Tirofiban vs. Abciximab during primary PCI in STEMI

M. Valgimigli, MD, PhD
On behalf of Multistrategy Investigators

ClinicalTrials.gov number, NCT00229515
Disclosures

- Speaker’s bureau: Iroko, Merck, Medicure
- Research grant: Iroko, Eli Lilly
- Advisory Board: Iroko, Eli Lilly, Medicine company
Background

There is limited data on the comparison between Abciximab vs. Tirofiban at high bolus dose (HDB: 25 µg/kg over 3 min)

- 4 RCTs have so far contrasted these two drugs in 719 pts undergoing PCI of whom less than 300 were recruited in the setting of STEMI

INCLUSION CRITERIA:
• Chest pain for >30 min with ST-segment elevation ≥ 1 mm in two or more contiguous leads, or with a new left bundle-branch block
• Admission either within 12 h of symptom onset or between 12 and 24 h after onset with evidence of continuing ischemia

EXCLUSION CRITERIA:
• Those related to controindications to the use of glycoprotein IIb/IIIa inhibitors

Trial Design
- Aspirin 160-325 mg orally or 250 mg intravenously, followed by 80-125 mg orally indefinitely
- Clopidogrel 300 mg orally and then 75 mg/day for at least 3 months
- Unfractioned Heparin (40-70 U/kg) Target ACT of at least 200 secs

No exclusion criteria based on:
• Haemodynamic Status
• Angiographic Findings
STEMI all-comer Patients
Aspirin + Clopidogrel + UFH
Before Arterial Sheath Insertion

Trial Design

1:1

1:1

Tirofiban*
Abciximab

SES
BMS
SES
BMS

Coronary Angiography±PCI
Stenting was the default strategy in pts with a RVD $\geq 2.5$ mm at visual estimation

*: given as a bolus of 25 $\mu$g/kg, followed by an 18-24 hour infusion at 0.15 $\mu$g/kg/min
Study Primary Endpoints

**Pharmacology Arm**

- Non-inferiority basis

\[ \geq 50\% \sum \text{ST segment elevation resolution within } 90' \text{ after last balloon inflation @ tt-EKG} \]

**Stent Arm**

- Superiority basis

Cumulative rate of MACE, defined as overall death, Reinfarction or TVR within 8 months

# Study Primary Endpoints

## Power Analysis

With 600 pts randomized and type I error set @2.5%

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Test</th>
<th>Abciximab</th>
<th>Tirofiban</th>
<th>SES</th>
<th>BMS</th>
<th>δ</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>Sup.</td>
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<td>—</td>
<td>16%</td>
<td>27%</td>
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<td>80%</td>
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* Assumed event rates

- $\geq \sum 50\%$ N-Inf.
- $>85\%$
- $\delta$:

$\geq \sum 50\%$ STR between Abciximab vs. placebo in the ACE trial (Antoniucci et al. J Am Coll Cardiol 2003)

*: ~50% of previously reported $\Delta \geq \sum 50\%$ STR
# Study Organization

<table>
<thead>
<tr>
<th>Sponsor:</th>
<th>University of Ferrara, <em>Italy</em></th>
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<tbody>
<tr>
<td>Data Management:</td>
<td>Medical Trial Analysis, <em>Switzerland</em></td>
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<td>Site and data monitoring:</td>
<td>Medical Trial Analysis, <em>Italy</em> ; Sermes C.R.O., <em>Spain</em></td>
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<td>Clinical Events Committee:</td>
<td>P. Agostoni (Chair), <em>Belgium</em>, E. Meliga, <em>The Netherlands</em>.</td>
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<td>ECG core lab:</td>
<td>MTA, C. Arcozzi (Chair)</td>
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<td>Angiographic core lab:</td>
<td>MTA, P. Malagutti (Chair)</td>
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<tr>
<td>DSMB:</td>
<td>P. Vranckx, (Chair), <em>Belgium</em></td>
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<td>Name</td>
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<td>A Rodriguez</td>
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<td>J Fernández</td>
<td>Huelva</td>
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<td>J Mieres</td>
<td>B Aires</td>
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</table>
1030 Patients Assessed for Eligibility

745 Randomized

72%  

285 Excluded
- 153 Not Meeting Inclusion Criteria
- 132 Refused to Participate

Abciximab and Uncoated Stent (n=186)

Abciximab and Uncoated Stent (n=186)

Tirofiban and Sirolimus-Stent (n=186)

Tirofiban and Sirolimus-Stent (n=186)

1:1:1:1

1 pt withdrew consent

99% received Abciximab
97% received PCI
90% received Abc+BMS
99% qualified as STEMI
3% non-interpretable ECG

100% received Abciximab
99% received PCI
87% received Abc+BMS
100% qualified as STEMI
2% non-interpretable ECG

100% received Tirofiban
98% received PCI
95% received Tir+BMS
99% qualified as STEMI
1% non-interpretable ECG

100% received Tirofiban
98% received PCI
89% received Abc+BMS
99.5% qualified as STEMI
4% non-interpretable ECG

N=186 N=186 N=186 N=186

ST Segment Resolution Study

N=179 N=182 N=184 N=177

8 month Follow-up Study
**ST Segment Resolution**

**Rationale for choosing this endpoint in STEMI**

- ST segment resolution correlates with infarct size and infarct transmurality as assessed at MRI or SPECT
  
  Jama 2005;293(9):1063-72.

- ST segment resolution has strong and independent prognostic implications in terms of both death or the composite of death or MI
  
  Lancet 1997;350(9078):615-9

- Interventions in STEMI which improve ST segment resolution have a consistent effect on outcomes and viceversa
  
  J Am Coll Cardiol 2003;42(11):1879-85
  Jama 2005;293(9):1063-72.
ST Segment Resolution
Internal Validity Assessment of the Chosen 1° Endpoint

P=0.023 at Log Rank test

ST-Res ≥50%

ST-Res <50%

Days after Randomization

Death/MI Free Survival (%)

0 20 40 60 80 100 120 140 160 180 200 220 240 260
ST Segment Elevation

P=0.78

Σ ST segment (mm)

Number of ECG leads with ↑ ST

P=0.62
Primary Endpoint
\[ \geq 50\% \sum \text{ST segment resolution} \]

Abciximab vs. Tirofiban

\[ P < 0.001 \text{ for non-inferiority}^* \]

\[ *: \text{at ITT and PP Analysis} \]
**1° Endpoint:** ≥50% ST segment resolution

Subgroup Analysis

<table>
<thead>
<tr>
<th>Risk Ratio (95% CI)</th>
<th>Primary End Point</th>
<th>P-Value</th>
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</thead>
<tbody>
<tr>
<td>Tirofiban %</td>
<td>Abciximab %</td>
<td>Non-Inferiority</td>
</tr>
<tr>
<td>85.3</td>
<td>83.6</td>
<td>0.001</td>
</tr>
<tr>
<td>86.6</td>
<td>84.6</td>
<td>0.002</td>
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<tr>
<td>84.5</td>
<td>82.3</td>
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<td>86.0</td>
<td>81.9</td>
<td>&lt;0.001</td>
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<tr>
<td>82.4</td>
<td>88.5</td>
<td>0.37</td>
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<tr>
<td>84.6</td>
<td>80.0</td>
<td>0.059</td>
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<tr>
<td>85.2</td>
<td>84.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>86.5</td>
<td>84.9</td>
<td>&lt;0.001</td>
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<tr>
<td>77.0</td>
<td>78.9</td>
<td>0.22</td>
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<tr>
<td>84.8</td>
<td>82.7</td>
<td>0.002</td>
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<tr>
<td>85.9</td>
<td>84.6</td>
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<tr>
<td>85.2</td>
<td>85.8</td>
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<tr>
<td>87.2</td>
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<td>84.2</td>
<td>72.8</td>
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<tr>
<td>79.6</td>
<td>71.9</td>
<td>&lt;0.001</td>
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<tr>
<td>89.4</td>
<td>92.1</td>
<td>0.01</td>
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<tr>
<td>84.7</td>
<td>88.4</td>
<td>0.004</td>
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<tr>
<td>85.6</td>
<td>85.1</td>
<td>0.001</td>
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<tr>
<td>85.8</td>
<td>76.3</td>
<td>&lt;0.001</td>
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**Endpoint:** ≥50% ST segment resolution
ECG Analysis
Core Lab Evaluation

N=722

Tirofiban: 85.3%
Abciximab: 83.6%

Percentage of ST segment resolution at 90'
30-Day Outcomes
Efficacy Endpoints
(CEC adjudicated)

- MACE: 4%
  - Abciximab: P=0.85
  - Tirofiban: P=0.98

- Death/MI: 2.5%
  - Abciximab: P=0.59
  - Tirofiban: P=0.56

- uTVR: 1%
  - Abciximab: P=0.59
  - Tirofiban: P=0.56

- Definite: 4%
  - Abciximab: P=0.22
  - Tirofiban: P=0.22

- Def/Prob: 4%
  - Abciximab: P=0.22
  - Tirofiban: P=0.22

Stent Thrombosis (ARC)
30-Day Outcomes
Safety Endpoints
(DSMB adjudicated)

- Major TIMI-Bleeding: P=0.44
- Minor TIMI-Bleeding: P=0.40
- RBC Transfusion: P=0.82
- Severe Thrombocytopenia: P=0.03
- Any Thrombocytopenia: P=0.004

Valgimigli et al, JAMA 2008
Does Thrombocytopenia impact on patient outcome?

- PLT <100K
  - Death: >5X (P=0.002)
  - Death/MI: ~3.5X (P=0.008)
  - MACE: >2.5X (P=0.023)

- PLT >100K
  - Death: ~3.5X (P=0.008)
  - Death/MI: >2.5X (P=0.023)
Rate of thrombocytopenia was 0.8% in tirofiban vs. 4.0% in abciximab group, p=0.004
8 Month Outcomes

MACE

(CEC adjudicated)

Valgimigli et al, JAMA 2008
8 Month Outcomes

Death/MI (CEC adjudicated)

Probability of Death or Myocardial Infarction (%)

Days after Randomization

Valgimigli et al, JAMA 2008
ARC Stent Thrombosis

(CEC adjudicated)

Valgimigli et al, JAMA 2008
Similar Short and long-term anti-ischemic effect

Meta-analysis of 7 RCT including 2,213 pts

<table>
<thead>
<tr>
<th></th>
<th>Abciximab</th>
<th>Tirofiban</th>
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<tbody>
<tr>
<td><strong>Death 30 Days</strong></td>
<td>1.3</td>
<td>1.8</td>
</tr>
<tr>
<td><strong>OR= 0.69</strong></td>
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<tr>
<td><strong>P=0.29</strong></td>
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<tr>
<td><strong>Death/MI 30 Days</strong></td>
<td>3.5</td>
<td>4.1</td>
</tr>
<tr>
<td><strong>OR= 0.87</strong></td>
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<td><strong>P=0.52</strong></td>
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<tr>
<td><strong>Death 8/12 Mos</strong></td>
<td>5.5</td>
<td>6.6</td>
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<tr>
<td><strong>OR= 0.82</strong></td>
<td></td>
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<tr>
<td><strong>P=0.29</strong></td>
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Pharmaco-economic Analysis

- Drug utilization and major procedural resources between groups were similar;
- Duration of HDB tirofiban infusion was longer 19.97h v. 11.44h (p<0.0001) whereas, amount of Glycoprotein inhibitor and number of required vials of drug was higher for Abciximab

\[ \Delta: 530/\text{patient}; 100,000 \text{ every 188 treated pt} \]
Summary

Our study provides evidence that in a broad population of largely unselected patients undergoing angioplasty for ST-elevation myocardial infarction:

- Tirofiban enables non-inferior STR within 90’ after intervention and similar outcomes at 8 months than Abciximab
- The safety profile favoured the use of tirofiban for a lower incidence of thrombocytopenia which has prognostic implications
- Tirofiban appeared a more cost-efficient drug than abciximab