Antiplatelet agents in the full spectrum of coronary artery disease

JP Bassand
University Hospital
Besançon France
Atherothrombosis: A Generalized and Progressive Disease

Adapted from Libby P. Circulation 2001; 104: 365–372
Pathogenesis of ACS

Adapted from Davies MJ. Circulation. 1990; 82 (supl II): 30-46.
Therapeutic interventions against platelet activation and aggregation

- Epinephrine
- Collagen
- Thrombin
- ADP
- ticlopidine clopidogrel
- aspirin
- heparin, LMW heparins, lepirudin desirudin, bivalirudin
- GP IIb-IIIa inhibitors: abciximab eptifibatide tirofiban HCl

White HD. Am J Cardiol. 1997; 80(4A):2B-10B.
Chronic manifestations of atherothrombosis
## Major adverse cardiovascular event rates at one year (unadjusted)

<table>
<thead>
<tr>
<th>Event</th>
<th>Total (N=63,129)</th>
<th>Symptomatic (N=51,685)</th>
<th>Multiple RF only (N=11,444)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death</td>
<td>1.5</td>
<td>1.7</td>
<td>0.6</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>1.2</td>
<td>1.2</td>
<td>0.8</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>1.6</td>
<td>1.8</td>
<td>0.8</td>
</tr>
<tr>
<td>CV death/MI/ stroke</td>
<td>3.5</td>
<td>3.9</td>
<td>1.7</td>
</tr>
<tr>
<td>CV death/MI/ stroke/hospitalization for atherothrombotic events*</td>
<td>12.9</td>
<td>14.5</td>
<td>5.4</td>
</tr>
</tbody>
</table>

* TIA, unstable angina, other ischemic arterial event including worsening of peripheral arterial disease
RF=risk factor
MACE – Symptomatic population

Rates adjusted for age and risk factors
Single vs multiple and overlapping atherothrombotic locations: the example of CAD

Rates adjusted for age and risk factors
*TIA, unstable angina, other ischemic arterial event including worsening of peripheral arterial disease
# Efficacy of Antiplatelet Therapy: Antiplatelet Trialists’ Collaboration

**Category of trial** | **No. of trials with data** | **MI, stroke, or vascular death** | **Odds ratio and confidence interval (Antiplatelet: control)** | **% odds reduction (SD)**
--- | --- | --- | --- | ---
Prior MI | 11 | 1331/9677 1693/9914 | | 25% (4)
Acute MI | 9 | 992/9388 1348/9385 | | 29% (4)
Prior stroke/TIA | 18 | 1076/5837 1301/5870 | | 22% (4)
Unstable angina | 7 | 182/1991 285/2027 | | 

TIA, transient ischemic attack

### Indirect Comparisons of ASA Doses on Vascular Events in High-Risk Patients

<table>
<thead>
<tr>
<th>Aspirin Dose</th>
<th>No. of Trials</th>
<th>OR* (%)</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>500-1500 mg</td>
<td>34</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>160-325 mg</td>
<td>19</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>75-150 mg</td>
<td>12</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>&lt;75 mg</td>
<td>3</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Any aspirin</td>
<td>65</td>
<td>23</td>
<td></td>
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</tbody>
</table>

* Odds reduction. 
Treatment effect $P<.0001$. 
ASA, acetylsalicylic acid. 
*Adapted with permission from* BMJ Publishing Group. Antithrombotic Trialists’ Collaboration. 
*BMJ. 2002;324:71-86.*
CAPRIE: Superior Efficacy of Clopidogrel versus ASA

Patients with recent ischemic stroke, recent MI or symptomatic PAD

*MI, ischemic stroke or vascular death
†Intent-to-treat analysis (n=19,185)

Overall Population: Primary Efficacy Outcome (MI, Stroke, or CV Death)†

*All patients received ASA 75-162 mg/day

†First Occurrence of MI (fatal or non-fatal), stroke (fatal or non-fatal), or cardiovascular death

§The number of patients followed beyond 30 months decreases rapidly to zero and there are only 21 primary efficacy events that occurred beyond this time (13 clopidogrel and 8 placebo)

Primary Efficacy Results (MI/Stroke/CV Death) by Pre-Specified Entry Category

<table>
<thead>
<tr>
<th>Population</th>
<th>RR (95% CI)</th>
<th>p value</th>
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<tbody>
<tr>
<td>Qualifying CAD, CVD or PAD (n=12,153)</td>
<td>0.88 (0.77, 0.998)</td>
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<tr>
<td>Multiple Risk Factors (n=3,284)</td>
<td>1.20 (0.91, 1.59)</td>
<td>0.20</td>
</tr>
<tr>
<td>Overall Population* (n=15,603)</td>
<td>0.93 (0.83, 1.05)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

* A statistical test for interaction showed marginally significant heterogeneity (p=0.045) in treatment response for these pre-specified subgroups of patients

Optimal Acute Coronary Syndromes Management with Antiplatelet Agents

Jean-Pierre Bassand, MD, FESC, FACC
ESC Past-president
University Hospital
Besançon France
**ACS with persistent ST-segment elevation**

Adapted from Michael Davies

CK- MB or Troponin

**ACS without persistent ST-segment elevation**

Adapted from Michael Davies

Troponin elevated or not
Acute Coronary Syndromes

Generally caused by a partially occlusive, platelet-rich thrombus in a coronary artery.

Results from cross-linking of platelets by fibrinogen at platelet receptors GP IIb-IIIa at site of plaque rupture.
Therapeutic Options

• Anti-ischemic treatment
• Antiplatelet agents
• Antithrombin agents
• Revascularization/Reperfusion
• Long term treatment/secondary prevention
Therapeutic interventions against platelet activation and aggregation

Epinephrine
ADP
Collagen
Thrombin
heparin, LMW heparins, lepurdin, desirudin, bivalirudin
aspirin
GP IIb-IIIa inhibitors: abciximab, eptifibatide, tirofiban HCl
GP IIb-IIIa Expression

White HD. Am J Cardiol. 1997; 80(4A):2B-10B.
STEMI versus NSTEMI - Hospital / 1-Year-Mortality -

STEMI: 9.3% (p<0.01) vs. NSTEMI: 5.7% (p<0.01)

STEMI: 7.1% (p<0.01) vs. NSTEMI: 10.8%

ESC Quality Assurance Programme to Improve Cardiac Care in Europe
STEMI versus NSTEMI
- Mortality after Discharge -

Survival (MI Patients discharged alive)

STEMI

NSTEMI

Months after Discharge

0 1 2 3 4 5 6 7 8 9 10 11 12

0.9 0.92 0.94 0.96 0.98 1
STEMI versus NSTEMI - Cumulative 1-Year-Mortality -

Survival after STEMI versus NSTEMI

Months after Acute STEMI / NSTEMI

STEMI

NSTEMI

0,7
0,8
0,9
1

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

Euro Heart Survey Programme
ESC Quality Assurance Programme to Improve Cardiac Care in Europe
Patients with Chronic Manifestations of Atherothrombosis
# Efficacy of Antiplatelet Therapy: Antiplatelet Trialists’ Collaboration

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<tr>
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<td>Anti-platelet</td>
<td>Adjusted controls</td>
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</tr>
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TIA, transient ischemic attack

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CAPRIE: Superior Efficacy of Clopidogrel versus ASA

Patients with recent ischemic stroke, recent MI or symptomatic PAD

*MI, ischemic stroke or vascular death
†Intent-to-treat analysis (n=19,185)

CAPRIE: Clopidogrel Reduced the Rate of Rehospitalization

Patients with recent ischemic stroke, recent MI or symptomatic PAD

![Graph showing cumulative event rate over months of follow-up](image)

- **ASA**
- **Clopidogrel**

9.1%† RRR (p=0.018)

*Rehospitalization for ischemia (angina pectoris, TIA, limb ischemia) or bleeding (gastrointestinal, intracranial or other)

†On-treatment analysis (n=19,099)

CAPRIE patients with CABG

Outcome: vascular death, stroke, MI, rehospitalization for ischemia or bleeding

Cumulative event rate (%)

Aspirin (n=705)
Clopidogrel (n=775)

Risk reduction = 29%
p = 0.001

All diabetic patients

<table>
<thead>
<tr>
<th>Event Rate (%)</th>
<th>Clopidogrel</th>
<th>Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non diabetic</td>
<td>12.7%</td>
<td>11.8%</td>
</tr>
<tr>
<td>All diabetic</td>
<td>17.7%</td>
<td>15.6%</td>
</tr>
<tr>
<td>With insulin</td>
<td>21.5%</td>
<td>17.7%</td>
</tr>
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Overall benefit p=0.032; multivariate analysis

Bhatt DL et al., AJC 2002;90:625-628.

IS, MI, VD, hospitalization for ischemic events / bleeding

Events prevented / 1000 patients over aspirin
Overall Population: Primary Efficacy Outcome (MI, Stroke, or CV Death)†

<table>
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<th>Drug</th>
<th>Cumulative Event Rate (%)</th>
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<td>Placebo + ASA*</td>
<td>7.3%</td>
</tr>
<tr>
<td>Clopidogrel + ASA*</td>
<td>6.8%</td>
</tr>
</tbody>
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RRR: 7.1% [95% CI: -4.5%, 17.5%]  
P=0.22

† First Occurrence of MI (fatal or non-fatal), stroke (fatal or non-fatal), or cardiovascular death
* All patients received ASA 75-162 mg/day
§ The number of patients followed beyond 30 months decreases rapidly to zero and there are only 21 primary efficacy events that occurred beyond this time (13 clopidogrel and 8 placebo)

Overall Population: Principal Secondary Efficacy Outcome (MI/Stroke/CV Death/Hospitalization)†

*All patients received ASA 75-162mg/day
†First Occurrence of MI, Stroke, CV Death, or Hospitalization for UA, TIA, or Revascularization
§The number of patients followed beyond 30 months decreases rapidly to zero and there are only 38 primary efficacy events that occurred beyond this time (23 clopidogrel and 15 placebo)

Primary Efficacy Results (MI/Stroke/CV Death) by Pre-Specified Entry Category

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## Primary Efficacy Results (MI/Stroke/CV Death)* by Category of Inclusion Criteria

<table>
<thead>
<tr>
<th>Population</th>
<th>N</th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qualifying CV Disease</td>
<td>12,153</td>
<td>0.88 (0.77, 0.998)</td>
<td>0.046</td>
</tr>
<tr>
<td>Coronary</td>
<td>5,835</td>
<td>0.86 (0.71, 1.05)</td>
<td>0.13</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>4,320</td>
<td>0.84 (0.69, 1.03)</td>
<td>0.09</td>
</tr>
<tr>
<td>PAD</td>
<td>2,838</td>
<td>0.87 (0.67, 1.13)</td>
<td>0.29</td>
</tr>
<tr>
<td>Multiple Risk Factors</td>
<td>3,284</td>
<td>1.20 (0.91, 1.59)</td>
<td>0.20</td>
</tr>
<tr>
<td><strong>Overall Population</strong></td>
<td>15,603</td>
<td>0.93 (0.83, 1.05)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

*First Occurrence of MI (fatal or not), Stroke (fatal or not), or CV Death

Bhatt DL. Presented at ACC 2006.
## Overall Population: Safety Results

<table>
<thead>
<tr>
<th>Safety Outcome* - N (%)</th>
<th>Clopidogrel + ASA (n=7802)</th>
<th>Placebo + ASA (n=7801)</th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GUSTO Severe Bleeding</td>
<td>130 (1.7)</td>
<td>104 (1.3)</td>
<td>1.25 (0.97, 1.61)</td>
<td>0.09</td>
</tr>
<tr>
<td>Fatal Bleeding</td>
<td>26 (0.3)</td>
<td>17 (0.2)</td>
<td>1.53 (0.83, 2.82)</td>
<td>0.17</td>
</tr>
<tr>
<td>Primary ICH</td>
<td>26 (0.3)</td>
<td>27 (0.3)</td>
<td>0.96 (0.56, 1.65)</td>
<td>0.89</td>
</tr>
<tr>
<td>GUSTO Moderate Bleeding</td>
<td>164 (2.1)</td>
<td>101 (1.3)</td>
<td>1.62 (1.27, 2.10)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Adjudicated outcomes by intention to treat analysis
ICH= Intracranial Hemorrhage

Acute coronary syndromes
ST Elevation Acute Myocardial Infarction
Current Recommended Therapeutic Options

- Aspirin I-A
- Anticoagulants I-B
- Reperfusion I-A
  - PCI I-A
  - Thrombolysis I-A
- Secondary prevention I-A
Long Term Outcomes in Individuals Treated with Primary PTCA or Thrombolytic Therapy

- **Death:** p=0.0019
- **Death, excl. SHOCK data:** p=0.0053
- **Non-fatal MI:** p<0.0001
- **Recurrent ischaemia:** p<0.0001
- **Death, non-fatal re-MI, or stroke:** p<0.0001

Keeley Lancet 2003;361:13
Time dependent effects of pharmacological reperfusion

EHS – ACS II

Primary Reperfusion Therapy

- **EHS - ACS I**
  - PPCI: 37%
  - TLx: 63%
  - Total: 61%

- **ESH - ACS II**
  - PPCI: 59%
  - TLx: 41%
  - Total: 61%

Implementation of Reperfusion in STEMI
Reperfusion Therapy: STEMI

- Either
  - IV Lytic: 58, 40, 32
  - PPCI: 7.3, 32

NRMI 2: 65
NRMI 3: 58
NRMI 4: 40, 72

Percent of Patients
**ISIS-2: Effects of aspirin & SK in 17,000 acute MI**

- Neither: 13%
- ASA: 10%
- SK: 10%
- SK+ ASA: 8%

*Lancet 1988;2(8607):349-60*
Double-blind, randomized, placebo-controlled trial in 3491 patients, age 18-75 yrs with STEMI < 12 hours

Fibrinolytic, ASA, Heparin

Randomize

Clopidogrel 300 mg + 75 mg qd

Placebo

Coronary Angiogram (2-8 days)

30-day clinical follow-up

Primary endpoint: Occluded artery (TIMI Flow Grade 0/1) or D/MI by time of angio
Primary Endpoint: Occluded Artery (or D/MI thru Angio/HD)

Odds Ratio 0.64
(95% CI 0.53-0.76)

P = 0.000000036

36% Odds Reduction

Occluded Artery or Death/MI (%)

Clopidogrel Placebo

n = 1752 n = 1739

Sabatine et al. NEJM 2005; 352: 1179
Subgroups – Primary Endpoint

Characteristics: OVERALL, Age (<65 yr, ≥65 yr), Gender (Male, Female), Infarct location (Anterior, Non-anterior), Fibrinolytic (Fibrin-specific, Non-fibrin specific), Predominant heparin (Low-molecular-weight, Unfractionated, None).

Event Rates (%): Clopidogrel, Placebo.

Odds Ratio (95% CI) and Odds Reduction:
- Overall: Clopidogrel better, Placebo better.
- Age: <65 yr (OR 0.4, 95% CI: 0.2-0.9, Odds Reduction: 13.2%), ≥65 yr (OR 0.7, 95% CI: 0.3-1.5, Odds Reduction: 19.0%)
- Gender: Male (OR 0.9, 95% CI: 0.6-1.5, Odds Reduction: 20.8%), Female (OR 0.8, 95% CI: 0.5-1.4, Odds Reduction: 22.2%)
- Infarct location: Anterior (OR 1.0, 95% CI: 0.5-2.2, Odds Reduction: 20.7%), Non-anterior (OR 0.9, 95% CI: 0.6-1.4, Odds Reduction: 22.2%)
- Fibrinolytic: Fibrin-specific (OR 0.8, 95% CI: 0.5-1.3, Odds Reduction: 20.1%), Non-fibrin specific (OR 1.0, 95% CI: 0.7-1.5, Odds Reduction: 24.9%)
- Predominant heparin: Low-molecular-weight (OR 0.7, 95% CI: 0.4-1.1, Odds Reduction: 15.7%), Unfractionated (OR 1.0, 95% CI: 0.7-1.4, Odds Reduction: 27.1%), None (OR 0.8, 95% CI: 0.5-1.3, Odds Reduction: 21.9%)

All interactions non-significant. 

NEJM 2005; 352: 1179
Need for Urgent or Additional Treatment

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Clotidogrel</th>
<th>Placebo</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Angio (w/in 48 hrs)</td>
<td>15.4%</td>
<td>18.6%</td>
<td>0.01</td>
</tr>
<tr>
<td>Urgent Revasc (index hosp)</td>
<td>19.5%</td>
<td>23.3%</td>
<td>0.005</td>
</tr>
<tr>
<td>GP IIb/IIIa if PCI</td>
<td>29.3%</td>
<td>33.0%</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Sabatine et al.  
*NEJM* 2005; 352: 1179
CV Death, MI, RI → Urg Revasc

Percentage with endpoint (%)

Placebo

Clopidogrel

Odds Ratio 0.80
(95% CI 0.65-0.97)
P=0.026

Sabatine et al. *NEJM* 2005; 352: 1179
Effect of Clopidogrel on ST segment resolution

Scirica et al. *Circulation* 2005;112(Suppl):II-568
Effect of Clopidogrel on 1° EP Stratified by STRes

Scirica et al. Circulation 2005;112(Suppl):II-568
Effect of Clopidogrel on Death Stratified by STRes

- Adj OR 0.97 (95% CI 0.55-1.72)
- Adj OR 0.89 (95% CI 0.44-1.79)
- Adj OR 0.28 (95% CI 0.08-1.05)

Interaction P=0.13

Scirica et al. *Circulation* 2005;112(Suppl):II-568
## Bleeding

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<th>Outcome</th>
<th>Clopidogrel (%)</th>
<th>Placebo (%)</th>
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<tr>
<td>Through angiography</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>TIMI major (Hgb ↓ &gt;5 g/dL or ICH)</td>
<td>1.3</td>
<td>1.1</td>
<td>NS</td>
</tr>
<tr>
<td>TIMI minor (Hgb ↓ 3-5 g/dL)</td>
<td>1.0</td>
<td>0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>0.5</td>
<td>0.7</td>
<td>NS</td>
</tr>
<tr>
<td>Through 30 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI major</td>
<td>1.9</td>
<td>1.7</td>
<td>NS</td>
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<tr>
<td>In those undergoing CABG</td>
<td>7.5</td>
<td>7.2</td>
<td>NS</td>
</tr>
<tr>
<td>CABG w/in 5 d of study med</td>
<td>9.1</td>
<td>7.9</td>
<td>NS</td>
</tr>
<tr>
<td>TIMI minor</td>
<td>1.6</td>
<td>0.9</td>
<td>NS</td>
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Sabatine et al. *NEJM* 2005; 352: 1179
## PCI-CLARITY: PCI Characteristics

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<th>Pretreatment</th>
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<tr>
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<td>Clopidogrel (n=933)</td>
</tr>
<tr>
<td>Time from randomization to PCI,</td>
<td></td>
</tr>
<tr>
<td>median days (inter-quartile range)</td>
<td>3.2 (1.7 – 5.5)*</td>
</tr>
<tr>
<td>GP IIb/IIIa use (%)</td>
<td>31.1</td>
</tr>
<tr>
<td>Coronary artery stenting (%)</td>
<td>95.2</td>
</tr>
<tr>
<td>Loading dose of open-label</td>
<td></td>
</tr>
<tr>
<td>thienopyridine given at time of PCI (%)</td>
<td>77.6</td>
</tr>
<tr>
<td>Maintenance dose of open-label</td>
<td></td>
</tr>
<tr>
<td>thienopyridine given after PCI (%)</td>
<td>89.3</td>
</tr>
</tbody>
</table>

*p=0.003

## PCI-CLARITY: Primary Results

<table>
<thead>
<tr>
<th>Outcomes from PCI to Day 30</th>
<th>Pretreatment, N (%)</th>
<th>Adjusted* OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clopidogrel (n=933)</td>
<td>Placebo (n=930)</td>
<td></td>
</tr>
<tr>
<td>CV Death, MI or Stroke</td>
<td>34 (3.6)</td>
<td>58 (6.2)</td>
<td>0.54 (0.35-0.85) 0.008</td>
</tr>
<tr>
<td>-CV Death or MI</td>
<td>31 (3.3)</td>
<td>50 (5.4)</td>
<td>0.58 (0.36-0.94) 0.03</td>
</tr>
<tr>
<td>-CV Death</td>
<td>13 (1.4)</td>
<td>24 (2.6)</td>
<td>0.49 (0.24-1.03)</td>
</tr>
<tr>
<td>-MI</td>
<td>18 (1.9)</td>
<td>29 (3.1)</td>
<td>0.60 (0.33-1.11)</td>
</tr>
<tr>
<td>-Stroke</td>
<td>4 (0.4)</td>
<td>11 (1.2)</td>
<td>0.35 (0.11-1.11)</td>
</tr>
</tbody>
</table>

*Odds ratios adjusted for propensity score for likelihood of PCI, type of lytic, initial type of heparin, and infarct location.

*Reduction in the odds of a recurrent MI or stroke prior to PCI.* Odds ratios adjusted for propensity score for likelihood of PCI, type of lytic, initial type of heparin, and infarct location.

PCI-CLARITY: Reduction in CV Events from PCI to 30 Days

*Reduction in the odds of CV death, MI or stroke after PCI through 30 days. Odds ratios adjusted for propensity score for likelihood of PCI, type of lytic, initial type of heparin, and infarct location.

PCI-CLARITY: Overall Results

**MI, Stroke, or CV Death**

Overall events includes events from randomization through 30 days. Percent reduction based on odds ratio for event rates. Odds ratios adjusted for propensity score for likelihood of PCI, type of lytic, initial type of heparin, and infarct location.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Clopidogrel OR (95% CI)</th>
<th>Placebo OR (95% CI)</th>
<th>Number of patients</th>
<th>Patients with event (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVERALL</td>
<td></td>
<td></td>
<td>1863</td>
<td>3.6 6.2</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>0.59 (0.33-1.07)</td>
<td>0.43 (0.21-0.87)</td>
<td>1337</td>
<td>3.2 4.7</td>
</tr>
<tr>
<td>≥65 years</td>
<td>0.43 (0.21-0.87)</td>
<td>0.43 (0.21-0.87)</td>
<td>526</td>
<td>4.7 10.4</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.59 (0.35-0.99)</td>
<td>0.59 (0.35-0.99)</td>
<td>1522</td>
<td>3.6 5.4</td>
</tr>
<tr>
<td>Female</td>
<td>0.41 (0.16-1.04)</td>
<td>0.41 (0.16-1.04)</td>
<td>341</td>
<td>4.0 10.3</td>
</tr>
<tr>
<td>Type of Fibrinolytic Agent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrin Specific</td>
<td>0.54 (0.33-0.89)</td>
<td>0.54 (0.19-1.53)</td>
<td>1470</td>
<td>3.5 6.4</td>
</tr>
<tr>
<td>Non-fibrin-specific</td>
<td>0.54 (0.19-1.53)</td>
<td>0.54 (0.19-1.53)</td>
<td>393</td>
<td>4.1 5.6</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.61 (0.24-1.53)</td>
<td>0.61 (0.24-1.53)</td>
<td>282</td>
<td>6.0 10.1</td>
</tr>
<tr>
<td>No</td>
<td>0.51 (0.30-0.87)</td>
<td>0.51 (0.30-0.87)</td>
<td>1555</td>
<td>2.9 5.3</td>
</tr>
<tr>
<td>Predominant heparin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UFH</td>
<td>0.72 (0.40-1.32)</td>
<td>0.72 (0.40-1.32)</td>
<td>888</td>
<td>5.0 6.5</td>
</tr>
<tr>
<td>LMWH</td>
<td>0.47 (0.22-1.02)</td>
<td>0.47 (0.22-1.02)</td>
<td>789</td>
<td>2.5 5.4</td>
</tr>
<tr>
<td>None</td>
<td>0.12 (0.01-1.03)</td>
<td>0.12 (0.01-1.03)</td>
<td>186</td>
<td>2.2 8.3</td>
</tr>
<tr>
<td>PCI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urgent</td>
<td>0.60 (0.33-1.08)</td>
<td>0.60 (0.33-1.08)</td>
<td>675</td>
<td>6.7 9.6</td>
</tr>
<tr>
<td>Elective</td>
<td>0.54 (0.27-1.09)</td>
<td>0.54 (0.27-1.09)</td>
<td>1186</td>
<td>2.1 4.1</td>
</tr>
<tr>
<td>Time from randomization to PCI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6 hours</td>
<td>0.45 (0.20-1.04)</td>
<td>0.45 (0.20-1.04)</td>
<td>352</td>
<td>5.3 12.8</td>
</tr>
<tr>
<td>6-48 hours</td>
<td>0.51 (0.16-1.65)</td>
<td>0.51 (0.16-1.65)</td>
<td>167</td>
<td>6.5 11.1</td>
</tr>
<tr>
<td>48-96 hours</td>
<td>0.61 (0.24-1.53)</td>
<td>0.61 (0.24-1.53)</td>
<td>573</td>
<td>3.0 4.5</td>
</tr>
<tr>
<td>&gt;96 hours</td>
<td>0.70 (0.28-1.78)</td>
<td>0.70 (0.28-1.78)</td>
<td>633</td>
<td>2.8 3.9</td>
</tr>
<tr>
<td>Gp IIb/IIIa inhibitor at time of PCI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.42 (0.21-0.88)</td>
<td>0.42 (0.21-0.88)</td>
<td>598</td>
<td>4.2 9.0</td>
</tr>
<tr>
<td>No</td>
<td>0.65 (0.36-1.17)</td>
<td>0.65 (0.36-1.17)</td>
<td>1254</td>
<td>3.4 4.9</td>
</tr>
<tr>
<td>Open-label loading dose at time of PCI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.50 (0.28-0.90)</td>
<td>0.50 (0.28-0.90)</td>
<td>1436</td>
<td>2.9 5.2</td>
</tr>
<tr>
<td>No</td>
<td>0.62 (0.30-1.29)</td>
<td>0.62 (0.30-1.29)</td>
<td>404</td>
<td>6.3 10.1</td>
</tr>
</tbody>
</table>

### PCI-CLARITY: Safety Outcomes

<table>
<thead>
<tr>
<th>Safety Outcomes</th>
<th>Pretreatment, N (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clopidogrel (n=923)</td>
<td>Placebo (n=918)</td>
</tr>
<tr>
<td>TIMI major or minor bleeding</td>
<td>18 (2.0)</td>
<td>17 (1.9)</td>
</tr>
<tr>
<td>-TIMI major bleeding</td>
<td>5 (0.5)</td>
<td>10 (1.1)</td>
</tr>
<tr>
<td>-TIMI minor bleeding</td>
<td>13 (1.4)</td>
<td>7 (0.8)</td>
</tr>
</tbody>
</table>

NS = not statistically significant

### PCI-CLARITY: Meta-Analysis of Clopidogrel Pretreatment in PCI

<table>
<thead>
<tr>
<th>Trial</th>
<th>Events, No./Total (%)</th>
<th>OR (95% CI)</th>
<th>Favors Pretreatment</th>
<th>Favors No Pretreatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clopidogrel</td>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial Infarction Before PCI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI-CURE</td>
<td>47/1313 (3.6%)</td>
<td>68/1345 (5.1%)</td>
<td>0.70 (0.48-1.02)</td>
<td></td>
</tr>
<tr>
<td>CREDO</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI-CLARITY</td>
<td>37/933 (4.0%)</td>
<td>57/930 (6.1%)</td>
<td>0.63 (0.41-0.97)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>84/2246 (3.7%)</td>
<td>125/2275 (5.5%)</td>
<td>0.67 (0.50-0.89)</td>
<td></td>
</tr>
<tr>
<td>CV Death or MI After PCI to 30 Days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI-CURE</td>
<td>38/1313 (2.9%)</td>
<td>59/1345 (4.4%)</td>
<td>0.65 (0.43-0.98)</td>
<td></td>
</tr>
<tr>
<td>CREDO</td>
<td>54/900 (6.0%)</td>
<td>65/915 (7.1%)</td>
<td>0.83 (0.57-1.21)</td>
<td></td>
</tr>
<tr>
<td>PCI-CLARITY</td>
<td>31/933 (3.3%)</td>
<td>50/930 (5.4%)</td>
<td>0.60 (0.38-0.96)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>123/3146 (3.9%)</td>
<td>174/3190 (5.5%)</td>
<td>0.71 (0.56-0.89)</td>
<td></td>
</tr>
</tbody>
</table>

*P* = 0.005

PCI-CLARITY: Conclusions

Clopidogrel pretreatment significantly reduced the incidence of CV death or ischemic complications both before and after PCI

- 46% reduction in the odds of CV death, MI, or stroke after PCI through 30 days (p=0.008)
- 41% reduction in the odds of CV death, MI, or stroke from randomization through 30 days (p=0.001)

No significant difference in TIMI major or minor bleeding

These data add further support for the early use of clopidogrel in STEMI and the strategy of clopidogrel pretreatment in patients with ACS undergoing PCI

Summary

In patients with STEMI ≤ 75 yrs, receiving a standard fibrinolytic regimen, a loading dose of 300 mg of clopidogrel followed by 75 mg daily resulted in:

• 36% reduction in the odds of an occluded infarct-related artery, or death/MI by angio (NNT = 16)

• Highly consistent benefit across all major subgroups

• 20% reduction in CV death, MI, or recurrent ischemia leading to urgent revasc through 30 days (NNT = 36)

• No excess in TIMI major or minor bleeding (including in those undergoing CABG) or in ICH
Clopidogrel in STEMI

- Improves infarct-related artery patency
- Reduces mortality and ischemic complications
- Should be started as soon as possible
- Does not increase risk of major bleeding or ICH
- Additive effect with enoxaparin
- Makes pharmacologic Rx a more attractive option when 1° PCI by experienced team not readily available
Patients with acute STEMI \( \leq 24 \) hours

\( n \approx 46,000 \)

\( n \approx 23,000 \)

Double-blind treatment until hospital discharge or for a maximum of 4 weeks

\( (n=\approx23,000) \)

Placebo*

**Study Design**

*All patients received a background of ASA 162 mg/day during the study

**COMMIT: Study design**

**TREATMENT:** Clopidogrel 75 mg daily vs placebo (aspirin 162mg daily in both groups)

**INCLUSION:** Suspected acute MI (ST change or LBBB) within 24 h of symptom onset

**EXCLUSION:** Primary PCI or high-risk of bleeding

**1° OUTCOMES:** Death & death, re-MI or stroke up to 4 weeks in hospital (or prior discharge)

*Mean treatment and follow-up: 16 days*
Commit: 45,852 patients from 1250 centres in China
**COMMIT: Baseline characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Clopidogrel (n=22,960)</th>
<th>Placebo (n=22,891)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 70+ years</td>
<td>26.0%</td>
<td>26.0%</td>
</tr>
<tr>
<td>Female</td>
<td>27.7%</td>
<td>27.9%</td>
</tr>
<tr>
<td>Time delay &lt;6 h</td>
<td>33.8%</td>
<td>33.7%</td>
</tr>
<tr>
<td>STEMI/LBBB</td>
<td>93.1%</td>
<td>93.1%</td>
</tr>
<tr>
<td>Killip class II/III</td>
<td>24.1%</td>
<td>24.0%</td>
</tr>
<tr>
<td>Fibrinolytic:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>49.7%</td>
<td>49.8%</td>
</tr>
<tr>
<td>STEMI &lt;12h</td>
<td>67.8%</td>
<td>67.7%</td>
</tr>
</tbody>
</table>

COMMIT: Primary Results - Death

Placebo (8.1%)

Clopidogrel (7.5%)

RRR=7%
p=0.03

COMMIT: Primary Results - Composite of Death, MI or Stroke

RRR = relative risk reduction

**COMMIT: Effects of CLOPIDOGREL on Death, Re-MI or Stroke by delay & fibrinolytic**

<table>
<thead>
<tr>
<th>Baseline features</th>
<th>Clopidogrel (22,958)</th>
<th>Placebo (22,891)</th>
<th>Odds ratio &amp; 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hour to entry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-6</td>
<td>776 (9.3%)</td>
<td>904 (10.9%)</td>
<td>Clopid. better</td>
</tr>
<tr>
<td>7-12</td>
<td>672 (9.7%)</td>
<td>735 (10.7%)</td>
<td>Placebo better</td>
</tr>
<tr>
<td>13-24</td>
<td>666 (8.8%)</td>
<td>666 (8.7%)</td>
<td></td>
</tr>
<tr>
<td>Lytic given</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1005 (8.8%)</td>
<td>1123 (9.9%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1120 (9.7%)</td>
<td>1188 (10.3%)</td>
<td></td>
</tr>
<tr>
<td>ALL</td>
<td>2125 (9.3%)</td>
<td>2311 (10.1%)</td>
<td></td>
</tr>
</tbody>
</table>

9% SE 3 (2P = 0.002)
## COMMIT: Fatal and Non-Fatal Major Bleeds

<table>
<thead>
<tr>
<th>Type</th>
<th>Clopidogrel (n=22,958)</th>
<th>Placebo (n=22,891)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cerebral</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal</td>
<td>39</td>
<td>40</td>
</tr>
<tr>
<td>Non-fatal</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td><strong>Non-cerebral</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal</td>
<td>36</td>
<td>37</td>
</tr>
<tr>
<td>Non-fatal</td>
<td>46</td>
<td>36</td>
</tr>
<tr>
<td><strong>Any major bleed</strong></td>
<td>134 (0.58%)</td>
<td>124 (0.54%)</td>
</tr>
</tbody>
</table>

**COMMIT: Effects of CLOPIDOGREL on any Stroke**

<table>
<thead>
<tr>
<th>Types</th>
<th>Clopidogrel (22,958)</th>
<th>Placebo (22,891)</th>
<th>Odds ratio &amp; 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic</td>
<td>162 (0.7%)</td>
<td>192 (0.8%)</td>
<td>Clopid. better</td>
</tr>
<tr>
<td>Haemorrhagic</td>
<td>55 (0.2%)</td>
<td>55 (0.2%)</td>
<td>Placebo better</td>
</tr>
<tr>
<td>ALL COMBINED</td>
<td>216 (0.9%)</td>
<td>249 (1.1%)</td>
<td>14% SE 9 (2P &gt; 0.1; NS)</td>
</tr>
</tbody>
</table>
COMMIT: Effects of CLOPIDOGREL on Death, Re-MI or Stroke by lytic & CLARITY criteria

<table>
<thead>
<tr>
<th>Baseline features</th>
<th>Clopidogrel (22,958)</th>
<th>Placebo (22,891)</th>
<th>Odds ratio &amp; 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lytic given</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1005 (8.8%)</td>
<td>1123 (9.9%)</td>
<td>Clopid. better</td>
</tr>
<tr>
<td>No</td>
<td>1120 (9.7%)</td>
<td>1188 (10.3%)</td>
<td>Placebo better</td>
</tr>
<tr>
<td>CLARITY criteria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>673 (8.4%)</td>
<td>785 (9.6%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1452 (9.7%)</td>
<td>1526 (10.4%)</td>
<td></td>
</tr>
<tr>
<td>ALL</td>
<td>2125 (9.3%)</td>
<td>2311 (10.1%)</td>
<td></td>
</tr>
</tbody>
</table>

9% SE 3 (2P = 0.002)
Occluded Artery or D/MI before angio

Adj Odds Ratio 0.76
(95% CI 0.60-0.97)

P=0.027

Adjusted for type of lytic, infarct location, h/o HTN, cardiac medications, time to angiography, and propensity score for LMWH use.

Sabatine et al. Circulation 2005;112:3846-54
Optimal Pharmacologic Reperfusion?

Fibrinolytic + Aspirin + Clopidogrel + LMWH

Sabatine et al. Circulation 2005;112:3846-54
Clopidogrel in STEMI

- Evidence from 2 large trials in ~ 50,000 patients
- Benefit in opening infarct-related artery, and in reducing mortality and morbidity
- No excess in major bleeding
- Low cost

A new addition to treatment of STEMI
Effect of clopidogrel on 1-year mortality in hospital survivors of acute STEMI – ACOS Registry

Zeymer Eur Heart J 2006; 27: 2661-2666
Effect of clopidogrel on 1-year mortality in hospital survivors of acute STEMI – ACOS Registry

MACEs @ 1 year FU

- Total group: 15.4% (Aspirin) vs 7.1% (Aspirin + clopidogrel)
- No reperfusion: 20.7% (Aspirin) vs 13.1% (Aspirin + clopidogrel)
- Fibrinolysis: 10.4% (Aspirin) vs 6.1% (Aspirin + clopidogrel)
- Primary PCI: 10.9% (Aspirin) vs 6.4% (Aspirin + clopidogrel)

Zeymer Eur Heart J 2006; 27: 2661-2666
Non ST Elevation Acute Coronary Syndromes
Current recommended treatments

- Anti-ischemic treatment  I-A
- Antiplatelet treatment  I-A
  - aspirin  I-A
  - Clopidogrel  I-B
  - IIbIIIa inhibitors  I-A
- Anticoagulants  I-A
- Revascularisation  I-A
- Long term prevention  I-A
Antithrombotic Agents
Randomized trials comparing LMWH vs. UFH

Death and non-fatal MI

<table>
<thead>
<tr>
<th>Trial</th>
<th>LMWH</th>
<th>Time of EP</th>
<th>LMWH</th>
<th>UFH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-term</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FRIC</td>
<td>Dalteparin</td>
<td>0-6d</td>
<td>3.9%</td>
<td>3.6%</td>
</tr>
<tr>
<td>ESSENCE</td>
<td>Enoxaparin</td>
<td>14d</td>
<td>5.2%</td>
<td>6.5%</td>
</tr>
<tr>
<td>TIMI-11B</td>
<td>Enoxaparin</td>
<td>14d</td>
<td>4.9%</td>
<td>4.5%</td>
</tr>
<tr>
<td>FRAXIS</td>
<td>Nadroparin</td>
<td>14d</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Long-term</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FRIC</td>
<td>Dalteparin</td>
<td>6-45d</td>
<td>4.3%</td>
<td>4.7%</td>
</tr>
<tr>
<td>ESSENCE</td>
<td>Enoxaparin</td>
<td>43d</td>
<td>7.1%</td>
<td>8.6%</td>
</tr>
<tr>
<td>TIMI-11B</td>
<td>Enoxaparin</td>
<td>43d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FRAXIS</td>
<td>Nadroparin</td>
<td>90d</td>
<td>8.9%</td>
<td>7.9%</td>
</tr>
</tbody>
</table>

**NSTEMI**

Total

- LMWH better: 0.86
- UFH better: 0.89

According to the trial data, LMWH was found to be better than UFH in terms of reducing the risk of death and non-fatal MI.
Efficacy and Bleeding Complications Among Patients Randomized to Enox or UFH in Non ST segment ACS

Death or MI at 30 Days

<table>
<thead>
<tr>
<th>Trial</th>
<th>Events, No./Total (%)</th>
<th>OR (95% CI)</th>
<th>Favors Enoxaparin</th>
<th>Favors UFH</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESSENCE</td>
<td>94/1607 (5.8)</td>
<td>0.76 (0.58-1.01)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>TIMI 11B</td>
<td>145/1953 (7.4)</td>
<td>0.88 (0.70-1.11)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ACUTE II</td>
<td>25/315 (7.9)</td>
<td>0.97 (0.51-1.83)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>INTERACT</td>
<td>19/380 (5.0)</td>
<td>0.54 (0.30-0.96)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>A to Z</td>
<td>137/1852 (7.4)</td>
<td>0.94 (0.73-1.20)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SYNERGY</td>
<td>696/4992 (14.0)</td>
<td>0.96 (0.86-1.07)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>OVERALL</td>
<td>1116/11099 (10.1)</td>
<td>0.91 (0.83-0.99)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Petersen. JAMA 2004;292:89–96
Safety Analysis, Overall Population
Major Bleeding up to 7 Days after Randomisation

<table>
<thead>
<tr>
<th>Trial</th>
<th>Events, No./Total (%)</th>
<th>OR (95% CI)</th>
<th>Favors</th>
<th>Favors</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESSENCE</td>
<td>Enoxaparin 64/1578 (4.1) UFH 69/1529 (4.5)</td>
<td>0.90 (0.63-1.27)</td>
<td>Enoxaparin</td>
<td>UFH</td>
</tr>
<tr>
<td>TIMI 11B</td>
<td>Enoxaparin 29/1938 (1.5) UFH 19/1936 (1.0)</td>
<td>1.52 (0.85-2.70)</td>
<td>Enoxaparin</td>
<td>UFH</td>
</tr>
<tr>
<td>INTERACT</td>
<td>Enoxaparin 12/380 (3.2) UFH 24/366 (6.6)</td>
<td>0.47 (0.24-0.95)</td>
<td>Enoxaparin</td>
<td>UFH</td>
</tr>
<tr>
<td>SYNERGY</td>
<td>Enoxaparin 276/4148 (6.7) UFH 274/4775 (5.7)</td>
<td>1.17 (0.99-1.39)</td>
<td>Enoxaparin</td>
<td>UFH</td>
</tr>
<tr>
<td>OVERALL</td>
<td>Enoxaparin 381/8044 (4.7) UFH 386/8606 (4.5)</td>
<td>1.04 (0.89-1.30)</td>
<td>Enoxaparin</td>
<td>UFH</td>
</tr>
</tbody>
</table>

Petersen. JAMA 2004;292:89–96
Anti-platelet Agents
<table>
<thead>
<tr>
<th>Category of trial</th>
<th>No. of trials with data</th>
<th>MI, stroke, or vascular death</th>
<th>Odds ratio and confidence interval (Antiplatelet: control)</th>
<th>% odds reduction (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Anti-platelet</td>
<td>Adjusted controls</td>
<td></td>
</tr>
<tr>
<td>Prior MI</td>
<td>11</td>
<td>1331/9677</td>
<td>1693/9914</td>
<td></td>
</tr>
<tr>
<td>Acute MI</td>
<td>9</td>
<td>992/9388</td>
<td>1348/9385</td>
<td></td>
</tr>
<tr>
<td>Prior stroke/ TIA</td>
<td>18</td>
<td>1076/5837</td>
<td>1301/5870</td>
<td></td>
</tr>
<tr>
<td>Unstable angina</td>
<td>7</td>
<td>182/1991</td>
<td>285/2027</td>
<td></td>
</tr>
</tbody>
</table>

TIA, transient ischemic attack

Indirect Comparisons of ASA Doses on Vascular Events in High-Risk Patients

<table>
<thead>
<tr>
<th>Aspirin Dose</th>
<th>No. of Trials</th>
<th>OR* (%)</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>500-1500 mg</td>
<td>34</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>160-325 mg</td>
<td>19</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>75-150 mg</td>
<td>12</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>&lt;75 mg</td>
<td>3</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Any aspirin</td>
<td>65</td>
<td>23</td>
<td></td>
</tr>
</tbody>
</table>

* Odds reduction.  
Treatment effect $P<.0001$.  
ASA, acetylsalicylic acid.  
Adapted with permission from BMJ Publishing Group. Antithrombotic Trialists’ Collaboration.  
*BMJ.* 2002;324:71-86.
Clopidogrel in NSTE ACS: CURE

12,563 Pts, GP IIb/IIIa & early invasive approach discouraged

RR 0.8, p<0.001

Placebo
(11.4%)

Clopidogrel
(9.3%)

Death, MI, Stroke

Months of follow-up

CURE. NEJM 2001; 345: 494
Efficacy of Clopidogrel across Risk Spectrum in NSTE ACS

Clopidogrel vs Placebo

<table>
<thead>
<tr>
<th>TIMI Risk Score Category</th>
<th>RR (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>28%</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td>Intermed</td>
<td>14%</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>High</td>
<td>23%</td>
<td>&lt;0.004</td>
</tr>
</tbody>
</table>

Rates of Primary Outcome in the Placebo and Clopidogrel groups Stratified by TIMI Risk Score for CV Death, MI and Stroke

Budaj A Circulation 2002;106:1622
CURE: Efficacy of Very Early Clopidogrel in NSTE ACS

CV Death, MI, Stroke, Severe Ischemia Within First 24 Hours

Cumulative Hazard Rate

Placebo + Aspirin (n=6303)

Clopidogrel + Aspirin (n=6259)

34% Relative Risk Reduction

P=.003

Relative Risk Reduction

With First 24 Hours

Hours After Randomization

CURE- Bleedings

Major Threatening life Other Maj Bl. Transfusion (2 + units) Minor Fatal bleeding ICH

Percentage

Placebo Clopidogrel

P=0.001 NS P=0.002 P=0.02 p<0.001

1822 patients (14.5%) underwent CABG

ASA + Clopid. ASA
Discontinuation for > 5d before CABG: 4.4% 5.3%
Discontinuation for < 5days before CABG: 9.6% 6.3%
Aspirin Dose and Incidence of Major Bleeding in the CURE Trial

- Aspirin
- Aspirin plus Clopidogrel

Aspirin Dose and Incidence of Primary Outcome in the CURE Trial

Aspirin Dose and Incidence of Primary Outcome in the CURE Trial

Aspirin
Aspirin plus Clopidogrel

≤100mg n=5320
10.5%
8.6%

101-199mg n=3109
9.8%
9.5%

≥200mg n=4110
13.6%
9.8%

Peters. Circulation 2003;108:1
PCI-CURE: Overall Long-Term Results

Composite of MI or CV death from randomization to end of follow-up

- Placebo + ASA*
- Clopidogrel + ASA*

* In addition to other standard therapies.

Unanswered Questions about Clopidogrel Use

• For whom? All? For selected patients only? High risk patients only?
• Which dose?
• For how long? Particularly after stent implantation.
• When? Only after anatomy is known?
• Dual or triple antiplatelet therapy?
• Withdrawal of antiplatelet agents
• What about ‘resistance’?
Selected Patients or Only High Risk Patients?
Rates of Primary Outcome in the Placebo and Clopidogrel groups Stratified by TIMI Risk Score for CV Death, MI and Stroke

**TIMI Risk Score**

Budaj A Circulation 2002;106:1622
When ?
**CV Death/MI/Stroke/Severe Ischemia**
*Within 24 hrs of Randomization*

Death/MI/Stroke within 24 hrs

- Placebo
- Clopidogrel
- Placebo + ASA
- Clopidogrel + ASA

**RR = 0.80 (0.48-1.32)**

NNT = 1000

**RR = 0.66**

**p=0.003**

Mehta SR et al. AHA, 2002
Clopidogrel before PCI

**Pre-loading + Pre-treatment**

- **Death, MI, UTVR**
- **Placebo**
- **Clopidogrel**

**Days following PCI**

**PCI-CURE**

**Pre-loading**

- **Death, MI, UTVR (per protocol)**
- **No Loading**
- **Loading**

**Effective if >15h**

**COMBINED ENDPOINT OCCURRENCE (%)**

**Days after randomization**

**CREDO**
Steinhubl S, *et al. JAMA* 2002;288: 2411 – 2420
PCI-CLARITY: Meta-Analysis of Clopidogrel Pretreatment in PCI

### Events, No./Total (%)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Clopidogrel</th>
<th>Placebo</th>
<th>OR (95% CI)</th>
<th>Favors Pretreatment</th>
<th>Favors No Pretreatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myocardial Infarction Before PCI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI-CURE</td>
<td>47/1313 (3.6%)</td>
<td>68/1345 (5.1%)</td>
<td>0.70 (0.48-1.02)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CREDO</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI-CLARITY</td>
<td>37/933 (4.0%)</td>
<td>57/930 (6.1%)</td>
<td>0.63 (0.41-0.97)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>84/2246 (3.7%)</td>
<td>125/2275 (5.5%)</td>
<td>0.67 (0.50-0.89)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CV Death or MI After PCI to 30 Days</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI-CURE</td>
<td>38/1313 (2.9%)</td>
<td>59/1345 (4.4%)</td>
<td>0.65 (0.43-0.98)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CREDO</td>
<td>54/900 (6.0%)</td>
<td>65/915 (7.1%)</td>
<td>0.83 (0.57-1.21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI-CLARITY</td>
<td>31/933 (3.3%)</td>
<td>50/930 (5.4%)</td>
<td>0.60 (0.38-0.96)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>123/3146 (3.9%)</td>
<td>174/3190 (5.5%)</td>
<td>0.71 (0.56-0.89)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clopidogrel and Bypass Graft Surgery
Clopidogrel & CABG

Event Rate

Placebo  Clopidogrel

D/MI/CVA

Bleeding

Before CABG

Before In-hosp CABG

After CABG

Study med d/c <5 d

Study med d/c ≥5 d

Major Bleeding in the CURE Study

Fox Circulation 2004;110:1202
# In-Hospital Outcomes by Clopidogrel Use in Patients Undergoing CABG Surgery

<table>
<thead>
<tr>
<th>Hospital Outcomes</th>
<th>Early CABG ≤ 5 days</th>
<th>Late CABG &gt;5 days*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Clop. CABG&lt;5 d (n=1826)</td>
<td>Clop. ≤ 5 d Before CABG (n=739)</td>
</tr>
<tr>
<td>Any RBC transfusion</td>
<td>56.9</td>
<td>65.0</td>
</tr>
<tr>
<td>Death</td>
<td>2.9</td>
<td>3.5</td>
</tr>
<tr>
<td>Death or reinfarction</td>
<td>5.7</td>
<td>5.0</td>
</tr>
<tr>
<td>Length of stay post-CABG (days)</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

Mehta. JACC 2006;48:281
ACUITY: Primary Outcomes in CABG Patients

- Patients with and without a thienopyridine administered in-hospital prior to CABG

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Thieno (+)</th>
<th>Thieno (–)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Net clinical outcome</td>
<td>15.5%</td>
<td>19.0%</td>
<td>0.066</td>
</tr>
<tr>
<td>Composite ischemia</td>
<td>12.5%</td>
<td>17.1%</td>
<td>0.013</td>
</tr>
<tr>
<td>Major bleeding (non-CABG)</td>
<td>3.8%</td>
<td>2.9%</td>
<td>0.362</td>
</tr>
</tbody>
</table>

*Heparin=unfractionated or enoxaparin
How Long ?
Benefit-Risk Ratio: the First 30 days & Long-term

**Acute phase (<30 days)**
- 12 events prevented per 1000 patients (p=0.002)
- 3 additional bleeds per 1000 patients (p=0.10)

**Long-term (>30 days)**
- 10 events prevented per 1000 patients (p=0.01)
- 1 additional bleeds per 1000 patients (p=0.66)

*Courtesy G Montalescot*
Primary Efficacy and Excess in Life Threatening Bleeding, Clopidogrel vs Placebo

Difference in no. of Events/1000 Patients Treated

CV death, MI, Strokes

Life Threatening Bleeds

Months of Follow-up

Yusuf Circulation 2003;107:966
1st Primary Event in CURE in Patients who Permanently Discontinued Study Drug due to Withdrawal of Consent
Overall Population: Primary Efficacy Outcome (MI, Stroke, or CV Death)†

Placebo + ASA* 7.3%
Clopidogrel + ASA* 6.8%

RRR: 7.1% [95% CI: -4.5%, 17.5%]  
P=0.22

†First Occurrence of MI (fatal or non-fatal), stroke (fatal or non-fatal), or cardiovascular death
*All patients received ASA 75-162 mg/day
§The number of patients followed beyond 30 months decreases rapidly to zero and there are only 21 primary efficacy events that occurred beyond this time (13 clopidogrel and 8 placebo)

Overall Population: Principal Secondary Efficacy Outcome (MI/Stroke/CV Death/Hospitalization)†

- Placebo + ASA*: 17.9%
- Clopidogrel + ASA*: 16.7%

RRR: 7.7% [95% CI: 0.5%, 14.4%]  
*p = 0.04

*All patients received ASA 75-162mg/day
†First Occurrence of MI, Stroke, CV Death, or Hospitalization for UA, TIA, or Revascularization
§The number of patients followed beyond 30 months decreases rapidly to zero and there are only 38 primary efficacy events that occurred beyond this time (23 clopidogrel and 15 placebo)

### Primary Efficacy Results (MI/Stroke/CV Death) by Pre-Specified Entry Category

<table>
<thead>
<tr>
<th>Population</th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qualifying CAD, CVD or PAD</td>
<td>0.88 (0.77, 0.998)</td>
<td>0.046</td>
</tr>
<tr>
<td>(n=12,153)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple Risk Factors</td>
<td>1.20 (0.91, 1.59)</td>
<td>0.20</td>
</tr>
<tr>
<td>(n=3,284)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Population*</td>
<td>0.93 (0.83, 1.05)</td>
<td>0.22</td>
</tr>
<tr>
<td>(n=15,603)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* A statistical test for interaction showed marginally significant heterogeneity (p=0.045) in treatment response for these pre-specified subgroups of patients

Primary Efficacy Results (MI/Stroke/CV Death)* by Category of Inclusion Criteria

<table>
<thead>
<tr>
<th>Population</th>
<th>N</th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qualifying CV Disease</td>
<td>12,153</td>
<td>0.88 (0.77, 0.998)</td>
<td>0.046</td>
</tr>
<tr>
<td>Coronary</td>
<td>5,835</td>
<td>0.86 (0.71, 1.05)</td>
<td>0.13</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>4,320</td>
<td>0.84 (0.69, 1.03)</td>
<td>0.09</td>
</tr>
<tr>
<td>PAD</td>
<td>2,838</td>
<td>0.87 (0.67, 1.13)</td>
<td>0.29</td>
</tr>
<tr>
<td>Multiple Risk Factors</td>
<td>3,284</td>
<td>1.20 (0.91, 1.59)</td>
<td>0.20</td>
</tr>
<tr>
<td>Overall Population</td>
<td>15,603</td>
<td>0.93 (0.83, 1.05)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

* First Occurrence of MI (fatal or not), Stroke (fatal or not), or CV Death

Bhatt DL. Presented at ACC 2006.
# Overall Population: Safety Results

<table>
<thead>
<tr>
<th>Safety Outcome* - N (%)</th>
<th>Clopidogrel + ASA (n=7802)</th>
<th>Placebo + ASA (n=7801)</th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GUSTO Severe Bleeding</td>
<td>130 (1.7)</td>
<td>104 (1.3)</td>
<td>1.25 (0.97, 1.61)</td>
<td>0.09</td>
</tr>
<tr>
<td>Fatal Bleeding</td>
<td>26 (0.3)</td>
<td>17 (0.2)</td>
<td>1.53 (0.83, 2.82)</td>
<td>0.17</td>
</tr>
<tr>
<td>Primary ICH</td>
<td>26 (0.3)</td>
<td>27 (0.3)</td>
<td>0.96 (0.56, 1.65)</td>
<td>0.89</td>
</tr>
<tr>
<td>GUSTO Moderate Bleeding</td>
<td>164 (2.1)</td>
<td>101 (1.3)</td>
<td>1.62 (1.27, 2.10)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Adjudicated outcomes by intention to treat analysis
ICH= Intracranial Hemorrhage

Triple or Dual Antiplatelet Therapy?
### Comparison of Dual vs Triple Anti-Platelet Therapy (ELISA-2): Outcome at 30 Days

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dual (n=163)</th>
<th>Triple (n=162)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, n(%)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1.0</td>
</tr>
<tr>
<td>Infarction, n(%)</td>
<td>92 (56)</td>
<td>74 (46)</td>
<td>0.05</td>
</tr>
<tr>
<td>Admission</td>
<td>42 (26)</td>
<td>30 (19)</td>
<td></td>
</tr>
<tr>
<td>Evolving</td>
<td>38 (23)</td>
<td>32 (20)</td>
<td></td>
</tr>
<tr>
<td>Peri-PCI</td>
<td>11 (7)</td>
<td>10 (6)</td>
<td></td>
</tr>
<tr>
<td>Re-infarction</td>
<td>1 (1)</td>
<td>2 (1)</td>
<td></td>
</tr>
<tr>
<td>Death or infarction, n(%)</td>
<td>92 (57)</td>
<td>74 (46)</td>
<td>0.05</td>
</tr>
<tr>
<td>Stroke, n</td>
<td>0</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Bleeding, n(%)</td>
<td>16 (10)</td>
<td>20 (12)</td>
<td>0.5</td>
</tr>
<tr>
<td>CABG-related</td>
<td>10 (6)</td>
<td>14 (9)</td>
<td>0.7</td>
</tr>
<tr>
<td>Surg. re-exploration</td>
<td>2 (1)</td>
<td>4 (2)</td>
<td>0.7</td>
</tr>
</tbody>
</table>
Survival Free of Death or MI in ELISA 2

(A)  
Event-free survival (%)  
\[ P = 0.098 \]  
- Triple: 54%  
- Dual: 43%  

Time (h)  

(B)  
Event-free survival (%)  
\[ P = 0.08 \]  
- Triple AP: 54%  
- Dual AP: 41%  

Time (days)  

Rasoul Eur Heart J 2006;27:14
The ISAR REACT Trial: 30 Day Results

Schömig et al. ACC Chicago 2003
The ISAR REACT Trial: Bleeding Results

Schömig et al. ACC Chicago 2003
ISAR-REACT 2
ISAR-REACT Trial
2159 Stable Patients with Elective PCI

Death/MI/UTVR, %

Abciximab vs. Placebo

RR = 1.05 [95% CI, 0.69-1.59]

ISAR-REACT, NEJM 2004
ISAR-SWEET Trial
701 Diabetic Patients with Elective PCI

Death/MI, %

RR = 0.97 [95% CI, 0.58-1.62]

ISAR-SWEET, Circ 2004
Primary End Point

Death/MI/UTVR, %

Days after randomization

RR = 0.75 [95% CI, 0.58-0.97]

Abciximab vs. Placebo
## Subset Analyses

<table>
<thead>
<tr>
<th></th>
<th>Abciximab No./Total (%)</th>
<th>Placebo No./Total (%)</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All</strong></td>
<td>90/1012 (8.9)</td>
<td>120/1010 (11.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Troponin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;0.03 µg/L</td>
<td>67/513 (13.1)</td>
<td>98/536 (18.3)</td>
<td></td>
</tr>
<tr>
<td>≤0.03 µg/L</td>
<td>23/499 (4.6)</td>
<td>22/474 (4.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Clopidogrel Pretreatment Duration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;3 hours</td>
<td>27/475 (5.7)</td>
<td>35/461 (7.6)</td>
<td></td>
</tr>
<tr>
<td>≤3 hours</td>
<td>63/537 (11.7)</td>
<td>85/549 (15.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>26/252 (10.3)</td>
<td>32/284 (11.3)</td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>64/760 (8.4)</td>
<td>88/726 (12.1)</td>
<td></td>
</tr>
</tbody>
</table>
Troponin Level and Benefit With Abciximab

Death/MI/UTVR, %

Days after randomization

Troponin-Positive: RR=0.71 [0.54-0.95]

Troponin-Negative: RR=0.99 [0.56-1.76]

Abciximab vs. Placebo
Primary Endpoint Measures (ITT)

UFH/Enoxaparin + GPI vs. Bivalirudin Alone

- 30-day events (%)
  - **Net clinical outcome**
    - UFH/Enoxaparin+GPI (N=4603): 11.7%
    - Bivalirudin alone (N=4612): 10.1%
    - $P_{NI} < 0.0001$
    - $P_{Sup} = 0.015$
  - **Ischemic composite**
    - UFH/Enoxaparin+GPI: 7.3%
    - Bivalirudin alone: 7.8%
    - $P_{NI} = 0.011$
    - $P_{Sup} = 0.32$
  - **Major bleeding**
    - UFH/Enoxaparin+GPI: 5.7%
    - Bivalirudin alone: 3.0%
    - $P_{NI} < 0.0001$
    - $P_{Sup} < 0.0001$
**Net Clinical Outcome Composite**

**UFH/Enoxaparin + IIb/IIIa vs. Bivalirudin Alone**

<table>
<thead>
<tr>
<th>Biomarkers (CK/Trop)</th>
<th>Risk ratio ±95% CI</th>
<th>Bival Alone</th>
<th>UFH/Enox + IIb/IIIa</th>
<th>RR (95% CI)</th>
<th>P</th>
<th>P_int</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated (n=5368)</td>
<td>12.2% 13.3%</td>
<td>0.92 (0.80-1.06)</td>
<td>0.23</td>
<td>0.35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (n=3841)</td>
<td>7.1% 9.4%</td>
<td>0.75 (0.61-0.93)</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ST Deviation</th>
<th>Risk ratio ±95% CI</th>
<th>Bival Alone</th>
<th>UFH/Enox + IIb/IIIa</th>
<th>RR (95% CI)</th>
<th>P</th>
<th>P_int</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes (n=3197)</td>
<td>13.0% 13.7%</td>
<td>0.96 (0.80-1.14)</td>
<td>0.61</td>
<td>0.42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n=6008)</td>
<td>8.6% 10.6%</td>
<td>0.81 (0.69-0.95)</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TIMI Risk Score</th>
<th>Risk ratio ±95% CI</th>
<th>Bival Alone</th>
<th>UFH/Enox + IIb/IIIa</th>
<th>RR (95% CI)</th>
<th>P</th>
<th>P_int</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (0-2) (n=1291)</td>
<td>6.4% 10.2%</td>
<td>0.63 (0.43-0.91)</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermed (3-4) (n=4407)</td>
<td>9.4% 10.2%</td>
<td>0.92 (0.77-1.10)</td>
<td>0.34</td>
<td>0.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High (5-7) (n=2449)</td>
<td>13.9% 15.2%</td>
<td>0.92 (0.76-1.11)</td>
<td>0.36</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pre Thienopyridine</th>
<th>Risk ratio ±95% CI</th>
<th>Bival Alone</th>
<th>UFH/Enox + IIb/IIIa</th>
<th>RR (95% CI)</th>
<th>P</th>
<th>P_int</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes (n=5192)</td>
<td>9.2% 12.2%</td>
<td>0.76 (0.65-0.89)</td>
<td>&lt;0.001</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n=4023)</td>
<td>11.3% 11.1%</td>
<td>1.02 (0.86-1.21)</td>
<td>0.83</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Bivalirudin alone better**

**UFH/Enox + IIb/IIIa better**
Withdrawal
Antiplatelet Agent Withdrawal

- Premature discontinuation of clopidogrel is associated with an 30 fold greater risk of STE-MI.

- Late thrombosis can arise very late (>400 days) after uncomplicated placement of a single drug eluting-stent in a large vessel when antiplatelet therapy is discontinued.

Jeremias A; Circulation 2004; 109: 1930-2
Antiplatelet Agent Withdrawal

- 5% of patients admitted for ACS
- Average delay after cessation = 11 days
- Scheduled surgery = 2/3 of cases
- Unnecessary cessation = 2/3 of cases

1 month FU

- Non Users
- Prior Users
- Recent withdrawal

% of patients

DEATHS (%)

BLEEDS (%)

§ significant difference between NU et RW

Cessation Predicts Death…

Interruption of OAA

2.02 (1.33-6.90)  \( P=0.003 \)

Creat. Clear.

(<30 vs >30 mL/min)

3.12 (1.10-8.83)  \( P=0.0003 \)

Age

(>65 vs <65)

3.30 (1.29-8.42)  \( P<0.00001 \)

Odds Ratio (95% CI)

Conclusions

- Risk / benefit of clopidogrel in NSTE ACS is excellent at 1 month and 1 year
- Benefit of clopidogrel (300/75) is already significant on day 1
- Risk / benefit beyond 1 year is unknown (in NSTE-ACS)
- Risk of clopidogrel withdrawal may not be trivial
Dual antiplatelet therapy after stent implantation
## Current Recommendations

### ACC/AHA Practice Guidelines

**Table 31.** Recommendations for Pharmacologic Management of Patients Undergoing PCI

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Class I Angina</th>
<th>Class II–IV, Angina Unstable, Angina NSTEMI</th>
<th>Clinical Status</th>
<th>Transmural MI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Acute Phase MI</td>
</tr>
<tr>
<td>Aspirin</td>
<td>I*</td>
<td>I</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Ticlopidine, clopidogrel†</td>
<td>I‡</td>
<td>I</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Warfarin‖</td>
<td>III ‖</td>
<td>III</td>
<td>III</td>
<td>II</td>
</tr>
<tr>
<td>GP blockers#</td>
<td>II</td>
<td>I</td>
<td>II</td>
<td>I</td>
</tr>
<tr>
<td>• Abciximab</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Tirofiban</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Eptifibatide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UF heparin**</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>Indication</td>
<td>Initiation &amp; Duration</td>
<td>Class &amp; LE</td>
<td>Random. Study for levels A-B</td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>------------</td>
<td>-----------------------------</td>
<td></td>
</tr>
<tr>
<td>Pre-treatment of planned PCI in stable CAD</td>
<td>Loading dose of 300mg at least 6h before PCI, ideally the day before</td>
<td>1 C</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Pre-treatment for Primary PCI in STEMI or immediate PCI, in NSTE-ACS or ad hoc PCI in stable CAD</td>
<td>Loading dose of 600mg, immediately after first medical contact, if clinical justifiable</td>
<td>1 C</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>After all BMS procedures</td>
<td>3-4 Weeks</td>
<td>1 A</td>
<td>CLASSICS TOPPS Bad Krozingen</td>
<td></td>
</tr>
<tr>
<td>After vascular brachytherapy</td>
<td>12 months</td>
<td>1 C</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>After DES</td>
<td>6-12 months</td>
<td>1 C</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>After NSTE-ACS</td>
<td>Prolonged for 9-12 months</td>
<td>1 B</td>
<td>CURE</td>
<td></td>
</tr>
</tbody>
</table>
Do drug-eluting stents increase deaths?

TWO SEPARATE, independent meta-analyses, presented in Hot Line session 1, suggest drug-eluting stents (DES) may increase death, Q-wave myocardial infarction (clinical surrogates of in-stent thrombosis) and cancer deaths, bringing the long-term safety of DES firmly into the spotlight. Discussant Salim Yusuf (McMaster University, Canada) hailed the data as one of the most important presentations to come out of this year’s meeting.

“Six million people in the world have been implanted with DES, yet their long-term safety and efficacy is unknown,” said Yusuf. “I’ve a feeling the data we’re seeing today is only the tip of the iceberg. We need to encourage more

obtain this data from the manufacturer,” said Nordmann. He speculated that the increase in cancer might be due to a rapid impairment of the immune system.

Yusuf widened the debate to include percutaneous coronary intervention (PCI). “The overuse of PCI is an insidious change in the culture of cardiology that needs to be reversed,” he said. The use of PCI was established in MI, high-risk unstable angina and cardiogenic shock. However, its use in stable disease was a totally different question.

“There’s no beneficial influence on mortality – PCI does nothing to prevent heart attack. All we are doing is providing short-term relief of chest
Safety of DES: Meta-Analysis

Relative excess death/Q-Wave MI of 1st generation DES vs BMS (%)

- **Sirolimus ES**: +38% (p=0.03)
- **Paclitaxel ES**: +16% (p=0.68)

N = 5,108 patients

E. Cammenzind, CH
Rate of Adverse Events (% Death & Q-wave MI)
RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS

* Based on peer reviewed publications or official presentations
Camenzind, Steg, Wijns; updated after WCC 2006
# DES Stent Thrombosis

<table>
<thead>
<tr>
<th></th>
<th>Day</th>
<th>Stent</th>
<th>Vessel</th>
<th>CK</th>
<th>Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>343</td>
<td>Taxus 3 x 16mm</td>
<td>LAD</td>
<td>6500</td>
<td>Stopped 5 days prior (bladder polyps)</td>
</tr>
<tr>
<td>2</td>
<td>442</td>
<td>Taxus 3.5 x 16mm</td>
<td>LAD</td>
<td>3500</td>
<td>Stopped 7 days prior (ca. colon)</td>
</tr>
<tr>
<td>3</td>
<td>375</td>
<td>Cypher* 3.0 x 33mm</td>
<td>Cx OM₂</td>
<td>--</td>
<td>Stopped 14 days prior</td>
</tr>
<tr>
<td>4</td>
<td>335</td>
<td>Cypher* 3.0 x 18mm</td>
<td>LAD</td>
<td>--</td>
<td>Stopped 14 days prior (colonoscopy)</td>
</tr>
</tbody>
</table>

*Patent BMS

Lancet 2004;364:1519–1521
Meta-analysis of Randomised Clinical Trials of Drug-eluting Stents

<table>
<thead>
<tr>
<th>Trial</th>
<th>DES n/N</th>
<th>BMS n/N</th>
<th>Odds ratio (95% CrI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sirolimus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAVEL 15</td>
<td>2/120</td>
<td>2/118</td>
<td>0.98 (0.14 to 7.20)</td>
</tr>
<tr>
<td>SIRIUS 16</td>
<td>5/533</td>
<td>3/525</td>
<td>1.55 (0.40 to 7.34)</td>
</tr>
<tr>
<td>C-SIRIUS 17</td>
<td>0/50</td>
<td>0/50</td>
<td>1.00 (0.00 to 690)</td>
</tr>
<tr>
<td>E-SIRIUS 18</td>
<td>2/175</td>
<td>1/177</td>
<td>1.70 (0.22 to 25.5)</td>
</tr>
<tr>
<td>Pooled</td>
<td>9/878</td>
<td>6/870</td>
<td>1.15 (0.45 to 3.06)</td>
</tr>
<tr>
<td>Paclitaxel, polymeric</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAXUS II 20</td>
<td>0/31</td>
<td>0/30</td>
<td>0.97 (0.00 to 668)</td>
</tr>
<tr>
<td>TAXUS IV 21</td>
<td>0/260</td>
<td>2/263</td>
<td>0.20 (0.00 to 1.99)</td>
</tr>
<tr>
<td>Pooled</td>
<td>9/953</td>
<td>9/945</td>
<td>1.25 (0.47 to 3.50)</td>
</tr>
<tr>
<td>Paclitaxel, non-polymeric</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASPECT 22</td>
<td>1/117</td>
<td>0/58</td>
<td>0.66 (0.00 to 8.32)</td>
</tr>
<tr>
<td>ELUTES 23</td>
<td>1/152</td>
<td>0/38</td>
<td>1.51 (0.08 to 1391)</td>
</tr>
<tr>
<td>DELIVER 24,25</td>
<td>5/517</td>
<td>5/512</td>
<td>0.76 (0.04 to 663)</td>
</tr>
<tr>
<td>PATENCY 26</td>
<td>0/24</td>
<td>1/26</td>
<td>0.99 (0.28 to 3.44)</td>
</tr>
<tr>
<td>Pooled</td>
<td>7/810</td>
<td>6/634</td>
<td>0.35 (0.00 to 6.45)</td>
</tr>
<tr>
<td>Total</td>
<td>25/2641</td>
<td>21/2449</td>
<td>1.11 (0.61 to 2.06)</td>
</tr>
</tbody>
</table>

Figure 2: Forest plot comparing all-cause mortality rates for DES and for BMS

Babapulle
Lancet 2004; 364: 583–91
Comparison between Rate of Stent Thrombosis
DES vs BMS

<table>
<thead>
<tr>
<th>Study</th>
<th>DES n/N</th>
<th>BMS n/N</th>
<th>OR (95% CI Fixed)</th>
<th>Weight %</th>
<th>OR (95% CI Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAVEL</td>
<td>0/120</td>
<td>0/118</td>
<td>-</td>
<td>0.0</td>
<td>Not estimable</td>
</tr>
<tr>
<td>SIRIUS</td>
<td>2/533</td>
<td>4/525</td>
<td>0.49 (0.09, 2.69)</td>
<td>27.6</td>
<td>0.49 (0.09, 2.69)</td>
</tr>
<tr>
<td>E-SIRIUS</td>
<td>2/175</td>
<td>0/177</td>
<td>5.12 (0.24, 107.32)</td>
<td>3.4</td>
<td>5.12 (0.24, 107.32)</td>
</tr>
<tr>
<td>C-SIRIUS</td>
<td>1/50</td>
<td>1/50</td>
<td>1.00 (0.06, 16.44)</td>
<td>6.7</td>
<td>1.00 (0.06, 16.44)</td>
</tr>
<tr>
<td>ASPECT</td>
<td>0/90</td>
<td>0/48</td>
<td>-</td>
<td>0.0</td>
<td>Not estimable</td>
</tr>
<tr>
<td>ELUTES</td>
<td>1/153</td>
<td>1/39</td>
<td>0.25 (0.02, 4.09)</td>
<td>10.9</td>
<td>0.25 (0.02, 4.09)</td>
</tr>
<tr>
<td>TAXUS-I</td>
<td>0/31</td>
<td>0/30</td>
<td>-</td>
<td>0.0</td>
<td>Not estimable</td>
</tr>
<tr>
<td>TAXUS-II</td>
<td>3/266</td>
<td>0/270</td>
<td>7.19 (0.37, 139.80)</td>
<td>3.4</td>
<td>7.19 (0.37, 139.80)</td>
</tr>
<tr>
<td>TAXUS-IV</td>
<td>4/662</td>
<td>5/652</td>
<td>0.79 (0.21, 2.94)</td>
<td>34.4</td>
<td>0.79 (0.21, 2.94)</td>
</tr>
<tr>
<td>DELIVER</td>
<td>2/522</td>
<td>2/519</td>
<td>0.99 (0.14, 7.09)</td>
<td>13.7</td>
<td>0.99 (0.14, 7.09)</td>
</tr>
</tbody>
</table>

Total (95% CI) 15/2602 : 13/2428

Test for heterogeneity $\chi^2$: 4.62 df=6 $p=0.59$
Test for overall effect: $z=0.13$ $p=0.9$

Moreno JACC 2005;45:954
DES and stent thrombosis
Rotterdam/Bern combined registries

8146 Patients – 152 stent thromboses
Rotterdam: 3 to 12 months of ASA/Clopi
Bern: 3 to 6 months ASA/Clopi

Wenaweser P et al. ESC ‘06
Angiographic DES Stent Thrombosis
Bern - Rotterdam Cohort Study

Cumulative probability of stent thrombosis (%)

Days after stent implantation

Early ST
91 pts
(60%)

(Very) Late ST 61 pts
(40%)

N=8,146 Patients

Courtesy dr S. Windecker
Angiographic DES Stent Thrombosis Bern - Rotterdam Cohort Study

Median 9 Days

Between 30 days to 3 years:
Slope = 0.6% / year

N=8,146 Patients

Cumulative probability of stent thrombosis (%)

Days after stent implantation

N=8,146 Patients

Courtesy dr S. Windecker
Stent Thrombosis: An Historical Perspective
Late Hazard with DES = 0.6 % per Year

Moreno, JACC 2005
Serruys, Lancet 1998
Colombo, Circ. 1995
Moric, CVD 1995
Serruys, NEJM 1991

Wallstent
Ticlopidine
IVUS
Heparin-coating
Brachytherapy

Incidence of stent thrombosis [%]
Stent Thrombosis: An Historical Perspective
Late Hazard with DES = 0.6 % per Year

Incidence of stent thrombosis [%]

- Wallstent
- Ticlopidine
- IVUS
- Heparin-coating
- Brachytherapy

Serruys, NEJM 1991: 24%
Morice, CVD 1995: 1.6%
Colombo, Circ. 1995: 1.6%
Serruys, Lancet 1998: 0.2%
Serruys, JACC 2004: 5.3%
Moreno, JACC 2005: 0.53%
Stent Thrombosis: An Historical Perspective
Late Hazard with DES = 0.6 % per Year

- Serruys, NEJM 1991: 24%
- Morice, CVD 1995: 1.6%
- Colombo, Circ. 1995: 1.6%
- Serruys, Lancet 1998: 0.2%
- Serruys, JACC 2004: 5.3%
- Moreno, JACC 2005: 0.53%
- BMS
- DES

Incidence of stent thrombosis [%]

Moreno, JACC 2005
Serruys, JACC 2004
Serruys, Lancet 1998
Colombo, Circ. 1995
Morice, CVD 1995
Serruys, NEJM 1991
Wallstent
Ticlopidine
IVUS
Heparin-coating
Brachytherapy
Clopidogrel Use and Long-term Clinical Outcomes After Drug-Eluting Stent Implantation

Mortality

Cumulative Incidence, %

Drug-Eluting Stent
- With Clopidogrel
- Without Clopidogrel

Bare-Metal Stent
- With Clopidogrel
- Without Clopidogrel

Months

## Overall Population: Safety Results

<table>
<thead>
<tr>
<th>Safety Outcome* - N (%)</th>
<th>Clopidogrel + ASA (n=7802)</th>
<th>Placebo + ASA (n=7801)</th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GUSTO Severe Bleeding</td>
<td>130 (1.7)</td>
<td>104 (1.3)</td>
<td>1.25 (0.97, 1.61)</td>
<td>0.09</td>
</tr>
<tr>
<td>Fatal Bleeding</td>
<td>26 (0.3)</td>
<td>17 (0.2)</td>
<td>1.53 (0.83, 2.82)</td>
<td>0.17</td>
</tr>
<tr>
<td>Primary ICH</td>
<td>26 (0.3)</td>
<td>27 (0.3)</td>
<td>0.96 (0.56, 1.65)</td>
<td>0.89</td>
</tr>
<tr>
<td>GUSTO Moderate Bleeding</td>
<td>164 (2.1)</td>
<td>101 (1.3)</td>
<td>1.62 (1.27, 2.10)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Adjudicated outcomes by intention to treat analysis

ICH= Intracranial Hemorrhage

What to recommend now?

- Stick to indications with proven superiority of DES over BMS
- Move towards second generation DES (Endeavor or Genous) – Little information on long term safety
- Move towards third generation BMS
- Favor CABG with all arterial conduits for X-vessel disease and/or diabetics
- Duration of clopidogrel treatment – At least one year
Platelet Response to Clopidogrel
Variability of Response Is a Common Phenomenon Also Observed With Clopidogrel
Multiple Causes for Clopidogrel response variability

**Reduced Clopidogrel Bioavailability**
- Failure to prescribe
- Poor compliance
- Inadequate dose (perhaps in ACS or stenting)
- Enhanced metabolism
- Interaction with other medications involving the cytochrome P-450 CYP3A4 system

**Baseline Individual Variability**
- Increased baseline platelet reactivity
- Increased body mass index
- Diabetes or insulin resistance
- Up-regulation of other platelet pathways in setting of stress
- Variations in metabolism by cytochrome P-450 CYP3A4

**Genetic Variation**
- Polymorphisms of the P2Y12 gene
- Polymorphisms of the P-450 CYP3A gene

**Accelerated Platelet Turnover**
- Increased platelet production by the bone marrow in response to stress
- Introducing new platelets unexposed to clopidogrel

**Clopidogrel: Pro-drug to Active Metabolite Formation**

**Clopidogrel**

- COOCH₃

**Inactive Metabolites**
- Carboxylic acid derivative (85% of ingested clopidogrel)

**Hepatic Metabolism**
- CYP 1A2
- CYP 2B6
- CYP 2C19

**2-oxo Compound**

- O=C\_O\_CH₃

**Active Metabolite**

- HOOC\_OCH₃

**Hepatic Metabolism**
- CYP 3A4
- CYP 2C9
- CYP 2C19
- CYP 2B6

**Esterases**
Cytochrome P450 2C29 Loss Of Function Polymorphism Determines Clopidogrel Responsiveness

Hulot. Blood 2006;108:2244
Role of P2Y$_1$ and P2Y$_{12}$ in platelet activation

- ATP → P2X$_1$
- ADP
- P2Y$_1$
  - G$\alpha$q
  - PLC-β
  - Ca$^{2+}$
- P2Y$_{12}$
  - G$\alpha$i$_2$
  - PI 3-K
  - PKB/Akt Rap1b
- AC → cAMP → ATP
- INTEGRIN ACTIVATION
- PLATELET AGGREGATION
- SECRETION
- SHAPE CHANGE
- INITIATION
- AMPLIFICATION
P2Y$_{12}$ and clopidogrel

ADP

P2Y$_{12}$

P2Y$_{1}$

Ca$^{2+}$

initiation

amplification

AMPc

Cytochrom P450 3A4

Active metabolite

Clopidogrel (Plavix$^\text{®}$) = prodrug

Savi et al., Thromb Haemost 2000
Savi et al., BBRC 2001
# Platelet Function Tests for the Detection of Clopidogrel Resistance

<table>
<thead>
<tr>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P2Y\textsubscript{12} signalling dependent</strong></td>
</tr>
<tr>
<td>Vasodilator stimulated phosphoprotein (VASP)</td>
</tr>
<tr>
<td><strong>ADP as the Stimulus</strong></td>
</tr>
<tr>
<td>VerifyNow (P2Y\textsubscript{12} assay)</td>
</tr>
<tr>
<td>Platelet aggregation (turbidometric)</td>
</tr>
<tr>
<td>Platelet aggregation (impedance)</td>
</tr>
<tr>
<td>Platelet surface P-selectin, platelet surface activated GPIIb/IIIa, leukocyte-platelet aggregates (flow cytometry)</td>
</tr>
<tr>
<td>Plateletworks</td>
</tr>
<tr>
<td>Thromboelastogram</td>
</tr>
<tr>
<td>Impact cone and plate(let) analyzer (with ADP)</td>
</tr>
</tbody>
</table>
Differences on platelet response with clopidogrel and Prasugrel

Healthy Volunteer Crossover Study

IPA (20 μM ADP) at 24 Hours

-20 0 20 40 60 80 100
Inhibition of Platelet Aggregation (%)

Response to Clopidogrel  Response to Prasugrel

Responder ≥ 25% IPA at 4 and 24 hours

Brandt J et al. ACC 2005; 2005 June 8–10; OR, USA
Comparative IPA with clopidogrel and prasugrel in atherosclerotic patients

- At 2–6 hrs., 40 mg and 60 mg LD of prasugrel generated significantly higher mean IPA than 300 mg LD of clopidogrel (p<0.05), with lower rate of non-responders in atherosclerotic patients.

- Prasugrel MD regimens achieved dose-proportional increases in IPA with significantly greater means for 7.5, 10, and 15 mg vs. 75 mg clopidogrel MD (p<0.05).

MACE: Time to Event
Death, MI, CTVT, Stroke, and Recurrent Ischemia

CLOPIDOGREL

PRASUGREL

Kaplan-Meier Estimate

Time since PCI (days)

RR = 0.77 [0.5, 1.2]

p = 0.26
Clinical Relevance of Level of IPA Is Unknown
What Are the Clinical Implications?

Are hypo-responders at risk for thrombotic events?
Are hyper-responders at risk for bleeding events?

Adapted from: Serebrauny V et al. J Am Coll Cardiol 2005;45:246-51
Differences between clopidogrel and prasugrel safety and efficacy profiles (phase II)

- No statistically significant differences in both safety (significant non-CABG bleeding) or in efficacy (MACE) between prasugrel and clopidogrel.

**Primary Endpoint: Safety**
(Significant non-CABG Bleeding)

<table>
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<tr>
<th>Treatment Group</th>
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<th>Pras Pool</th>
<th>Prasugrel LD/MD</th>
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<tr>
<td>R/N</td>
<td>3/254</td>
<td>11/650</td>
<td>40/7.5</td>
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<td></td>
<td>1.2%</td>
<td>1.7%</td>
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**Secondary Endpoint: MACE**
(Death, MI, CTVT, Stroke, Recurrent Ischemia)

RR = 0.77 [0.5, 1.2]

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Wiviott SD et al. Circulation 2005;111:3366-73
Consistency of IPA and Clinical Events
Consistency of IPA and Clinical Events

• More generally, some authors found correlation between clinical events and level of IPA

• Although this has been challenged by other authors

• In addition, in comparison with other new P2Y12 receptor antagonist agents, any comparison extrapolating pharmacological response to the clinical one should be done very carefully

• Experience proved that for clinical practice, only the clinical/safety profile, based on clinical endpoint assessment of a drug is important

5. Cannon CP et al. AHA 2005
Clopidogrel ‘resistance’ is associated with increased risk of recurrent thrombotic events

Clopidogrel Resistance Is Associated With Increased Risk of Recurrent Atherothrombotic Events In Patients with Acute Myocardial Infarction

Study patients (pts) were stratified into quartiles according to the degree of platelet activity inhibition in response to clopidogrel treatment. Patients in 4 quartiles were compared with regard to (a) changes in ADP-induced platelet aggregation expressed as percentage of baseline activity; (b) percentage reduction in aggregate size at day 6 compared with baseline values; and (c) incidence of recurrent major adverse cardiovascular events during a 6-month follow-up.

High loading dose of clopidogrel
Could Higher Dosing of Clopidogrel Achieve Higher IPA?

• From a clinical perspective, clopidogrel has been shown to act quickly
  – in COMMIT, clinical efficacy seen the first days of treatment with 75mg daily
  – In CURE clinical efficacy seen within the first hours of treatment with a clopidogrel loading dose of 300mg
  – in CREDO post-hoc analyses shown that the timing for loading patients is also crucial for ensuring a quicker protection

• It has been shown in ISAR-CHOICE and ALBION studies that higher loading regimen can achieve higher IPA although there were no significant difference between 600mg and 900mg. Variability of response still exists with higher doses
In ISAR-CHOICE, there was a greater suppression of ADP-induced (5 and 20µM/L) maximal platelet aggregation with clopidogrel 600mg loading than 300mg loading; there was no further significant aggregation enhancement with 900 mg LD.
Percentage inhibition of platelet aggregation after stimulation with 5 μmol/L ADP

Montalescot et al. The ALBION study – JACC 2006 in press
Percentage inhibition of platelet aggregation after stimulation with 20 μmol/L ADP

Montalescot et al. The ALBION study – JACC 2006 in press
Impact of Dose on « Resistance »

IPA <10% at 6 hrs

% of Patients

5 microM
20 microM

P=.007

Dose of Clopidogrel

300 mg
600 mg
900 mg

Montalescot et al. The ALBION study
What Are the Clinical Implications?

- Are hypo-responders at risk for thrombotic events?
- Are hyper-responders at risk for bleeding events?

Adapted from: Serebrauny V et al. J Am Coll Cardiol 2005;45:246-51
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**Primary Endpoint: Safety**
*Significant non-CABG Bleeding*

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**Secondary Endpoint: MACE**
*(Death, MI, CTVT, Stroke, Recurrent Ischemia)*

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**P = NS**

Wiviott SD et al. *Circulation* 2005;111:3366-73
ARMYDA-2 study: 300 vs 600mg

255 CAD patients
Randomized 300 / 600
Drug 4 to 8hrs before PCI

![Comparison of Composite EP](chart1)
P = 0.041

![Comparison of any CK-MB elev. vs any Tn I elev.](chart2)
P = 0.036 & P = 0.004

Di Sciascio G - Circ 2005
CLEAR PLATELETS: Platelet effects vs clopidogrel dose and GP IIb/IIIa inhibition

Platelet inhibition*

Relative inhibition (%)

Time (post-stenting)

Platelet reactivity*

Aggregation (%)

Group

A: Clopidogrel 300 mg
B: Clopidogrel 600 mg
C: Clopidogrel 300 mg + eptifibatide
D: Clopidogrel 600 mg + eptifibatide

†P = 0.001 C or D vs A or B
‡P = 0.001 A vs B

§P = 0.002 A vs B
ρP < 0.001 C or D vs A or B

*Response to adenosine diphosphate 5 µmol/L

CLEAR PLATELETS: Effect of clopidogrel dose and GP IIb/IIIa inhibition on cardiac biomarkers

- **CK-MB release**
  - Patients (%)
  - Clopidogrel 300 mg: *P < 0.05 vs clopidogrel 300 or 600 mg
  - Clopidogrel 600 mg: *P < 0.05 vs clopidogrel 300 or 600 mg

- **Troponin release**
  - Troponin-I (> ULN)
  - Clopidogrel 300 mg + eptifibatide: †P = 0.04 vs clopidogrel 300 mg
  - Clopidogrel 600 mg + eptifibatide: †P = 0.08 vs clopidogrel 600 mg
  - ULN = upper limit of normal

Incidence of MACE within 30 Days after PCI

Hochholzer. JACC 2006;48:1742
Low response to clopidogrel is associated with outcome after stent implantation

Table 2  Number of events at 3-month follow-up

<table>
<thead>
<tr>
<th>Event</th>
<th>Total (n = 363)</th>
<th>Response to clopidogrel</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Adequate n = 341</td>
<td>Low n = 22</td>
</tr>
<tr>
<td>Death from cardiovascular cause, no. (%)</td>
<td>14 (3.9)</td>
<td>10 (2.9)</td>
<td>4 (18.2)</td>
</tr>
<tr>
<td>Myocardial infarction, no. (%)</td>
<td>5 (1.4)</td>
<td>4 (1.2)</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Stroke, no. (%)</td>
<td>5 (1.4)</td>
<td>5 (1.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Composite CV endpoints, no. (%)</td>
<td>24 (6.6)</td>
<td>19 (5.6)</td>
<td>5 (22.7)</td>
</tr>
<tr>
<td>Death from any cause, no. (%)</td>
<td>19 (5.2)</td>
<td>14 (4.1)</td>
<td>5 (22.7)</td>
</tr>
<tr>
<td>Cumulative events, no. (%)</td>
<td>29 (8.0)</td>
<td>23 (6.7)</td>
<td>6 (27.3)</td>
</tr>
</tbody>
</table>

MACES at 3 months according to response to clopidogrel

Death from cardiovascular causes at 3 months according to response to clopidogrel

![Graph showing event-free survival (death from cardiovascular causes) over days for normal and low response to clopidogrel. The log rank P value is 0.001.]

<table>
<thead>
<tr>
<th>Response to clopidogrel</th>
<th>No. at risk</th>
<th>0</th>
<th>30</th>
<th>60</th>
<th>90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate</td>
<td>341</td>
<td>333</td>
<td>332</td>
<td>331</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>22</td>
<td>19</td>
<td>18</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>363</td>
<td>352</td>
<td>350</td>
<td>349</td>
<td></td>
</tr>
</tbody>
</table>

Increased Risk in Patients with High Platelet Aggregation Receiving Chronic Clopidogrel Therapy Undergoing PCI

Study Design

100 patients ≥ 18 yrs receiving clopidogrel for ≥1 month before non-emergent PCI.
Exclusion criteria: history of bleeding diathesis, acute MI within 48 h, elevated cardiac markers, cerebrovascular event within 3 months, illicit drug or alcohol abuse, prothrombin time >1.5 times control, platelet count < 100,000/mm³, hematocrit < 30%, creatinine > 4.0 mg/dl, and glycoprotein (GP) IIb/IIIa use before the procedure.

LTA and TEG to determine platelet reactivity

Hi On-treatment Platelet Reactivity* (HPR)
- n=22

Normal On-Treatment Platelet Reactivity (NPR)
- n=78

1, 6, and 12 mos. follow-up

Primary Endpoint: Ischemic events defined as: death secondary to any cardiovascular cause, stroke, myocardial infarction, ischemia requiring a hospital stay, and target vessel revascularization (TVR), nontarget vessel revascularization (NTVR), or medical management.

*HPR defined as ≥ 50% ADP-induced aggregation after stimulation with 5-µmol ADP as measured by LTA or ≥ 70% ADP-platelet induced aggregation with 2-µmol ADP as measured by TEG.

Increased Risk in Patients with High Platelet Aggregation Receiving Chronic Clopidogrel Therapy Undergoing PCI

Baseline on-treatment aggregation

As measured by LTA

<table>
<thead>
<tr>
<th></th>
<th>With Events</th>
<th>Without Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (%)</td>
<td>50±13%</td>
<td>31±13%</td>
</tr>
<tr>
<td>n</td>
<td>23</td>
<td>77</td>
</tr>
</tbody>
</table>

p < 0.0001

As measured by TEG

<table>
<thead>
<tr>
<th></th>
<th>With Events</th>
<th>Without Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (%)</td>
<td>76±13%</td>
<td>49±13%</td>
</tr>
<tr>
<td>n</td>
<td>23</td>
<td>77</td>
</tr>
</tbody>
</table>

p < 0.0001

Inhibition of Maximal and Late Platelet Aggregation: OPTIMUS Study

Cumulative Distribution Curves of Change of Maximal Platelet Aggregation & Inhibition of Maximal Platelet Aggregation

A

Change in Platelet Aggregation (%)

B

Inhibition of Platelet Aggregation (%)

P2Y12 Reactivity Index at T1, T2 and T3 in Patients Randomized to Clopidogrel Maintenance Doses of 75mg and 150mg

Influence of Thienopyridine Exposure – PCI pts

30 Day Primary Endpoint Adverse Events - ACUITY

Thienopyridine Exposed

- UFH/Enoxaparin + IIb/IIIa (N=1722)
- Bivalirudin Alone (N=1789)

<table>
<thead>
<tr>
<th>Event</th>
<th>UFH/Enoxaparin + IIb/IIIa</th>
<th>Bivalirudin Alone</th>
<th>RR [95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Net clinical outcomes</td>
<td>13.8%</td>
<td>11.1%</td>
<td>0.81 (0.68-0.96)</td>
</tr>
<tr>
<td>Ischemic composite</td>
<td>7.2%</td>
<td>8.1%</td>
<td>0.96 (0.77-1.20)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>4.4%</td>
<td>7.5%</td>
<td>0.50 (0.37-0.67)</td>
</tr>
</tbody>
</table>

Not Thienopyridine Exposed

- UFH/Enoxaparin + IIb/IIIa (N=811)
- Bivalirudin Alone (N=804)

<table>
<thead>
<tr>
<th>Event</th>
<th>UFH/Enoxaparin + IIb/IIIa</th>
<th>Bivalirudin Alone</th>
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<tr>
<td>Net clinical outcomes</td>
<td>11.8%</td>
<td>12.7%</td>
<td>1.07 (0.83-1.39)</td>
</tr>
<tr>
<td>Ischemic composite</td>
<td>7.5%</td>
<td>10.3%</td>
<td>1.37 (1.00-1.88)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>5.7%</td>
<td>7.5%</td>
<td>0.61 (0.39-0.97)</td>
</tr>
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</table>
Has the Benefit of Higher Clopidogrel Regimen Been Established?
Clinical Outcomes According to Loading Dose of Clopidogrel
30-Day CV Events by Loading Dose of Clopidogrel

Cuisset. JACC 2006;48:1339
Conclusions

• There is no established and definitive demonstration of an association between low responsiveness to clopidogrel and thrombotic events

• The optimal level of clopidogrel-induced platelet inhibition, which will correlate quantitatively with clopidogrel’s ability to prevent atherothrombotic events is still to be confirmed

• Because there is no single and validated platelet function assay to measure clopidogrel’s antiplatelet effect, it is not justified to routinely look for clopidogrel resistance in the clinical setting
Has the Benefit of Higher Clopidogrel Regimen Been Established?

- When patients cannot be pre-treated with clopidogrel, there is a need for a quicker protection in the acute setting.
- Rather than a certain level of IPA to be reached, a faster onset of action is required for ensuring an adequate protection in the acute setting but without exposing the patient to a higher bleeding risk.
- Some authors showed promising with higher clopidogrel loading dose results based on cardiac enzymes and clinical endpoints.
- Nevertheless, there is a need to confirm the clinical benefit-risk of higher regimen of clopidogrel in the peri-procedural phase in a double-blind controlled study in ACS patients.
14,000 patients with UA/NSTEMI planned for early invasive strategy, i.e. intended for PCI as early as possible within 24 h

RANDOMIZE

Clopidogrel high-dose group
600 mg LD Day 1 followed by 150 mg from Day 2 to Day 7; 75 mg from Day 8 to 30

Clopidogrel standard-dose group
300 mg LD Day 1 followed by 75 mg from Day 2 to Day 7; 75 mg from Day 8 to 30

RANDOMIZE

ASA low-dose group
At least 300 mg Day 1; 75–100 mg from D2 to D30

ASA high-dose group
At least 300mg Day 1; 300–325 mg from D2 to D30

ASA low-dose group
At least 300 mg Day 1; 75–100 mg from D2 to D30

ASA high-dose group
At least 300 mg Day 1; 300–325 mg from D2 to D30

Primary endpoint: CV death, MI, stroke at 30 days
Conclusions

- There is no established and definitive demonstration of an association between low responsiveness to clopidogrel and thrombotic events.

- The optimal level of clopidogrel-induced platelet inhibition, which will correlate quantitatively with clopidogrel’s ability to prevent atherothrombotic events is still to be confirmed.

- Because there is no single and validated platelet function assay to measure clopidogrel’s antiplatelet effect, it is not justified to routinely look for clopidogrel resistance in the clinical setting.

Nguyen TA et al. J Am Coll Cardiol 2005;45:1157-64
Prasugrel: A Novel Thienopyridine

Ticlopidine
(1st generation)

Clopidogrel
(2nd generation)

Prasugrel (CS-747) (LY640315)
(3rd generation)
Thienopyridine MOA

ADP

Ticlopidine
Clopidogrel
CS-747

( irreversibly )

Receptor subtype

P2X1

P2Y1

P2Y12

Molecular structure
Intrinsic ion channel

↑[Na+/Ca2+]i

Secondary Messenger system
PLC/PIP3

↑Ca2+

Functional response
Shape Change
Aggregation

Shape change
Transient aggregation

Sustained aggregation
Secretion
Prasugrel vs. Clopidogrel in Patients with Stable Coronary Artery Disease

Inhibition of platelet aggregation (28 days; 20 \( \mu \text{M ADP} \))

 IPA (%; meanadjusted + 95% CI)

H post-dose
Day

- Clopidogrel 300/75
- Prasugrel 60/10
- 25 %IPA
Inhibition of Platelet Aggregation (%)

**Response to Prasugrel**

**Non-responders**

Clopidogrel (300 mg) vs. Prasugrel (60 mg)
Phase I – Healthy subjects

- **Respoder** = ≥ 25% IPA at 4 and 24 h

*Brandt et al., ACC, 2005*
Inhibition of Platelet Aggregation (%)

Response to Prasugrel

Response to Clopidogrel

*Responder = ≥ 25% IPA at 4 and 24 h

Brandt et al., ACC, 2005

Clopidogrel (300 mg) vs. Prasugrel (60 mg)
Phase I – Healthy subjects

Non-responders
IPA (%) = 100*{(Baseline maximum PA) - (Maximum PA at timepoint)}/(Baseline maximum PA)}

Significantly higher level of platelet inhibition – 50% greater level of inhibition relative to clopidogrel
Early Time Course for Inhibition

*Prasugrel IPA significantly greater than clopidogrel from 30 minutes to 24 hours after oral administration (p<0.05)
Results shown as mean ± sd

Brandt et al., ACC, 2005
Comparison of Active Metabolite Levels for Prasugrel and Clopidogrel

![Graph showing plasma concentration over time for Prasugrel and Clopidogrel](image)
Prasugrel: Active Metabolite Formation

Clopidogrel

Pro-drug

Pre-hepatic metabolism
Esterases in blood
(? Small Intestine)

85% Inactive Metabolites
Esterases in blood

Clopidogrel

Prasugrel

Hepatic Metabolism
Cytochrome P450

Active Metabolite

Active Metabolite
Prasugrel: Pro-drug to Active Metabolite Formation

Prasugrel

Pre-hepatic metabolism
Esterases in blood
(?
Small Intestine)

Pre-hepatic and hepatic metabolism
CYP 3A4
CYP 2C9
CYP 2C19
CYP 2B6

2-oxo Compound

Active Metabolite
STUDY DESIGN

ACS (STEMI or UA/NSTEMI) & PCI

Stratified Randomization:
UA/NSTEMI vs STEMI

ASA ↓ N= 14,200

Double-blind

Anti GP IIb/IIIa at investigator’s discretion

CLOPIDOGREL
300 mg LD/ 75 mg MD

PRASUGREL
60 mg LD/ 10 mg MD

Median duration of therapy - 12 months

1º endpoint: CV death, MI or Stroke, at a median follow-up of at least 12 months

2º endpoints: CV death, MI, Stroke or Rehosp for cardiac isch event
CV death, MI or UTVR (Urgent Target Vessel Revasc.)
Intravenous P2Y12 Platelet Receptor Antagonist in PCI: Mean Platelet Aggregation with Cangrelor (Part 1)

Greenbaum. Am Heart J 2006;151:689
Intravenous P2Y12 Platelet Receptor Antagonist in PCI: Mean Platelet Aggregation with Cangrelor (Part 2)

Greenbaum. Am Heart J 2006;151:689
Steady-State Bleeding Time Estimates For Escalating Doses of Cangrelor and Abciximab

Estimated Ratio of Bleeding Times
(Parts 1 & 2 combined)

Ratio of Bleeding Time

1µg/min vs Placebo
2µg/min vs Placebo
4µg/min vs Placebo
Abciximab vs Placebo
Abciximab vs 4µg/min

Greenbaum. Am Heart J 2006;151:689
Loading Dose
Clopidogrel load: How much?

NSTE-ACS patients

LOAD

300mg

600mg

900mg

Aggregometry
Flow cytometry
Inflammation
Necrosis

Courtesy G Montalescot
Percentage inhibition of platelet aggregation after stimulation with 5 μmol/L ADP
Percentage inhibition of platelet aggregation after stimulation with 20 µmol/L ADP

Montalescot et al. The ALBION study – JACC 2006 in press
Areas under the curves for inhibition of adenosine diphosphate (ADP)-induced platelet aggregation between 0 and 24 hours

Montalescot et al. The ALBION study – JACC 2006 in press
Mean fluorescence intensity at 6 hours post-dosing.
VASP index at 6 hours post-dosing.
Proportion of patients with increased troponin release over the first 24 hours of medical treatment

Montalescot et al. The ALBION study – JACC 2006 in press
Impact of Dose on « Resistance »

IPA <10% at 6 hrs

Montalescot et al. The ALBION study
Plasma Concentrations of Active Metabolite, Clopidogrel and Carboxyl Metabolite before and after 300/600/900mg Clopidogrel

ISAR-CHOICE

Von Beckerath. Circulation 2005;112:2946
Plasma Concentrations of Active Metabolite and Clopidogrel with 300/600/900mg Clopidogrel

Von Beckerath. Circulation 2005;112:2946
Maximal ADP-induced Platelet Aggregation 4h after Administration of 300/600/900mg Clopidogrel
ISAR-CHOICE

Von Beckerath. Circulation 2005;112:2946
ISAR-CHOICE: No additional platelet effect with doses >600 mg

Intracoronary Stenting and Antithrombotic Regimen: Choose Between 3 High Oral Doses for Immediate Clopidogrel Effect

Maximal ADP-induced platelet aggregation after 4 hours

- 300 mg: P = 0.01
- 600 mg: P = 0.001
- 900 mg: P = 0.59

What do the Guidelines (will) tell us?
Antiplatelet Agents
Antiplatelet Agents

- Clopidogrel
  - Loading dose – unresolved
  - Pretreatment vs no pretreatment
- Dual vs triple antiplatelet therapy
  - Isar-React 2
- Timing of GP IIb/IIIa Inhibitors if any
  - Acuity timing
Recommendations for oral antiplatelet drugs

- Aspirin is recommended for all patients presenting with NSTE-ACS without contraindication at an initial loading dose of 160 - 325mg (non-enteric) (I-A), and at a maintenance dose of 75 to 100mg long-term (I-A).

- For all patients immediate 300mg loading dose of clopidogrel is recommended, followed by 75mg clopidogrel daily (I-A). Clopidogrel should be maintained for 12 months unless there is an excessive risk of bleeding (I-A).

- In patients considered for an invasive procedure/PCI, a loading dose of 600mg of clopidogrel may be used to achieve more rapid inhibition of platelet function (IIa-B).
Revascularisation
Revascularisation

Many issues to resolve:

• Invasive vs conservative strategy
• Timing of intervention, if any
• Pharmacological environment of PCI
Invasive vs Conservative Strategies

1. New data coming from long-term follow-up of RITA-3, FRISC-2 and Mehta meta-analysis show significant risk reduction for death and death+MI at long-term follow-up

2. Early hazard shown in ICTUS trial (excess of death & MI observed within 1st month after revascularisation in immediate invasive group)

3. Early hazard shown in Mehta meta-analysis
Invasive vs Conservative Strategies

Death, MI, Rehospitalization for ACS

- Early invasive
- Selective invasive

Relative Risk: 1.07
95% CI: 0.87 - 1.33
P = 0.63

Primary Outcome: Death or Non-Fatal MI

Conservative 20.0%
Intervention 16.6%

p = 0.044
odds ratio: 0.78
95% CI 0.61 - 0.99
Timing of Intervention

1. Few studies have shown superiority of very early intervention vs deferred intervention.
   - ISAR-COOL (small sample size)

2. Many trials, registries and meta-analysis have shown early hazard with early intervention vs deferred intervention
   - ICTUS trial
   - Mehta Meta-analysis
   - GRACE & CRUSADE registries

3. Timing of intervention recommended on the basis of risk stratification
Pharmacological Environment of PCI
1. **Loading dose of clopidogrel**
   - 300 vs 600mg
   - pre-treatment vs no pre-treatment

2. **Anticoagulant in the cathlab**
   - UFH
   - Bivalirudin
   - Enoxaparin if started in the ward (no cross-over)
   - Fondaparinux cannot be used stand-alone

3. **Triple antiplatelet therapy**
   - Recommended on the basis of ISAR-REACT-2
Double vs Triple Antiplatelet Therapy in the Cathlab – ISAR-REACT-2

**Primary End Point**

- Death/MI/UTVR, %
  - Abciximab vs. Placebo: 8.9%
  - Placebo: 11.9%
  - RR = 0.75 [95% CI, 0.58-0.97]

**Troponin Level and Benefit With Abciximab**

- Troponin-Positive: RR=0.71 [0.54-0.95]
- Troponin-Negative: RR=0.99 [0.56-1.76]

Days after randomization
### ACUITY Timing - Primary Endpoint Measures

**Routine Upstream IIb/IIla vs. Deferred PCI IIb/IIla**

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>Risk ratio ±95% CI</th>
<th>Upstream IIb/IIla</th>
<th>Deferred IIb/IIla</th>
<th>RR (95% CI)</th>
<th>p value (non inferior) (superior)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Net clinical outcome</td>
<td>11.7%</td>
<td>11.7%</td>
<td>1.00 (0.89-1.11)</td>
<td>&lt;0.001</td>
<td>0.93</td>
</tr>
<tr>
<td>Ischemic composite</td>
<td>7.1%</td>
<td>7.9%</td>
<td>1.12 (0.97-1.29)</td>
<td>0.06</td>
<td>0.13</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>6.1%</td>
<td>4.9%</td>
<td>0.80 (0.67-0.95)</td>
<td>&lt;0.001</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Deferred PCI GPI better Routine Upstream GPI better
Recommendations for anticoagulants in PCI

- At PCI procedures the initial anticoagulant should be maintained also during the procedure regardless whether this treatment is UFH (I-C), enoxaparin (IIa-B) or bivalirudin (IIa-B), while additional UFH in standard dose (50-100 IU/kg bolus) is necessary in case of fondaparinux (IIa-C).

- Anticoagulation can be interrupted within 24 hours after invasive procedure. (IIa-C) In a conservative strategy, fondaparinux, enoxaparin or other LMWH may be maintained up to hospital discharge. (I-B)
Recommendations for GP IIb/IIIa inhibitors

• In patients at intermediate to high risk, particularly patients with elevated troponins, ST-depression, or diabetes, either eptifibatide or tirofiban for initial early treatment are recommended in addition to oral antiplatelet agents (I-A).

• Patients who received initial treatment with eptifibatide or tirofiban prior to angiography, should be maintained on the same drug during and after PCI (IIa-B)

• In high risk patients not pretreated with GP IIb/IIIa inhibitors and proceeding to PCI, abciximab is recommended immediately following angiography. (I-A)

• Bivalirudin may be used as an alternative to GPIIb/IIIa inhibitors plus UFH/LMWH. (I-B)
Management Strategy
Risk Stratification

GRACE
Global Registry of Acute Coronary Events

ACS Risk Model

At Admission (in-hospital/to 6 months)

- Age: Years
- HR: bpm
- SBP: mmHg
- Creat.: μmol/l
- CHF: Killip Class

At Discharge (to 6 months)

- Cardiac arrest at admission
- ST-segment deviation
- Elevated cardiac enzymes/markers

Probability of

<table>
<thead>
<tr>
<th>Death</th>
<th>Death or MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital</td>
<td>--</td>
</tr>
<tr>
<td>To 6 months</td>
<td>--</td>
</tr>
</tbody>
</table>

US Units

Reset
1. Features of high risk that mandates urgent angiography / revascularization
   - Refractory angina or recurrent angina associated with ST changes (> 3 mm) or deep negative T waves despite intense antianginal treatment.
   - Clinical symptoms of heart failure or haemodynamic instability (progress to shock)
   - Life threatening arrhythmias (VF, VT)
Risk Stratification

2 - Features of high risk that mandates early (within 24/72 hours) angiography / revascularization

- Elevated troponin levels (I-A)
- Dynamic ST or T wave changes (symptomatic or silent) (I-A)
- Diabetes mellitus (I-A)
- Depressed left ventricular function (EF < 35%) (I-C)
- Early postinfarction angina (I-A)
- PCI within 6 months
- Prior CABG
- Moderate to high risk according to Grace Risk Score
Risk Stratification

3 - No features of high risk
- No recurrence of chest pain
- No signs of heart failure
- No new ECG changes  
  (Arrival and at 6 – 12 hours)
- No elevation of troponins  
  (Admission and at 6 – 12 hours)
Management Strategy

Orientation
- Quality of chest pain
- Symptom-orientated physical examination
- Short history for the likelihood of CAD
- Electrocardiogram (ST elevation?)

No CAD

NSTE-ACS possible

Validation

STEMI immediate reperfusion
Management Strategy

Validation

- Routine biochemistry, particularly troponins (on presentation and after 6 to 12 hours) and other markers on request
- Repeat or continuous ST segment monitoring - Echocardiogram and for special questions other imaging techniques (CT, MRI)
- Responsiveness to antianginal treatment

**Urgent < 120 min**

1. Refractory or recurrent angina despite intense Rx
2. Heart failure or haemodynamic instability
3. Life threatening arrhythmias (VF, VT)

**Early < 72 hours**

- Elevated troponin levels
- ST depression or T wave changes
- Diabetes mellitus
- Depressed LVEF < 35%
- Early postinfarction angina
- PCI within 6 months
- Prior CABG

**Elective**

- No recurrence of chest pain
- No signs of heart failure
- No new ECG changes
- No elevation of troponins (Admission and at 6 12 hours)