MISTRAL

Myocardial Infarction with ST-elevation Treated by Primary Percutaneous Intervention Facilitated by Early Reopro Administration in Alsace

Pre-hospital abciximab initiation in STEMI. MISTRAL: a prospective controlled double blinded trial

Patrick Ohlmann

On behalf of MISTRAL Study Investigators
Hopitaux Universitaires de Strasbourg
FRANCE
Presenter disclosures

Patrick Ohlmann

• Research grants
  ▪ Eli Lilly
    (provided abciximab/placebo kits for the study)

• Speaker/consultant honoraria
  ▪ BMS, MSD, Schering Plough, Sanofi-Aventis
Background (1)

Beneficial effect of routine GP2b3a-inhibitors in STEMI

De Luca
JAMA 2005, 1759-1765

ESC recommandation: IIAB

MISTRAL study
### Background (2)

**Early vs. late GP2b3a-inhibitors in STEMI**

**Conflicting results**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Result</th>
<th>n</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADMIRAL, 2001</td>
<td>Rand. trial</td>
<td>+</td>
<td>78/300</td>
<td>Abcx./placebo</td>
</tr>
<tr>
<td>EUROTRANSFER, 2008</td>
<td>Registry</td>
<td>+</td>
<td>1650</td>
<td>Abcx. early/late</td>
</tr>
<tr>
<td>ON-TIME 2, 2008</td>
<td>Rand. trial</td>
<td>+</td>
<td>936</td>
<td>Tiro. early/Tiro. bail-out</td>
</tr>
<tr>
<td>FINESSE, 2007</td>
<td>Rand. trial</td>
<td>-</td>
<td>2452</td>
<td>Abcx. early/late</td>
</tr>
</tbody>
</table>

**FINESSE main limitation**

*per-protocol long* door to balloon time: median 132 min
Background (3)

ST segment resolution

- Easy to perform
- Powerful surrogate of myocardial perfusion
- Strong correlation with mortality

MISTRAL Study hypothesis

Improvement of ST segment resolution by early ambulance vs routine cathlab abciximab administration in STEMI patients undergoing primary PCI
MISTRAL Study design

- Investigator initiated study, NCT 00638638
- Sponsor: University Hospital of Strasbourg, France
- Prospective, multi-center
- Double blind
- Early vs late groups
  - Early abciximab: ambulance
    - Early abciximab (Ambulance)/ late placebo (Cathlab)
  - Late abciximab: cathlab
    - Early placebo (Ambulance)/ late abciximab (Cathlab)
  - 12 h abciximab infusion after 2\textsuperscript{nd} bolus in both groups
- Low dose heparin
  - 40 UI/kg bolus (max 3000 UI) in ambulance
  - 25-35 UI/kg bolus (according to ACT, max 3000 UI) at cathlab
- No clopidogrel pretreatment per protocol
MISTRAL METHODS
Endpoints

- **Primary endpoint**
  - Complete (>70%) ST resolution 60 minutes after PCI

- **Secondary endpoints**
  - Residual absolute ST segment elevation (in mm)
  - TIMI flow and TIMI fc pre- and post-PCI, Blush score
  - LVEF
  - Enzymatic infarct size
  - MACE (death, MI, TVR) at
    - 30 days
    - 6 months

**Independent ECG lab**: Pr. R Schroeder Berlin

**Independent angiographic Core Lab**: “Angio LAP” Paris-Creteil
## MISTRAL Methods
### Power calculation

**Sample size**

18% absolute increase proportion of patients with complete (i.e. > 70%) ST resolution in the ambulance group

<table>
<thead>
<tr>
<th></th>
<th>Cathlab</th>
<th>Ambulance</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST-resolution</td>
<td>26%</td>
<td>44%</td>
</tr>
</tbody>
</table>

alpha 5%, power 90%: 146 patients/group total of 292 patients

Amendment in may 2009 (due to slow enrolment)

alpha 5%, power 83%: **120 patients/group total of 240 patients**
MISTRAL study

Myocardial Infarction with ST-elevation treated by primary percutaneous intervention facilitated by early Reopro administration in Alsace

- Alsace (n=192)
  2 MICU, 3 cathlabs
    - Strasbourg
    - Mulhouse

Extended to
- Paris (n=57)
  4 MICU, 7 cathlabs

- Nancy (n=3)
  1 MICU, 1 cathlab

- Overall
  7 MICU, 11 cathlabs

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Participating centers

- **Strasbourg n=141**
  - MICU: Dr Reydel, Dr Bartier, Dr Weiss
  - Cathlab: Pr Ohlmann (PI), Dr Morel, Dr Zupan, Dr Bronner, Dr Faure

- **Mulhouse n=53**
  - MICU: Dr Wolff, Dr Rottner
  - Cathlab: Dr Jacquemin, Dr Monassier

- **Nancy n=3**
  - Dr Chouihed, Dr Angioi

- **Paris n=59**
  - **MICU**
    - Bobigny: Pr Adnet, Dr Lapostolle
    - La Pitié: Dr Ecollan
    - Aulnay: Dr Biens
    - Beaujon: Dr Belpomme
  - **Cathlabs**
    - La Roseraie: Drs Benhamer, Gaultier, Salengro (30)
    - Montfermeil: Dr Catan (8)
    - CCN: Dr Schmitt, Dr Guyon, Dr Chevalier (11)
    - Clinique Ambroise Parré: Dr Estagnasie (3)
    - Aulnay: Dr Montely (2) La Pitié Salpetrière : Pr Montalescot (4)
    - Bichat: Pr Steg (1)
MISTRAL study population

- 256 patients included (jan 2005 - may 2009)
- 21 drop out
  - Non confirmed MI (myocarditis, Tako-Tsubo): 5
  - Major protocol violations: 16
    (No death or major events in drop out patients)
- 235 cases available for analysis
## Patients baseline characteristics

### Risk factors

<table>
<thead>
<tr>
<th></th>
<th>Ambulance</th>
<th>In-Hospital</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>56.1 ± 11.9</td>
<td>57.7 ± 12.9</td>
<td>0.32</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>79</td>
<td>82</td>
<td>0.74</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>55</td>
<td>53</td>
<td>0.76</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>40</td>
<td>36</td>
<td>0.59</td>
</tr>
<tr>
<td>BMI</td>
<td>27±5</td>
<td>27±5</td>
<td>0.86</td>
</tr>
<tr>
<td>Obesity (%)</td>
<td>20</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Dyslipemia (%)</td>
<td>38</td>
<td>39</td>
<td>1</td>
</tr>
<tr>
<td>Type2 diabetes (%)</td>
<td>8.5</td>
<td>9.3</td>
<td>0.62</td>
</tr>
</tbody>
</table>

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### Patients characteristics

#### Antecedents

<table>
<thead>
<tr>
<th></th>
<th>Ambulance</th>
<th>In-hospital</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior MI (%)</td>
<td>5</td>
<td>3</td>
<td>0.54</td>
</tr>
<tr>
<td>Prior CABG (%)</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Prior PCI (%)</td>
<td>4</td>
<td>2</td>
<td>0.75</td>
</tr>
<tr>
<td>Prior stroke (%)</td>
<td>1</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>PVD (%)</td>
<td>3</td>
<td>2</td>
<td>0.68</td>
</tr>
<tr>
<td>COPD (%)</td>
<td>3</td>
<td>2</td>
<td>0.44</td>
</tr>
</tbody>
</table>
## Patients characteristics

### Presentation

<table>
<thead>
<tr>
<th></th>
<th>Ambulance</th>
<th>In-Hospital</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior location (%)</td>
<td>37.6</td>
<td>39</td>
<td>1</td>
</tr>
<tr>
<td>Killip class (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>91</td>
<td>91</td>
<td>0.51</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>&gt;1</td>
<td>8</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>TIMI risk score &gt;3</td>
<td>17 (14)</td>
<td>25 (21)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

*MISTRAL study*
Patients characteristics
Delays (medians in min)

Symptoms
MICU arrival
Rando.
Angio.
Balloon, stent

Door to balloon 103'

Symptoms - 1st bolus 115'

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## Patients characteristics

### PCI procedure

<table>
<thead>
<tr>
<th></th>
<th>Ambulance</th>
<th>In-Hospital</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of stents (%)</strong></td>
<td>0</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>70</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>21</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>DES (%)</strong></td>
<td>6</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td><strong>Direct stenting (%)</strong></td>
<td>53</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td><strong>Thrombectomy (%)</strong></td>
<td>10.3</td>
<td>14.3</td>
<td></td>
</tr>
</tbody>
</table>
Complete ST-Resolution post-PCI

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1ary endpoint (ECG lab)

Complete ST-resolution (%)

- Ambulance abcx.
- Cathlab abcx.

Pre-PCI

- Complete ST-resolution (Pre-PCI: 21%, Ambulance abcx., P=0.44)
- Complete ST-resolution (Pre-PCI: 15%, Cathlab abcx., P=0.44)

Post-PCI

- Complete ST-resolution (Post-PCI: 70%, Ambulance abcx., P=0.67)
- Complete ST-resolution (Post-PCI: 67%, Cathlab abcx., P=0.67)

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2ary endpoint (ECG lab)

Residual cumulative ST elevation (mm)

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Pre-PCI</th>
<th>Post-PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambulance abcx.</td>
<td>8.1</td>
<td>3.0</td>
</tr>
<tr>
<td>Cathlab abcx.</td>
<td>9.6</td>
<td>3.2</td>
</tr>
</tbody>
</table>

P-values:
- P=0.92
- P=0.17
- P=0.62
2ary endpoint (Corelab)

TIMI flow pre-PCI

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Distal embolisation / Slow flow

Corrected TIMIʃc (frames)

- **Distal embolisation**
  - Ambulance: 8 frames
  - Cathlab: 21 frames
  - $P = 0.008$

- **Slow flow**
  - Ambulance: 6 frames
  - Cathlab: 14 frames
  - $P = 0.066$

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2ary endpoint (Corelab)

TIMI flow post-PCI

- **P=0.077**
- **P=0.37**

**TIMI flow post (%)**

- Ambulance abcx.
- Cathlab abcx.

**TIMI 0**: 1, 3
**TIMI 1**: 6, 10
**TIMI 2-3**: 99, 96

**TIMI 0-1**: 1, 4

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2ary endpoint

BLUSH score

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**LVEF**

- **Ambulance abcx.**
- **Cathlab abcx.**

**P = 0.34**

<table>
<thead>
<tr>
<th>LVEF (%)</th>
<th>Ambulance</th>
<th>Cathlab</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>53</td>
<td>52</td>
</tr>
</tbody>
</table>
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2ary endpoint

Centralized biology
Infarct size

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MACE (%)

Ambulance abcx.
Cathlab abcx.

Troponin peak
CK peak
Troponin H72
BNP adm
BNP discharge

69 84
2296 2445
13 18
32 37
120 150

NS
2ary endpoint

MISTRAL study

Cumulative 30 days MACE

- Death
- MI
- TLR
- MACE
- Major bleed

P=NS

MACE (%): Ambulance abcx. vs Cathlab abcx.
2ary endpoint

Cumulative 6 month MACE

<table>
<thead>
<tr>
<th>Event</th>
<th>Ambulance abcx.</th>
<th>Cathlab abcx.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1.7</td>
<td>0.8</td>
</tr>
<tr>
<td>MI</td>
<td>2.6</td>
<td>0.8</td>
</tr>
<tr>
<td>TLR</td>
<td>6.0</td>
<td>9.3</td>
</tr>
<tr>
<td>MACE</td>
<td>10.3</td>
<td>11.0</td>
</tr>
<tr>
<td>Major bleed</td>
<td>0.9</td>
<td>1.7</td>
</tr>
</tbody>
</table>

P=NS
DISCUSSION (1)
Pre-procedural effect of early ambulance abciximab TIME matter?

Symptoms → MICU arrival → Rando. → Angio. → Balloon, stent

- Sympt. - 1st bolus 115'
- Sympt. - 1st bolus 165’ FINESSE
- Sympt. - 1st bolus 76’ ON TIME2

Door to balloon 103'
FINESSE: Door to balloon 132'
ON-TIME2: Door to balloon 80'

MISTRAL study
DISCUSSION (2)
Risk matter

• Abciximab is more effective in high risk patients
  - ADMIRAL, ACE trial
  - Eurotransfert registry: TIMI risk>3, Age>
  - De Luca Metaanalysis Eur H J 2009 p 2705

• MISTRAL: low risk patients
  – Very low mortality rate 1.28%
  – Young patients 56 yo
  – Low diabetes rate < 10%
  – Low Killip class (>1 in 8%)
  – Low TIMI risk score (>3 in 17%)
Conclusion (1)
MISTRAL STUDY

Early ambulance vs routine cathlab abciximab in STEMI-PCI

- Early ambulance vs. routine cathlab administration of abciximab in STEMI does not improve ST resolution post-PCI, final TIMI flow rate, LVEF, infarct size and MACE

- When given early after symptoms onset (median 90 min) early ambulance abciximab tends to improve TIMI 2-3 flow rates pre-PCI and to reduce slow flow and distal embolisation during procedure
  - Early abciximab tends to “facilitate” PCI procedure since more arteries are opened at the time of angio (45 vs 34 % TIMI2-3) and less embolisation or slow flow occurs during procedure
Conclusion (2) MISTRAL STUDY

Early ambulance vs routine cathlab abciximab in STEMI-PCI

- The MISTRAL study population was at low risk (mortality 1.25% only). This point may have impacted the results and reduced the potential benefit of early abciximab.

- Short- and long term benefit of routine use of abciximab in STEMI is already well established. MISTRAL study only addressed the issue of the optimal time of initiation of the drug.