The Efficacy of Early versus Delayed P2Y12 Inhibition in Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction: A Systematic Review and Meta-Analysis

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for the ACTION Study Group
DISCLOSURES

Personal disclosures: Research grants from Daiichi-Sankyo, Eli Lilly, Fédération Française de Cardiologie and Société Française de Cardiologie, consulting fees from AstraZeneca, Daiichi-Sankyo and Eli Lilly, and speaker honoraria from AstraZeneca, Daiichi-Sankyo, Servier, Biotronik and Novartis.

There was no external source of funding.

This meta-analysis was led by the academic ACTION-study-group (www.action-coeur.org).
Background
PRIMARY PCI OF STEMI: Platelet inhibition and MACEs

Matetzky et al., *Circulation*, 2004;109:3171-3175

Clopidogrel 300mg LD

Favor Thrombolysis
N=3 867

Favor Primary PCI
N=3 872


*p<0.05 for all EP

MACE 6 months (death, MI, UVR, stroke)

Relation between FMC-PCI and death

STEMI

Koul S et al. *J Am Heart Assoc* 2014;3:e000486

Need for a POTENT AND FAST Platelet Inhibition

Matetzky et al., *Circulation*, 2004;109:3171-3175
CLOPIDOGREL pre-treatment primary PCI of STEMI

META-ANALYSIS Primary PCI STEMI


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

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>P</th>
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<tbody>
<tr>
<td><strong>Jackknife Estimation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI grade 2/3 flow</td>
<td>1.51 (1.31–1.74)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.57 (0.40–0.81)</td>
<td>0.0019</td>
</tr>
<tr>
<td>Death/reinfarction</td>
<td>0.54 (0.39–0.73)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td><strong>Propensity Score-Adjusted Treatment Effect</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI grade 2/3 flow</td>
<td>1.53 (1.39–1.68)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.52 (0.41–0.67)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Death/reinfarction</td>
<td>0.50 (0.40–0.62)</td>
<td>&lt;0.0001</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.
MA clopidogrel pre-tt; sub-analysis PCI STEMI  
Bellemain-Appaix et al. JAMA2012;308(23):2507-2517

### Events / Size, Clopidogrel Pretreatment No OR [CI 95%] Relative Weight [%]

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>CIPAMI</th>
<th>CLARITY PCI</th>
<th>All</th>
<th>RCT* N=2198</th>
<th>Observational studies N=6338</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1/164</td>
<td>13/933</td>
<td>14/1097</td>
<td>0·26 [0·03-2·32] 8·7%</td>
<td>Dorler et al. 209/4879 110/1076 0·39 [0·31-0·50] 56·4%</td>
</tr>
<tr>
<td></td>
<td>4/171</td>
<td>24/930</td>
<td>28/1101</td>
<td>0·53 [0·27-1·05] 91·3%</td>
<td>Fefer et al. 12/217 6/166 1·56 [0·57-4·25] 43·6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0·50 [0·26-0·96] 100%</td>
<td>All 221/5096 116/1242 0·72 [0·19-2·75] 100%</td>
</tr>
</tbody>
</table>

### RCT*

<table>
<thead>
<tr>
<th>CIPAMI</th>
<th>CLARITY PCI</th>
<th>All</th>
<th>Observational studies</th>
</tr>
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<tbody>
<tr>
<td>14/164</td>
<td>5/933</td>
<td>19/1097</td>
<td>Dorler et al. 42/4879 15/1076 0·61 [0·34-1·11] 85·3%</td>
</tr>
<tr>
<td>15/171</td>
<td>10/930</td>
<td>25/1101</td>
<td>Fefer et al. 3/217 1/166 2·31 [0·24-22·44] 14·7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>All 45/5096 16/1242 0·75 [0·30-1·88] 100%</td>
</tr>
</tbody>
</table>

### Observational studies

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>CIPAMI</th>
<th>CLARITY PCI</th>
<th>All</th>
<th>Observational studies</th>
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<tr>
<td></td>
<td>5/164</td>
<td>34/933</td>
<td>39/1097</td>
<td>0·42 [0·14-1·21] 14·2%</td>
</tr>
<tr>
<td></td>
<td>12/171</td>
<td>58/930</td>
<td>70/1101</td>
<td>0·57 [0·37-0·88] 85·8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0·54 [0·36-0·81] 100%</td>
</tr>
</tbody>
</table>

### PreTreatment better

- DEATH: OR=0·50 CI 95% [0·26-0·96] p=0·04
- MAJOR BLEEDING: OR=0·72 CI 95% [0·19-2·75] p=0·63
- MACE: OR=0·57 CI 95% [0·48-0·67] p<0·0001

* RCT=Randomized Controlled Trials

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2 RCTs; N=2 198 pts  
2 Registries; N=6 338 pts
**PRASUGREL - TRITON STEMI - PCI**

Administration pre-PCI: 27%
during: 72%, after: 1%

NFH 72% GI 64% pPCI, 60% 2° PCI
Clopidogrel prett excluded

![Graph showing outcomes of Prasugrel vs Clopidogrel](image)

**NO COMPARISON between pretreatment vs no pretreatment**

Montalescot et al; Lancet. 2009 Feb 28; 373(9665): 723-31
TICAGRELOR - PLATO STEMI - PCI

RCT 7 544 STEMI/LBB (9.5%) primary PCI < H24
Ticagrelor 180/90bd vs Clopidogrel 300(+300PCI)/75mg

Steg et al; Circulation. 2010;122:2131-2141

44% clopi pré-rando
PCI 82%
CABG 2.5%
Stent 75%, DES 21%

TIMI non CABG bleeding
ST: definite & probable
1862 patients, STEMI <6 hours

- Median time: random-angio=48 min
- Between the two treatment=31 min

No ST-segment resolution (≥70%)
Major adverse CV events up to 30 days

- Ticagrelor in-hospital
- Ticagrelor pre-hospital

Definite stent thrombosis up to 10 days

- Ticagrelor pre-hospital
- Ticagrelor in-hospital

P = 0.0225

MACE: death, MI, stent thrombosis, stroke or urgent revascularization

Major bleeding no different at 48 h and 30 days
Pre-hospital GPIIbIIIa inhibitors - Primary PCI of STEMI

TIMI Flow 3 [% patients]

- Placebo: 5.4% at admission, 16.8% at end of procedure
- Abciximab: 86.7% at admission, 95.1% at end of procedure

Death, MI or urgent TVR [% patients]

- Stent plus placebo: 15.9% at 200 days
- Stent plus abciximab: 7.4% at 200 days

Montalescot G for the ADMIRAL Investigators. NEJM 2001
CANGRELOM: CHAMPION meta-analysis – STEMI subgroup

N=2,891 patients (11.6% of CHAMPION studies): Cangrelor (N=1,412) vs Clopidogrel (N=1,479)

GI 12.7%. Bivalirudin 25%; DES 53%; clopidogrel 600mg 89%; pretreatment 56%

MACEs (death, MI, IDR, ST) H48

Stent thrombosis H48

MACE H48 PCI for
STEMI (OR 0.84, 95% CI 0.55–1.27, p=0.4104)
NSTEACS (0.82, 0.68–0.99, p=0.0421)
stable angina (0.77, 0.64–0.93, p=0.0053)

no interaction between treatment effect and clinical presentation (interaction p=0.8663).

Patients undergoing primary PCI should receive a combination of DAPT with ASA and a P2Y₁₂ receptor blocker, as early as possible before angiography, and a parenteral anticoagulant.

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiplatelet therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA is recommended for all patients without contraindications at an initial loading dose of 150–300mg (or 80–150mg i.v.) and at a maintenance dose of 75–100mg daily to support the success of treatment strategy.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>A P2Y₁₂ inhibitor is recommended in addition to ASA continued over 12 months unless there are contraindications such as excessive risk of HIT. If so use:</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>• Prasugrel (60-mg loading dose, 10-mg dose) if no contraindication</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>• Ticagrelor 180-mg loading dose, 90 mg twice daily if no contraindication</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>• Clopidogrel (600-mg loading dose, 75 mg daily dose), only when prasugrel or ticagrelor are not available or are contraindicated</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>P2Y₁₂ inhibitors should be given at time of first medical contact.</td>
<td>I</td>
<td>B</td>
</tr>
</tbody>
</table>

European Heart Journal DOI 10.1093/eurheartj/ehu278
Meta-Analysis: Design
OBJECTIVES

To conduct a meta-analysis of randomized controlled trials (RCTs) comparing a strategy of P2Y12 inhibition before versus after (or during) PCI for STEMI.
METHODS

We pooled data from RCTs which
- compared early vs delayed P2Y12 inhibition in STEMI patients scheduled for PCI
- provided data on Major Adverse Cardiac Events (MACE), all cause death, and major bleeding

✓ Primary endpoint was MACE
✓ Secondary endpoints included definite ST, death, CV death, MI, Stroke, Urgent Target Vessel Revascularisation, minor and any bleeding.
✓ Additional surrogate endpoints: TIMI 2-3 flow rate before and after PCI, ST segment elevation resolution on the ECG before and after PCI, and use of GpIIbIIIa inhibitors.

All endpoints were analysed at shortest follow-up available.
DEFINITIONS: EARLY vs DELAYED strategy of P2Y12 inhibition

The “early strategy” was defined as follows

i) administration of the drugs before arrival of the STEMI patients in the catheterization laboratory (i.e., in the ambulance or in the emergency department or at a referring hospital), in comparison with the same drugs administered after arrival in the catheterization laboratory (delayed strategy) or

ii) administration in the catheterization laboratory before PCI of P2Y12 inhibitors rapidly active (i.e. intravenous P2Y12 inhibitors or prasugrel or ticagrelor) in comparison with clopidogrel used in the control arm (delayed strategy).
METHODS

The risk of bias: Cochrane Collaboration Tool (7 parameters).

DATA SYNTHESIS AND ANALYSIS

Mantel Hanszel fixed-effect model, confirmed with a random-effect model
Heterogeneity between trials: Q Cochran test (p cut-off value of 0.1 considered as significant). Probability values: two tailed with p=0.05 considered as significant.

The main analysis was performed on all RCTs (entire group of STEMI)
After assessment of heterogeneity, several sensitivity analyses were performed according to:
(1) The route of administration: IV vs. oral
(2) The type of drug: clopidogrel vs. new P2Y12 inhibitors
(3) Primary vs. secondary PCI.
9648 patients
9648 patients
6,914 primary PCI
6,694 oral drug
7,282 new P2Y12 inhib.

ATLANTIC ¹
LOAD and GO ²
PCI CLARITY ³
CIPAMI ⁴
CHAMPION PCI STEMI ⁵
CHAMPION PHOENIX ⁶
TRITON STEMI ⁷
ERASE MI ⁸

² Ducci K et al; Int J Cardiol 2013; 168(5): 4814-6.

*Data on STEMI patients from the 2 CHAMPION studies where pooled by the corresponding author and they were considered as one simple study for analysis
The overall risk of bias never exceeded 25%.

No publication bias was observed, with linear regression test of funnel plot asymmetry (p=NS for all explored outcomes).
ADDITIONAL ANALYSES ON REPERFUSION CRITERIA

- **TIMI flow 2-3 before PCI**
  - OR 1.12
  - CI95% (1-1.25)
  - $P=0.04$
  - Early 47.7%, Delayed 45.4%

- **Bail out GI use**
  - OR 0.87
  - CI95% (0.75-1)
  - $P=0.04$
  - Early 17.4%, Delayed 19.5%

**ST resolution (2 studies): NS**

**TIMI flow after PCI: NS**
Route of administration

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>« EARLY » group (n/N)</th>
<th>« DELAYED» group (n/N)</th>
<th>ODD RATIO (95% CI)*</th>
<th>Heterogeneity or trend X² p for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>7/2206 (0.0032%)</td>
<td>14/2199 (0.0064%)</td>
<td></td>
<td>0.26</td>
</tr>
<tr>
<td>Intravenous</td>
<td>16/1441 (0.0111%)</td>
<td>24/1513 (0.0159%)</td>
<td></td>
<td>0.61 (P=0.61)</td>
</tr>
</tbody>
</table>

Clopidogrel vs New i-P2Y12

<table>
<thead>
<tr>
<th>Treatment</th>
<th>« EARLY » group (n/N)</th>
<th>« DELAYED» group (n/N)</th>
<th>ODD RATIO (95% CI)*</th>
<th>Heterogeneity or trend X² p for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel</td>
<td>0/112</td>
<td>0/56</td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>New P2Y12 antagonist</td>
<td>23/3535 (0.0065%)</td>
<td>38/3656 (0.0104%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Primary vs secondary PCI

<table>
<thead>
<tr>
<th>PCI Type</th>
<th>« EARLY » group (n/N)</th>
<th>« DELAYED» group (n/N)</th>
<th>ODD RATIO (95% CI)*</th>
<th>Heterogeneity or trend X² p for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary PCI</td>
<td>23/3223 (0.0071%)</td>
<td>38/3295 (0.0115%)</td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>Secondary PCI</td>
<td>0/424 (0.0053%)</td>
<td>0/417 (0%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ALL PATIENTS

<table>
<thead>
<tr>
<th>« EARLY » group (n/N)</th>
<th>« DELAYED» group (n/N)</th>
<th>ODD RATIO (95% CI)*</th>
<th>Heterogeneity or trend X² p for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>23/3647 (0.0063%)</td>
<td>38/3712 (0.010%)</td>
<td>0.63 (0.38-1.06) (P=0.08)</td>
<td></td>
</tr>
</tbody>
</table>
CONCLUSION

This meta-analysis done on RCTs, regrouping nearly 10,000 STEMI patients shows that a strategy of early P2Y12 inhibition before revascularization:

1/ is associated with a significant **27% relative risk reduction of MACE** (p=0.0008), mainly driven by the **29% relative risk reduction of MI** (p=0.004) and to a lesser degree a reduction of stent thrombosis (NS)

2/ is safe, as it was **not associated with an increase of bleeding**
It was even associated with a **less frequent bailout use of GPI** (p=0.04)

3/ is associated with a **better coronary reperfusion before stenting** (TIMI flow grade 2-3)
LIMITATIONS

1. Those of the included studies, and those of the meta-analysis technique itself. However, we included only RCTs, or sub-analysis of RCTs, and we used formal analytic methods to decrease the risk of bias.

2. MACE definitions differed although several studies used common definitions.

3. The duration of follow-up also varied but we were mostly interested in short-term follow-up, when we expect a benefit from a strategy which shortens the time to effective P2Y12 inhibition. (Beyond 24 hours after PCI, both strategies had effective P2Y12 inhibition.)

4. Heterogeneity between studies may exist and was searched; we also provided results from both fixed and random effect models for all the endpoints.

5. Finally, although it is important to reduce MACE with no increase in bleeding rate, our meta-analysis did not show improved survival with this strategy.