When should we start a P2Y$_{12}$ inhibitor in patients with an acute coronary syndrome?

G. Montalescot

Dr. Montalescot reports research Grants to the Institution or Consulting/Lecture Fees from ADIR, Amgen, AstraZeneca, Bayer, Berlin Chimie AG, Boehringer Ingelheim, Bristol-Myers Squibb, Beth Israel Deaconess Medical, Brigham Women’s Hospital, Cardiovascular Research Foundation, Celladon, CME Resources, Daiichi-Sankyo, Eli-Lilly, Europa, Elsevier, Fédération Française de Cardiologie, Fondazione Anna Maria Sechi per il Cuore, Gilead, ICAN, Janssen, Lead-Up, Menarini, Medtronic, MSD, Pfizer, Sanofi-Aventis, The Medicines Company, TIMI Study Group, WebMD.
The concept...
Definition of Pre-treatment

♦ Working diagnosis of ACS
♦ Invasive strategy decided
♦ On aspirin + anticoagulation

→ P2Y\textsubscript{12} antagonist given before coronary visualization

Cath Lab

✓ PCI → benefit expected
✓ Medical treatment → ?
✓ CABG → no benefit expected
✓ Other diagnosis (pericarditis, aortic dissection, heart failure, LVH, pulmonary embolism, GI ulcer, pancreatitis...) → harm expected
The concept...was never proved
ACCOAST: The only prospective trial in NSTEMI to investigate pre-treatment with a P2Y$_{12}$-receptor antagonist

A comparison of prasugrel at the time of percutaneous coronary intervention (PCI) or as pre-treatment at the time of diagnosis in patients with non-ST elevation myocardial infarction

Randomised, N=4038

Treated, n=4033

No pre-treatment n=1996

Pre-treatment n=2037

The rate of the primary efficacy endpoint (death from CV causes, MI, stroke, urgent revascularisation, or glycoprotein inhibitor rescue therapy) through Day 7, did not differ significantly between the groups (HR 1.02; 95% CI: 0.84–1.25; p=0.81)

ACCOAST: Pre-treatment showed similar efficacy but an increase in TIMI major bleeding

The rate of TIMI major bleeding episodes through Day 7 was increased with pre-treatment (HR 1.90; 95% CI: 1.19–3.02; p=0.006)

Overall (pre-treatment vs no pre-treatment)

<table>
<thead>
<tr>
<th></th>
<th>Total patients</th>
<th>Pre-tx n (%)</th>
<th>No pre-tx n (%)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>4033</td>
<td>52 (2.55)</td>
<td>27 (1.35)</td>
<td>1.90 (1.19–3.02)</td>
</tr>
<tr>
<td>PCI</td>
<td>2781</td>
<td>22 (1.57)</td>
<td>11 (0.80)</td>
<td>1.98 (0.96–4.09)</td>
</tr>
<tr>
<td>CABG</td>
<td>238</td>
<td>25 (20.66)</td>
<td>16 (13.68)</td>
<td>1.59 (0.85–2.98)</td>
</tr>
</tbody>
</table>

ACCOAST: Is there a risk of waiting angio to treat?

Primary efficacy endpoint prior to angiography

Montalescot G et al – ACCOAST Unpublished data
ACCOAST: Are the results different for PCI patients?

Montalescot et al. *J Am Coll Cardiol* 2014;64:2563–71

**CV death, MI or stroke**

- **No pre-treatment**: HR 1.01 (95% CI: 0.78–1.31) \(p=0.92\)
- **Pre-treatment**: HR 1.05 (95% CI: 0.82–1.34) \(p=0.72\)

**Non-CABG-related TIMI major or minor bleeding**

- **No pre-treatment**: HR 2.94 (95% CI: 1.67–5.18) \(p<0.001\)
- **Pre-treatment**: HR 3.11 (95% CI: 1.86–5.22) \(p<0.001\)
The controversy...
CURE Efficacy

- Placebo: 11.4%
- Clopidogrel: 9.3%
- RR = 0.80, p < 0.001
- 95% CI = 0.72-0.90

CURE Safety*

- Event Rate (%): Placebo vs. Clopidogrel
  - Major Bleeding: 2.7 vs. 3.7
  - Minor Bleeding: 2.4 vs. 5.1
  - P = 0.001
  - P < 0.001

- When cath, 10 days waiting ...

- Our study primarily included centers in which there was no routine policy of early use of invasive procedures, since such a policy would have led to a high rate...

- 20% PCI

- 57% no cath...

- A total of 71 patients in the clopidogrel group (1.1 percent) and 126 patients in the placebo group (2.0 percent) received thrombolytic therapy (relative risk, 0.57; 95 percent confidence interval, 0.43 to 0.76; P < 0.001); 369 patients in the clopidogrel group (5.9 percent) ...
CURE Efficacy

Placebo 11.4%
Clopidogrel 9.3%

RR=0.80, p<0.001
95% CI=0.72-0.90

CURE Safety*

P=0.001
P<0.001


CREDO Efficacy

All Cause Death, MI or UTVR (%)

RR=18.5%
95% CI=-14.2% to 41.8%
p=0.23

CREDO Safety**

P=0.19
P=0.33


*12 month Major Bleeding
Minor Bleeding

**28 days Any TIMI Major Bleeding
Any TIMI Minor Bleeding
Studies of pretreatment with oral P2Y$_{12}$ receptor inhibitors in patients with stable CAD and NSTE-ACS

Efficacy

<table>
<thead>
<tr>
<th>Study</th>
<th>Pretreatment</th>
<th>No pretreatment</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CREDO</td>
<td>6.8%</td>
<td>8.3%</td>
<td>0.23</td>
</tr>
<tr>
<td>PRAGUE 8</td>
<td>0.8%</td>
<td>1.0%</td>
<td>0.75</td>
</tr>
<tr>
<td>ACCOAST</td>
<td>10.8%</td>
<td>10.8%</td>
<td>0.98</td>
</tr>
</tbody>
</table>

- **Patients**
  - Stable CAD: 2,116
  - ACS: 33%
  - % PCI: 67%
  - Drug: Clopidogrel 300 mg
  - Follow-up: 28 days
  - Efficacy endpoint displayed: D/MI/Urev
  - Safety endpoint displayed: TIMI major bleeding

- **CREDO**
  - 4,033
  - No
  - All NSTEMI: 69%
  - Drug: Clopidogrel 600 mg
  - Follow-up: 7 days
  - Efficacy endpoint displayed: D/MI/CVA/Rev
  - Safety endpoint displayed: All TIMI bleeding

- **PRAGUE 8**
  - 1,028
  - 87%
  - 13%
  - 29%
  - Drug: Clopidogrel 600 mg
  - Follow-up: 7 days
  - Efficacy endpoint displayed: D/MI/CVA/Rev
  - Safety endpoint displayed: All TIMI bleeding

- **ACCOAST**
  - 2.6%
  - 1.4%
  - Drug: Prasugrel 30 mg
  - Follow-up: 30 days
  - Efficacy endpoint displayed: CD/MI/CVA/Urev/GPI
  - Safety endpoint displayed: All TIMI bleeding

Capodanno D & Angiolillo DJ. Circ Cardiovasc Interv 2015
Analysis of PCI treated patients only

All deaths (7-30 days)

<table>
<thead>
<tr>
<th></th>
<th>Pretreatment better</th>
<th>No pretreatment better</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CREDO</td>
<td>36.7</td>
<td>0.11 (0.01 to 2.09)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>56.0</td>
<td>1.10 (0.52 to 2.36)</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>92.7</td>
<td>0.54 (0.07 to 4.53)</td>
</tr>
<tr>
<td>ACCOAST</td>
<td>7.3</td>
<td>0.98 (0.25 to 3.95)</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>0.92 (0.43 to 1.98)</td>
</tr>
</tbody>
</table>

Major adverse cardiovascular events (7-30 days)

<table>
<thead>
<tr>
<th></th>
<th>Pretreatment better</th>
<th>No pretreatment better</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CREDO</td>
<td>27.4</td>
<td>0.80 (0.57 to 1.14)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>28.3</td>
<td>0.69 (0.49 to 0.97)</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>55.7</td>
<td>0.74 (0.58 to 0.95)</td>
</tr>
<tr>
<td>ACCOAST</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>44.3</td>
<td>1.00 (0.80 to 1.25)</td>
</tr>
</tbody>
</table>

Major bleeding (7-30 days)

<table>
<thead>
<tr>
<th></th>
<th>Pretreatment better</th>
<th>No pretreatment better</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CREDO</td>
<td>51.2</td>
<td>1.34 (0.87 to 2.07)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>30.8</td>
<td>1.13 (0.61 to 2.12)</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>82.0</td>
<td>1.27 (0.89 to 1.82)</td>
</tr>
<tr>
<td>ACCOAST</td>
<td>18.0</td>
<td>2.70 (1.13 to 6.44)</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>1.45 (0.97 to 2.15)</td>
</tr>
</tbody>
</table>

*Endpoint at 9 months
### Randomized studies only (All patients)

#### Analysis of all patients
- **All deaths (7-30 days)**
  - Clopidogrel
    - CREDO: 0/900, 4/915
    - CURE*: 359/6259, 390/6303
    - Subtotal: 359/7159, 394/7218
  - Prasugrel
    - ACCOAST: 8/2037, 10/1996
  - Total: 367/9196, 404/9214

**Table:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Pretreatment</th>
<th>No pretreatment</th>
<th>Odds ratio (95% CI)</th>
<th>Weight (%)</th>
<th>Odds ratio (95% CI)</th>
<th>I² value (%) (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CREDO</td>
<td>0/900</td>
<td>4/915</td>
<td>0.7 0.11 (0.01 to 2.09)</td>
<td>50 (P=0.16)</td>
<td>0.92 (0.80 to 1.07)</td>
<td>93.0</td>
</tr>
<tr>
<td>CURE*</td>
<td>359/6259</td>
<td>390/6303</td>
<td>93.0</td>
<td>93.7</td>
<td>0.54 (0.09 to 3.26)</td>
<td>93.7</td>
</tr>
<tr>
<td>Subtotal</td>
<td>359/7159</td>
<td>394/7218</td>
<td>6.3 0.78 (0.31 to 1.99)</td>
<td>100</td>
<td>0.90 (0.71 to 1.14)</td>
<td>100</td>
</tr>
<tr>
<td>ACCOAST</td>
<td>8/2037</td>
<td>10/1996</td>
<td>36.3</td>
<td>44.6</td>
<td>0.79 (0.67 to 0.93)</td>
<td>44.6</td>
</tr>
<tr>
<td>Total</td>
<td>367/9196</td>
<td>404/9214</td>
<td>100 0.87 (0.73 to 1.04)</td>
<td>100</td>
<td>0.87 (0.73 to 1.04)</td>
<td>100</td>
</tr>
</tbody>
</table>

#### Major adverse cardiovascular events (7-30 days)
- Clopidogrel
  - CREDO: 61/900, 76/915
    - 19.1 0.80 (0.57 to 1.14) | 0 (P=0.94) |
    - 63.7 0.79 (0.68 to 0.92) | 0 (P=0.94) |
  - CURE*: 275/6259, 346/6303
  - Subtotal: 336/7159, 422/7218
  - ACCOAST: 203/2037, 195/1996
  - Total: 539/9196, 617/9214

**Table:**

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<th>Odds ratio (95% CI)</th>
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<tr>
<td>CREDO</td>
<td>61/900</td>
<td>76/915</td>
<td>19.1 0.80 (0.57 to 1.14)</td>
<td>0 (P=0.94)</td>
<td>0.80 (0.57 to 1.14)</td>
<td>0 (P=0.94)</td>
</tr>
<tr>
<td>CURE*</td>
<td>275/6259</td>
<td>346/6303</td>
<td>63.7 0.79 (0.68 to 0.92)</td>
<td>0 (P=0.94)</td>
<td>0.79 (0.68 to 0.92)</td>
<td>0 (P=0.94)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>336/7159</td>
<td>422/7218</td>
<td>36.3 1.02 (0.83 to 1.26)</td>
<td>0 (P=0.94)</td>
<td>1.02 (0.83 to 1.26)</td>
<td>0 (P=0.94)</td>
</tr>
<tr>
<td>ACCOAST</td>
<td>203/2037</td>
<td>195/1996</td>
<td>100 0.87 (0.73 to 1.04)</td>
<td>0 (P=0.94)</td>
<td>0.87 (0.73 to 1.04)</td>
<td>0 (P=0.94)</td>
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<tr>
<td>Total</td>
<td>539/9196</td>
<td>617/9214</td>
<td>100 0.87 (0.73 to 1.04)</td>
<td>0 (P=0.94)</td>
<td>0.87 (0.73 to 1.04)</td>
<td>0 (P=0.94)</td>
</tr>
</tbody>
</table>

#### Major bleeding (7-30 days)
- Clopidogrel
  - CREDO: 50/16, 27/1996
  - 22.7% 1.34 (0.87 to 2.07) | 0 (P=0.97) |
  - 80.9% 1.34 (1.06 to 1.68) | 0 (P=0.97) |
  - CURE*: 83/766
  - Subtotal: 83/766, 27/1996
  - 19.1 1.91 (1.20 to 3.05) | 0 (P=0.97) |
  - 100 1.43 (1.16 to 1.76) | 0 (P=0.97) |

**Table:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Pretreatment</th>
<th>No pretreatment</th>
<th>Odds ratio (95% CI)</th>
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<th>I² value (%) (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CREDO</td>
<td>50/16</td>
<td>27/1996</td>
<td>22.7% 1.34 (0.87 to 2.07)</td>
<td>0 (P=0.97)</td>
<td>1.34 (0.87 to 2.07)</td>
<td>0 (P=0.97)</td>
</tr>
<tr>
<td>CURE*</td>
<td>83/766</td>
<td>27/1996</td>
<td>80.9% 1.34 (1.06 to 1.68)</td>
<td>0 (P=0.97)</td>
<td>1.34 (1.06 to 1.68)</td>
<td>0 (P=0.97)</td>
</tr>
<tr>
<td>Subtotal</td>
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<td>19.1 1.91 (1.20 to 3.05)</td>
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<td>0 (P=0.97)</td>
</tr>
<tr>
<td>ACCOAST</td>
<td></td>
<td></td>
<td>100 1.43 (1.16 to 1.76)</td>
<td>0 (P=0.97)</td>
<td>1.43 (1.16 to 1.76)</td>
<td>0 (P=0.97)</td>
</tr>
<tr>
<td>Total</td>
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<td></td>
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<td>0 (P=0.97)</td>
<td>1.43 (1.16 to 1.76)</td>
<td>0 (P=0.97)</td>
</tr>
</tbody>
</table>

*Endpoint at 9 months
All patients were pretreated before the angiogram...

Cath 74%
PCI 46%
The controversy... was seen before
EARLY-ACS: GPI pre-treatment vs. no pre-treatment

TIMI major hemorrhage (2.6% vs. 1.8%, P=0.02)

Giugliano RP et al. NEJM 2009;360(21):2176-90
The controversy...in the guidelines
Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes

Recommendations for glycoprotein IIb/IIa 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 is recommended in addition to oral antiplatelet agents (IIa-A).

- In high-risk patients not pre-treated with GP IIb/IIa inhibitors and proceeding to PCI, abciximab is recommended immediately following angiography (I-A). The use of eptifibatide or tirofiban in this setting is less well established (IIa-B).
GPI pre-treatment in NTE-ACS

### SCAD Guidelines

- **Pretreatment with clopidogrel** (when coronary anatomy is not known) is not recommended.  
  - III A

### NSTE-ACS Guidelines

- **A P2Y$_{12}$ inhibitor is recommended, in addition to aspirin**, for 12 months unless there are contra-indications such as excessive risk of bleeds.  
  - I A

- It is not recommended to administer **prasugrel** in patients in whom coronary anatomy is not known.  
  - III B

### Revasc Guidelines

- **Pretreatment with prasugrel** in patients in whom coronary anatomy is not known, is not recommended.  
  - III B

### DAPT Guidelines

- In patients with SCAD **pre-treatment with clopidogrel** may be considered if the **probability of PCI is high**.  
  - IIb C

- **Pre-treatment with a P2Y12 inhibitor** is generally recommended in patients in whom **coronary anatomy is known** and the decision to proceed to PCI is made as well as in **patients with STEMI**.  
  - I A

- **In NSTE-ACS patients undergoing invasive** management, ticagrelor or clopidogrel if ticagrelor is not an option, should be considered **as soon as the diagnosis is established**.  
  - IIa C

- **In NSTE-ACS patients** it is not recommended to administer **prasugrel** in patients in whom coronary anatomy is not known.  
  - III B
### P2Y₁₂ inhibitors

<table>
<thead>
<tr>
<th>Item</th>
<th>Dose/Regimen</th>
<th>Level</th>
<th>Evidence Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel loading dose followed by daily maintenance dose in patients unable to take aspirin</td>
<td>75 mg</td>
<td>I</td>
<td>(291)</td>
</tr>
<tr>
<td>P2Y₁₂ inhibitor, in addition to aspirin, for up to 12 mo for patients treated initially with either an early invasive or initial ischemia-guided strategy:</td>
<td>300-mg or 600-mg loading dose, then 75 mg/d</td>
<td>I</td>
<td>(289,292)</td>
</tr>
<tr>
<td>– Clopidogrel</td>
<td>180-mg loading dose, then 90 mg BID</td>
<td>I</td>
<td>(293,294)</td>
</tr>
<tr>
<td>– Ticagrelor*</td>
<td>Ia</td>
<td></td>
<td>(293,296,302, 330,331)</td>
</tr>
</tbody>
</table>
Applying the evidence
NSTE-ACS in the Real World of All-Comers

→ Shall we treat them all before the angio?

Clinical situations where administration of antiplatelet therapy is delayed

- Intubated patient
- Vomiting, dysphagia...
- STEMI and limited pre-hospital care
- NSTE-ACS or SCAD → no pre-treatment
CHAMPION-PHOENIX: IV P2Y12 inhibitor cangrelor

Death/ MI/ IDR/ Stent Thrombosis within 48 Hours


cangrelor

clopidogrel

Log Rank P Value = 0.006

<table>
<thead>
<tr>
<th>Event Rate (%)</th>
<th>clopidogrel</th>
<th>cangrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI Major 48h</td>
<td>0.1%</td>
<td>0.1%</td>
</tr>
<tr>
<td>TIMI Minor 48h</td>
<td>0.2%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Death 48h</td>
<td>0.3%</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

Crushed, chewed or orodispersible

Ticagrelor

Lower platelet reactivity (Verify Now)

Greater inhibition of platelet reactivity


Prasugrel

Asher E et al. Thromb Haemost 2017

Rollini F et al. JACC 2016

P2Y12 Reaction Units (PRU)

ANOVA p=0.008
Conclusions

When should we start a P2Y$_{12}$ inhibitor?

- Guidelines uncertain: LOE B for prasugrel / LOE C for ticagrelor and clopidogrel
- Bleeding risk increases with early administration
- Ischemic risk reduction is uncertain
  - Early start more justified when long wait (>48hrs) for cath or no cath strategy
  - Start after angio more justified when expeditive care with preferred use of crushed pills or IV P2Y12 inhibitor

Slides available at www.action-coeur.org