P2Y12 inhibition should be started at the time of NSTEMI diagnosis — **No!**

*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 term “pretreatment” refers to the *initiation* of a treatment (P2Y<sub>12</sub> inhibitor) either in the ambulance, an emergency department, in the coronary care unit, or in the catheterization laboratory *prior to the definition of coronary anatomy*. 
A “concept” born with CURE

... not confirmed with CREDO
CURE Efficacy


When cath, 10 days waiting ...

20% PCI
N=2,658

57% no cath...

N=12,562

20% PCI

Cumulative Hazard Rate

Days following PCI

<table>
<thead>
<tr>
<th>Days</th>
<th>0.00</th>
<th>0.02</th>
<th>0.04</th>
<th>0.06</th>
<th>0.08</th>
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<tbody>
<tr>
<td>5</td>
<td>0.10</td>
<td>0.30</td>
<td>0.50</td>
<td>0.70</td>
<td>0.90</td>
</tr>
<tr>
<td>10</td>
<td>0.20</td>
<td>0.40</td>
<td>0.60</td>
<td>0.80</td>
<td>1.00</td>
</tr>
<tr>
<td>15</td>
<td>0.30</td>
<td>0.60</td>
<td>0.90</td>
<td>1.20</td>
<td>1.50</td>
</tr>
<tr>
<td>20</td>
<td>0.40</td>
<td>0.80</td>
<td>1.20</td>
<td>1.60</td>
<td>2.00</td>
</tr>
<tr>
<td>25</td>
<td>0.50</td>
<td>1.00</td>
<td>1.50</td>
<td>2.00</td>
<td>2.50</td>
</tr>
<tr>
<td>30</td>
<td>0.60</td>
<td>1.20</td>
<td>1.80</td>
<td>2.40</td>
<td>3.00</td>
</tr>
</tbody>
</table>

Placebo

RR 0.70
95% CI 0.50-0.97
P=0.03

Clopidogrel

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


1°EP: CV Death, MI, Urgent Revascularization

ACS

CURE Efficacy

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...

When cath, 10 days waiting...

N=12,562
CURE Efficacy

Placibo 11.4%
Clopidogrel 9.3%

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

CURE Safety

Event Rate (%)

Placebo
Clopidogrel


CREDO Efficacy

Composite Endpoint
All Cause Death, MI or UTVR (%)

8.3%
6.8%

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

No Pretreatment
Pretreatment

CREDO Safety

Event Rate (%)

Placebo
Clopidogrel

A “concept” invalidated by ACCOAST
ACCOAST
Randomization before angiography (mandatory)

NSTEMI + Troponin ≥ 1.5 times ULN local lab value
Clopidogrel naive or on long term clopidogrel 75 mg

Randomize 1:1
Double-blind

n~4100 (event driven)

Prasugrel 30 mg

Coronary Angiography

PCI

Prasugrel 30 mg

CABG or Medical Management (no more prasugrel)

Placebo

Coronary Angiography

PCI

Prasugrel 60 mg

CABG or Medical Management (no prasugrel)

Prasugrel 10 mg or 5 mg (based on weight and age) for 30 days

1° Endpoint: CV Death, MI, Stroke, Urg Revasc, GP IIb/IIIa inh. Bailout, at 7 days

The licensed loading dose of prasugrel is 60mg

Primary Efficacy and Safety Endpoints (All Patients)

Timing? risk of waiting


Silvain et al. ACCOAST-timing, *JACC* 2018
Studies of pretreatment with oral P2Y$_{12}$ receptor inhibitors

**Efficacy**

- **Patients**
  - Stable CAD: 33%
  - ACS: 67%
  - PCI: 86%
- **Drug**
  - Clopidogrel 300 mg
  - Clopidogrel 600 mg
  - Prasugrel 30 mg
- **Follow-up**
  - CREDO: 28 days
  - PRAGUE 8: 7 days
  - ACCOAST: 30 days
- **Efficacy endpoint displayed**
  - D/MI/Urev
  - D/MI/CVA/Rev
  - CD/MI/CVA/Urev/GPI
- **Safety endpoint displayed**
  - TIMI major bleeding
  - All TIMI bleeding

**Safety**

- **CREDO**
  - 4.8%
  - 3.8%
  - P = 0.24
- **PRAGUE 8**
  - 3.5%
  - 1.4%
  - P = 0.025
- **ACCOAST**
  - 2.6%
  - 1.4%
  - P < 0.001

Capodanno D & Angiolillo DJ. Circ Cardiovasc Interv 2015
<table>
<thead>
<tr>
<th>Study</th>
<th>No of events/patients</th>
<th>Odds ratio (95% CI)</th>
<th>Weight (%)</th>
<th>Odds ratio (95% CI)</th>
<th>I^2 value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All deaths (7-30 days)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CREDO</td>
<td>0/900</td>
<td>0.7</td>
<td>93.0</td>
<td>0.11 (0.01 to 2.09)</td>
<td>50 (P=0.16)</td>
</tr>
<tr>
<td>CURE*</td>
<td>359/6259</td>
<td>93.7</td>
<td>93.0</td>
<td>0.92 (0.80 to 1.07)</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>359/7159</td>
<td>93.7</td>
<td>93.0</td>
<td>0.92 (0.80 to 1.07)</td>
<td></td>
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<tr>
<td>Prasugrel</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACCOAST</td>
<td>8/2037</td>
<td>6.3</td>
<td>100</td>
<td>0.78 (0.31 to 1.99)</td>
<td>5 (P=0.35)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>367/9196</td>
<td>100</td>
<td></td>
<td>0.90 (0.71 to 1.14)</td>
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<tr>
<td><strong>Major adverse cardiovascular events (7-30 days)</strong></td>
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<td></td>
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<tr>
<td>Clopidogrel</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CREDO</td>
<td>61/900</td>
<td>19.1</td>
<td>19.1</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>44.6</td>
<td>44.6</td>
<td>0.79 (0.67 to 0.93)</td>
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<tr>
<td>Subtotal</td>
<td>336/7159</td>
<td>63.7</td>
<td>63.7</td>
<td>0.79 (0.68 to 0.92)</td>
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<tr>
<td>Prasugrel</td>
<td></td>
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<td></td>
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<tr>
<td>ACCOAST</td>
<td>203/2037</td>
<td>36.3</td>
<td>100</td>
<td>1.02 (0.83 to 1.26)</td>
<td>48 (P=0.13)</td>
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<tr>
<td><strong>Total</strong></td>
<td>539/9196</td>
<td>100</td>
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<td>0.87 (0.73 to 1.04)</td>
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<tr>
<td><strong>Major bleeding (7-30 days)</strong></td>
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<tr>
<td>Clopidogrel</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CREDO</td>
<td>50/105</td>
<td>22.7%</td>
<td>22.7%</td>
<td>1.34 (0.87 to 2.07)</td>
<td>0 (P=0.97)</td>
</tr>
<tr>
<td>CURE*</td>
<td>366</td>
<td>58.2%</td>
<td>58.2%</td>
<td>1.33 (1.02 to 1.74)</td>
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<tr>
<td>Subtotal</td>
<td>366</td>
<td></td>
<td></td>
<td>1.33 (1.02 to 1.74)</td>
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<tr>
<td>Prasugrel</td>
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<tr>
<td>ACCOAST</td>
<td>27/1996</td>
<td>19.1</td>
<td>19.1</td>
<td>1.91 (1.20 to 3.05)</td>
<td>0 (P=0.40)</td>
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<tr>
<td><strong>Total</strong></td>
<td>793/4996</td>
<td>100</td>
<td></td>
<td>1.43 (1.16 to 1.76)</td>
<td></td>
</tr>
</tbody>
</table>

*Endpoint at 9 months

Bellemain-Appaix A et al. BMJ 2014
In conclusion, pretreatment with clopidogrel reduced the occurrence of death and thrombotic outcomes at the cost of minor bleeding. Those benefits exclusively affected ST-elevation myocardial infarction cases. The potential benefit of routine upstream pretreatment in patients with non–ST-elevation ACS should be reappraised at the present. © 2015 Elsevier Inc. All rights reserved. (Am J Cardiol 2015;115:1019–1026)
PRAGUE 18 study
n=1230, prasugrel vs ticagrelor

1° Endpoint
Death, MI, Stroke, urg revasc, MB @D7

Key 2° Endpoint
Death, MI, Stroke @D30

Motovska Z et al. Circ 2016
Meta-analysis of clopidogrel pretreatment in acute coronary syndrome patients undergoing invasive strategy

Ramez Nairooz a,*, Marco Valgimigli b, Yogita Rochlani c, Naga Venkata Pothineni a, Sameer Pathna a, Partha Sardar d, Debrabrata Mukherjee e, Srihari S Naidu f, David M. Shavelle g

International Journal of Cardiology 229 (2017) 82–89

- Prasugrel and ticagrelor excluded (= Class I recommendations)
- PCI patients only (= post-hoc studies only)
- Mixing of STEMI and NSTE-ACS (= mixing of opposite situations)
- >90% of patients come from registries (= multiple biases)
- No loading in no pretreatment arm of some studies (= no treatment at all)
The Timing of P2Y₁₂ Inhibitor Initiation in the Treatment of ACS? Does the Evidence Exist in This Era?☆

Harsh Golwala, Deepak L. Bhatt *

Brigham and Women's Hospital Heart & Vascular Center, Harvard Medical School, Boston, MA, United States

Conclusion

Pretreatment strategy with a P2Y₁₂ inhibitor in patients with ACS still remains an area of debate. Randomized trials, which supported their use, are from an older era and precede the state of the art management of patients with ACS including primary PCI for STEMI and a routine early invasive approach for NSTEMI. Pretreatment may be considered in certain groups of patients, such as when there is an expected delay of >48 h for PCI, low bleeding risk, high recurrent ischemic risk, and/or low likelihood of requiring CABG. However, based on the above data, routine pretreatment with oral P2Y₁₂ inhibitors may not be an optimal option.

Progress in Cardiovascular Diseases 60 (2018) 471–477
## ISAR-REACT 5

### STEMI
- **Randomization**
  - Ticagrelor 180 mg loading
  - Prasugrel 60 mg loading

- **Angiography + PCI**
  - Ticagrelor 90 mg 1-0-1
  - Prasugrel 10 mg 1-0-0

### NSTE-ACS
- **Randomization**
  - Ticagrelor 180 mg loading
  - Prasugrel 60 mg loading

- **Angiography**
  - Prasugrel 60 mg loading

- **PCI**
  - Ticagrelor 90 mg 1-0-1
  - Prasugrel 10 mg 1-0-0

### Primary Endpoint:
- Composite of Death, Myocardial infarction or Stroke at 12 Months After Randomization

### Clinical Presentation
<table>
<thead>
<tr>
<th>Condition</th>
<th>STEMI</th>
<th>NSTEMI</th>
<th>Unstable Angina</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases/Total</td>
<td>83/833 (10.1)</td>
<td>81/930 (8.8)</td>
<td>20/249 (8.2)</td>
</tr>
<tr>
<td>Events/Total</td>
<td>64/820 (7.9)</td>
<td>60/925 (6.6)</td>
<td>13/261 (5.1)</td>
</tr>
</tbody>
</table>

### Graphs
- Hazard ratio 1.36 [1.09-1.70], $P = 0.006$
- Hazard ratio 1.12 [0.83-1.51], $P = 0.46$
A debate also in the guidelines!
### SCAD Guidelines

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

### Revasc Guidelines

**NSTE-ACS:** It is recommended to give P2Y$_{12}$ inhibitors at the **time of first medical contact**

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

### 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.

It is not recommended to administer prasugrel in patients in whom coronary anatomy is not known.

### DAPT Guidelines

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

**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**

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.

In **NSTE-ACS** patients it is not recommended to administer prasugrel in patients in whom coronary anatomy is not known.
<table>
<thead>
<tr>
<th>P2Y&lt;sub&gt;12&lt;/sub&gt; inhibitors</th>
<th></th>
<th></th>
<th></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>B</td>
</tr>
<tr>
<td>- P2Y&lt;sub&gt;12&lt;/sub&gt; 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>B</td>
</tr>
<tr>
<td>- Clopidogrel</td>
<td>180-mg loading dose, then 90 mg BID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Ticagrelor*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- P2Y&lt;sub&gt;12&lt;/sub&gt; inhibitor therapy (clopidogrel, prasugrel, or ticagrelor) continued for at least 12 mo in post-PCI patients treated with coronary stents</td>
<td>N/A</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>- Ticagrelor in preference to clopidogrel for patients treated with an early invasive or ischemia-guided strategy</td>
<td>N/A</td>
<td>IIA</td>
<td>B</td>
</tr>
</tbody>
</table>
Just apply the evidence and use the right options
NO pre-treatment

- CREDO
- ISAR-REACT 5
- PRAGUE8
- ACCOAST
Crushed, chewed or orodispersible

**Ticagrelor**

![Graph showing lower platelet reactivity](image1)

![Graph showing greater inhibition of platelet reactivity](image2)


Asher E et al. *Thromb Haemost* 2017

**Prasugrel**

![Graph showing inhibition of platelet aggregation](image3)

Rollini F et al. *JACC* 2016

PSY's Reaction Units (PRU)

ANOVA p=0.008

p=0.053  p<0.001  p=0.022  p=0.023  p=0.102  p=0.178
CHAMPION-PHOENIX: IV P2Y12 inhibitor cangrelor
Death/ MI/ IDR/ Stent Thrombosis within 48 Hours

Conclusions

♦ Bleeding risk increases with pretreatment
♦ Ischemic risk is not reduced with pretreatment
♦ No mortality effect with pretreatment

➤ Look first (at coronaries) and Treat (selectively)

➤ Do not Treat (routinely) and Watch (complications)

➤ Early start only justified if long wait (>48hrs) for cath or no cath strategy

Slides available at www.action-coeur.org