Pretreatment With Oral P2Y12 Inhibitors in NSTE-ACS and STEMI-Against

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Definition

Pre-treatment in ACS: a treatment given before the coronary angiogram when an invasive strategy is used.
Pretreatment in NSTE-ACS
NSTE-ACS in the Real World of All-comers

Mandelzweig et al., Eur Heart J. 2006;27:2285-2293
Patel et al; Am Heart J 2006; 152: 641–47.
Selection of NSTE-ACS treatment strategy

Symptoms Onset

First medical contact -> NSTE-ACS diagnosis

PCI center

EMS or Non-PCI center

Risk Identification

Very high

High

Intermediate

Low

Immediate invasive (<2hr)

Early invasive (<24hr)

Invasive (<72hr)

Immediate transfer to PCI center

Same day transfer

Transfer

Optional Transfer

Non-invasive testing if appropriate

Therapeutic strategy
### Oral Antiplatelet Therapy in NSTE-ACS

#### Recommendations Antiplatelet therapy

<table>
<thead>
<tr>
<th></th>
<th>Class&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Level&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral Antiplatelet Therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A P2Y&lt;sub&gt;12&lt;/sub&gt; inhibitor is recommended, in addition to aspirin, for 12 months unless there are contra-indications*</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>It is not recommended to administer prasugrel in patients in whom coronary anatomy is not known.</td>
<td>III</td>
<td>B</td>
</tr>
</tbody>
</table>

*Contra-indications for ticagrelor: previous intracranial haemorrhage or ongoing bleeds. Contra-indications for prasugrel: previous intracranial haemorrhage, previous stroke or transient ischaemic attack, or ongoing bleeds; prasugrel is generally not recommended for patients aged 75 years or more or with body weight <60 kg.

#### Recommendations Antiplatelet therapy in patients **in need for OAC**

<table>
<thead>
<tr>
<th></th>
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<th>Level&lt;sup&gt;b&lt;/sup&gt;</th>
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<td><strong>Oral Antiplatelet Therapy</strong></td>
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<tr>
<td>Initial DAPT with aspirin plus a P2Y12 inhibitor in addition to OAC before coronary angiography is not recommended</td>
<td>III</td>
<td>C</td>
</tr>
</tbody>
</table>
Pre-treatment in NSTE-ACS + PCI (Rx trials)

Bellemain-Appaix A, BMJ. 2014 Oct 24;349:g626
CURE vs. ACCOAST according to PCI

Before PCI

After PCI
Up to 30 days

Ischemic endpoint (%)

CURE-PCI  ACCOAST-PCI  CURE-PCI  ACCOAST-PCI

Placebo  Clopidogrel  Prasugrel

CURE vs. ACCOAST according to PCI


Ticagrelor data

- No dedicated study exists assessing early (i.e. before coronary angiography) vs. delayed (i.e. after coronary angiography) ticagrelor

- A drug approach instead of a Strategy
The only dedicated study for ticagrelro is ongoing: Dubius study

**DUBIUS trial** $n \approx 2528$

**UA/NSTEMI <72 hours - initial invasive indication**
ASA + open label anticoagulants

1st Randomization

Downstream strategy

If PCI

2nd Randomization

Prasugrel* Ticagrelor

II EP powered for non-inferiority
II EP powered for EQUIVALENCE

Primary EP: 30-d NACE (CV death, MI, stroke, BARC 3, 4, 5)

*60 mg oral bolus then 5 mg/die if >75 yrs or < 60 kg
Pretreatment in STEMI
## Antiplatelet therapy for STEMI undergoing PCI

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class(^a)</th>
<th>Level(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiplatelet therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P2Y(_{12}) inhibitors should be given at time of first medical contact.</td>
<td>I</td>
<td>B</td>
</tr>
</tbody>
</table>
### Table 4. Effect of Pretreatment With Clopidogrel on Early Reperfusion and Adverse Event Rates in Multivariate-Weighted and Propensity Score–Adjusted Logistic Regression Analysis

<table>
<thead>
<tr>
<th>Event</th>
<th>Multivariate-Adjusted Treatment Effect*</th>
<th>Jackknife Estimation*</th>
<th>Propensity Score–Adjusted Treatment Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>P</td>
</tr>
<tr>
<td>TIMI grade 2/3 flow</td>
<td>1.51</td>
<td>1.31–1.74</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mortality</td>
<td><strong>0.57</strong></td>
<td>0.38–0.85</td>
<td>0.0055</td>
</tr>
<tr>
<td>Death/reinfarction</td>
<td><strong>0.54</strong></td>
<td>0.38–0.75</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

OR is for the occurrence of TIMI grade 2/3 flow, mortality, and death/reinfarction for pretreatment with clopidogrel.

*Adjusted for age, gender, history of diabetes mellitus, history of hypertension, heparin dose (high vs low dose), symptom duration, smoking, and year of publication.

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![Clopidogrel Diagram](image)

**CLOPIDOGREL – Metanalysis**

- **DEATH**
  - CIPAMI: 1/164, 0.50 [0.26-0.96], p=0.04
  - CLARITY PCI: 24/930, 0.53 [0.27-1.05], p=0.008
  - All: 28/1101, 0.50 [0.26-0.96], p=0.003

- **MACE**
  - CIPAMI: 5/164, 0.54 [0.36-0.81], p=0.003
  - CLARITY PCI: 56/166, 0.54 [0.34-0.86], p<0.0001
  - All: 527/5096, 0.57 [0.48-0.67], p<0.00001

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**RCT***

- CIPAMI: 5/164, 0.42 [0.14-1.21], p=0.14
- CLARITY PCI: 58/930, 0.57 [0.37-0.88], p=0.003
- All: 70/1101, 0.54 [0.36-0.81], p=0.001

**Observational studies**

- Dorler et al.: 173/1076, 0.57 [0.47-0.69], p=0.03
- Fefer et al.: 56/166, 0.54 [0.34-0.86], p=0.14
- All: 229/1242, 0.57 [0.48-0.67], p=0.001

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* RCT=Randomized Controlled Trials

A. Bellemain-Appaix et al., JAMA 2012;308(23):2507-2517
Major adverse CV events up to 30 days: Kaplan–Meier curves

Ticagrelor pre-hospital 41/906 (4.5%) versus ticagrelor in-hospital 42/952 (4.4%)
OR 1.03 (95% CI 0.66, 1.0); p=0.9056

Major adverse CV events: death, myocardial infarction, stroke or urgent revascularisation
2014 nejm
Definite acute stent thrombosis up to 30 days: Kaplan–Meier curves

Ticagrelor pre-hospital 2/906 (0.2%) versus ticagrelor in-hospital 11/952 (1.2%)
OR 0.19 (95% CI 0.04, 0.86), p=0.0225
Biases of interpretation

- Most of the benefit derives from secondary PCI
- Most of the benefit derives from old clopidogrel data

Bellemain-appaix et al. JACC Int (submitted)
CONCLUSIONS

- Outdated, Ineffective, Harmful in NSTE-ACS
  - No access to a cath lab/need to wait several days for a cath → Apply CURE/PLATO and be ready for the safety consequences.
  - Treating after the angiogram → flexibility, avoids over-treatment & select the right treatment for the right patient.

- Recommended in STEMI when there is no doubt with respect to the diagnosis