridine

UFH + GP IIb/IIIa inhibitor (abciximab or eptifibatide)
Bivalirudin monotherapy (± provisional GP IIb/IIIa)

Emergent angiography, followed by triage to primary PCI, CABG or medical therapy

3006 pts eligible for stent randomization

R 1:1

R 1:3

Bare metal EXPRESS stent
Paclitaxel-eluting TAXUS stent

Clinical FU at 30 days, 6 months, 1 year, and then yearly through 5 years
Primary Outcome Measures (ITT)

- **Heparin + GPIIb/IIIa Inhibitor (N=1802)**
  - Diff = -2.9% [-4.9, -0.8]
  - RR = 0.76 [0.63, 0.92]
  - $P_{NI} \leq 0.0001$
  - $P_{sup} = 0.005$

- **Bivalirudin monotherapy (N=1800)**
  - Diff = -3.3% [-5.0, -1.6]
  - RR = 0.60 [0.46, 0.77]
  - $P_{NI} \leq 0.0001$
  - $P_{sup} \leq 0.0001$

**1° endpoint**
- Net adverse clinical events: 12.1 vs. 9.2
- Major bleeding*: 8.3 vs. 4.9
- MACE**: 5.5 vs. 5.4

*Not related to CABG
**MACE; Death, reMI, iTVR, or stroke

Stone GW et al. NEJM 2008;358:2218-30
**Thrombocytopenia**

- **Heparin + GPlIb/IIa Inhibitor (n=1802)**
  - Moderate: <100,000 cells/mm³
    - 3.9%
    - *P = 0.002*
  - Severe: <50,000 cells/mm³
    - 1.8%
    - *P = 0.04*
  - Profound: <20,000 cells/mm³
    - 0.5%
    - *P = 0.02*

- **Bivalirudin monotherapy (n=1800)**
  - Moderate: <100,000 cells/mm³
    - 0.5%
  - Severe: <50,000 cells/mm³
    - 0.5%
  - Profound: <20,000 cells/mm³
    - 0.1%

Stone GW et al. NEJM 2008;358:2218-30
1-Year All-Cause Mortality

- **Bivalirudin alone (n=1800)**
  - 0 months: 3.1%
  - 12 months: 4.8%
  - **P=0.049**

- **Heparin + GPIIb/IIIa (n=1802)**
  - 0 months: 2.1%
  - 12 months: 3.4%
  - **P=0.029**

**Number at risk**
- Bivalirudin alone: 1800, 1705, 1684, 1669, 1520
- Heparin + GPIIb/IIIa: 1802, 1678, 1663, 1646, 1486

**Mortality (%)**
- 0
- 1
- 2
- 3
- 4
- 5

**Time in Months**
- 0
- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- 10
- 11
- 12

**Diff [95%CI]**
- -1.5% [-2.8, -0.1]

**HR [95%CI]**
- 0.69 [0.50, 0.97]

**Mehran R. TCT 2008**
1-Year Mortality: Cardiac and Non Cardiac

Mortality (%)

Time in Months

Bivalirudin alone (n=1800) HR [95%CI] = 0.57 [0.38, 0.84] P=0.005
Heparin + GPIIb/IIIa (n=1802) 3.8% Δ = 1.7%

Cardiac

Mehran R. TCT 2008

Number at risk
Bivalirudin alone 1800 1705 1684 1669 1520
Heparin+GPIIb/IIIa 1802 1678 1663 1646 1486

Non Cardiac

2.9% 1.8%
Δ = 1.1% P=0.03

1.3% 1.1%
Core Pharmacotherapy to Support Primary PCI in STEMI

- Aspirin 324 mg chewed
- Clopidogrel* 600 mg load
- Bivalirudin 0.75 mg/kg IV or UFH 2500-5000 U IV

Immediate angiography followed by PCI if appropriate (~90%)

- Bivalirudin 0.75 mg/kg IV + 1.75 mg/kg/hr; d/c post PCI

*Consider prasugrel 60 mg in pts with low/mod bleeding risk
Core Pharmacotherapy in NSTEMI

Early angiography
(mod and high risk pts)

- Aspirin
- Clopidogrel*
(pre angio/PCI
(preferred)

- Bivalirudin alone
(provisional GPI)

- UFH + deferred
GPI for PCI

No or delayed
angio (low risk pts)

- Aspirin
- Clopidogrel
(provisional GPI)

- Bivalirudin alone
(provisional GPI)

If PCI

OR

± Fondaparinux

*Consider prasugrel 60 mg
in pts with low/mod bleeding risk