Adjunctive Platelet GP IIb/IIIa Receptor Inhibition with Tirofiban before Primary Angioplasty Improves Angiographic Outcomes: Results of the TIGER-PA Pilot Trial

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Stanford University School of Medicine
“Prejunctive” Therapy

- A strategy to promote very early patency for some patients (drug responders) and very high final patency rates (assured by PTCA) for all patients

*Antithrombin agents, antiplatelet agents, and fibrinolytic agents.
Plasminogen-activator Angioplasty Compatibility Trial (PACT)

- Multicenter, randomized, double-blind trial
- 606 AMI patients
- ≤ 75 years old, low-risk infarctions
- 50 mg IV bolus of rtPA vs placebo
- Rescue PTCA if TIMI-3 flow not immediately achieved

### PACT

**Reperfusion, LV function, and adverse events**

<table>
<thead>
<tr>
<th></th>
<th>rtPA (n=302)</th>
<th>Placebo (n=304)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI-3 flow immediately following drug treatment</td>
<td>33%</td>
<td>15%</td>
</tr>
<tr>
<td>%LVEF immediately following drug treatment</td>
<td>$59.4 \pm 13.8$&lt;sup&gt;1&lt;/sup&gt;</td>
<td>$57.7 \pm 14.1$&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>TIMI-3 flow achieved following rescue PTCA</td>
<td>78.6%&lt;sup&gt;3&lt;/sup&gt;</td>
<td>80.5%&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rate of major hemorrhaging</td>
<td>12.9%</td>
<td>13.5%</td>
</tr>
</tbody>
</table>

1 ventriculogram available for analysis for only 220 patients
2 ventriculograms available for analysis for only 224 patients
3 in 169 patients with TIMI 0, 1, or 2 flow after drug treatment
4 in 231 patients with TIMI 0, 1, or 2 flow after drug treatment
<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>t-PA</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>12.9%</td>
<td>13.5%</td>
<td>0.84</td>
</tr>
<tr>
<td>Stroke (any)</td>
<td>0.7%</td>
<td>0.7%</td>
<td>0.99</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>0.3%</td>
<td>0.3%</td>
<td>0.99</td>
</tr>
<tr>
<td>Emergency revascularization</td>
<td>7.3%</td>
<td>7.2%</td>
<td>0.98</td>
</tr>
<tr>
<td>Hospital death</td>
<td>3.6%</td>
<td>3.0%</td>
<td>0.64</td>
</tr>
<tr>
<td>30-day death</td>
<td>3.6%</td>
<td>3.3%</td>
<td>0.81</td>
</tr>
</tbody>
</table>

Patency of the Infarct Artery on Catheter Laboratory Arrival (Core Laboratory)


*All comparisons P<0.001.
Fibrinolytic + GP IIb/IIIa inhibitor

% pts with TIMI 3 Flow

- Lytic alone
- Combination

- GUSTO I 90 min
- T14 tPA 90 min
- T14 rPA 90 min
- SPEED 60-90 min
- INTRO-AMI 60 min
- Pooled 60-90 min

Stanford
GUSTO-V
Primary Endpoint: 30 Day Death

% Mortality

p = 0.43 for superiority
Non-Inferiority RR 0.95
(95% CI, 0.84-1.08)

Days

Lancet 2001; 357:1905-14

Std. Reteplase (n = 8260)
Abciximab + ↓ Dose Reteplase (n = 8328)
GUSTO V: ICH by Age Group

- **Std. Dose Reteplase (n = 8260)**
- **Abciximab + ↓ Dose Reteplase (n = 8328)**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Std. Dose</th>
<th>Abciximab + ↓ Dose</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 70 yrs</td>
<td>0.4/6230</td>
<td>0.3/6193</td>
<td>0.66</td>
</tr>
<tr>
<td>&gt; 70 yrs</td>
<td>1.2/2030</td>
<td>1.5/2135</td>
<td>0.53</td>
</tr>
<tr>
<td>≤ 75 yrs</td>
<td>0.5/7172</td>
<td>0.4/7179</td>
<td>0.27*</td>
</tr>
<tr>
<td>&gt; 75 yrs</td>
<td>1.1/1088</td>
<td>2.1/1149</td>
<td>0.069*</td>
</tr>
</tbody>
</table>

* Significant treatment interaction for the age 75 dichotomy; p = 0.033; * Significant treatment interaction for the age 75 dichotomy; p = 0.033; * Significant treatment interaction for the age 75 dichotomy; p = 0.033;

*Lancet* 2001; 357:1905-14
ReoPro in Acute myocardial infarction and Primary PTCA Organization Randomized Trial

- N=483
- Abciximab in the ER or Cath Lab

<table>
<thead>
<tr>
<th></th>
<th>30-day MACE (n=409)</th>
<th>Int to treat (n=483)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>12.0</td>
<td>11.2</td>
</tr>
<tr>
<td>Abciximab</td>
<td>4.6</td>
<td>5.8</td>
</tr>
<tr>
<td>P value</td>
<td>0.005</td>
<td>0.038</td>
</tr>
</tbody>
</table>

- 6 month MACE: no difference
**ADMIRAL**

Abciximab before Direct angioplasty and stenting in Myocardial Infarction Regarding Acute and Long-term follow-up

<table>
<thead>
<tr>
<th>Event</th>
<th>*Abciximab (n=150)</th>
<th>Placebo (n=150)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, MI, urgent TVR at 30 d</td>
<td>10.7%</td>
<td>20.0%</td>
<td>0.03</td>
</tr>
<tr>
<td>*26% received in ambulance or ER</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI-3 initial</td>
<td>21%</td>
<td>10%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>24 h</td>
<td>86%</td>
<td>78%</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>LVEF 24 h</td>
<td>55%</td>
<td>51%</td>
<td></td>
</tr>
<tr>
<td>30 d</td>
<td>63%</td>
<td>55%</td>
<td></td>
</tr>
</tbody>
</table>
Tirofiban Given in the Emergency Room before Primary Angioplasty (TIGER-PA) Pilot Study

David P. Lee, M.D., Alan C. Yeung, M.D., Donald Schreiber, M.D., Michelle Huston, M.D.
Acute myocardial infarction

Meets inclusion criteria

Tirofiban in ER

Angiogram

PTCA/stent

Final angiogram

No PTCA if lesion <50%

No PTCA

No tirofiban in ER

Angiogram

Tirofiban if PTCA to be performed

Final angiogram

No PTCA
• Dosing
  – Tirofiban: 10 µg/kg over 3 minutes, then 0.15 µg/kg/min x 24 hours
  – Heparin
    • Early: 70U/kg IV bolus, then 7.5 U/kg/hr
    • Delayed: 100U/kg IV bolus, then 10 U/kg/hr
  – All other medications including NTG, β-blockers at the investigator’s discretion
• Endpoints
  – Primary endpoint
    • TIMI flow
    • TIMI frame counts
  – Secondary endpoint
    • Bleeding
      – minor: Hct ↓ ≥10% or Hb↓ ≥3g/dl
      – major: Hct ↓ ≥15% or Hb↓ ≥5g/dl
      – Thrombocytopenia (PLTs< 90000)
• **Endpoints**
  
  – Tertiary endpoint (30 days)
    • Repeat coronary revascularization
      – urgent vs. nonurgent
    • Death (from any cause)
    • New MI (CPK>2x normal)
    • Hospitalization for refractory ischemia
• Adjuvant therapy

  – If a stent is placed, ticlopidine 250 mg POBID or clopidogrel 75 mg POQD x ≥ 14 d

  – Heparin may be stopped temporarily for early sheath removal
• Data analysis
  – Primary endpoint
    • Blinded observer for TIMI frame count and flow at baseline and after PTCA
  – Secondary endpoint
    • Data monitoring for CBC and CPKs
    • Safety monitor for bleeding events
  – Tertiary endpoint
    • Clinical follow-up by chart review and telephone
TIGER-PA

Pilot

Demographics

• N=100

• Patients screened
  – Declined enrollment 32
  – Shock/IABP 9
  – Signif comorbidities 14
  – Recent IIb/IIIa 2

50 ER, 50 cath lab

157
## Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Early</th>
<th>Late</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>63.5 ± 12.6</td>
<td>66.4 ± 14.3</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (%male)</td>
<td>60</td>
<td>64</td>
<td>NS</td>
</tr>
<tr>
<td>%Diabetes</td>
<td>24</td>
<td>24</td>
<td>NS</td>
</tr>
<tr>
<td>%HTN</td>
<td>36</td>
<td>40</td>
<td>NS</td>
</tr>
<tr>
<td>%Hyperlipidemia</td>
<td>32</td>
<td>32</td>
<td>NS</td>
</tr>
<tr>
<td>%Prev CAD</td>
<td>12</td>
<td>10</td>
<td>NS</td>
</tr>
</tbody>
</table>
### TIGER-PA Pilot

#### Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Early</th>
<th>Late</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP duration (h)</td>
<td>3.0 ± 2.0</td>
<td>3.0 ± 1.8</td>
<td>NS</td>
</tr>
<tr>
<td>Door-to-tirofiban (min)</td>
<td>55.7 ± 18.0</td>
<td>81.8 ± 17.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Door-to-balloon (min)</td>
<td>88.9 ± 20.7</td>
<td>82.7 ± 20.0</td>
<td>NS</td>
</tr>
</tbody>
</table>

33 minute mean from drug-to-balloon
## Angiographic Outcomes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Early</th>
<th>Late</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culprit Vessel (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>40</td>
<td>36</td>
<td>NS</td>
</tr>
<tr>
<td>LCX</td>
<td>20</td>
<td>20</td>
<td>NS</td>
</tr>
<tr>
<td>RCA</td>
<td>40</td>
<td>44</td>
<td>NS</td>
</tr>
<tr>
<td>Initial TGF (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>32</td>
<td>10</td>
<td>0.007</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>44</td>
<td>80</td>
<td></td>
</tr>
</tbody>
</table>
## Angiographic Outcomes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Early</th>
<th>Late</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial CTFC</td>
<td>44 ± 20</td>
<td>66 ± 23</td>
<td>0.005</td>
</tr>
<tr>
<td>% Initial TMPG-3</td>
<td>32</td>
<td>6</td>
<td>0.001</td>
</tr>
<tr>
<td>% Final TGF-3</td>
<td>92</td>
<td>92</td>
<td>NS</td>
</tr>
<tr>
<td>Final CTFC</td>
<td>18 ± 8</td>
<td>16 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>% Final TMPG-3</td>
<td>50</td>
<td>40</td>
<td>NS</td>
</tr>
</tbody>
</table>
TIGER-PA
Pilot

Initial TIMI-Grade Flow

* $P < 0.007$

# Patients

<table>
<thead>
<tr>
<th>#</th>
<th>Early</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI-3</td>
<td>32%</td>
<td>10%</td>
</tr>
<tr>
<td>TIMI-2</td>
<td>14%</td>
<td>8%</td>
</tr>
<tr>
<td>TIMI-0 or 1</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>
TIGER-PA Pilot

Initial CTFC

* $P = 0.005$

Early CTFC: 44 ± 20
Late CTFC: 66 ± 23
Initial TIMI-Myocardial Perfusion Grade

* $P < 0.001$

- **Early**
  - TMPG-3: 32%
  - TMPG-2: 16%
  - TMPG-0 or 1: 12%

- **Late**
  - TMPG-3: 6%
  - TMPG-2: 12%
  - TMPG-0 or 1: 12%

TIGER-PA

Pilot
## TIGER-PA Pilot

### Clinical Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Early</th>
<th>Late</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak CPK</td>
<td>1924 ±</td>
<td>2260 ± 1959</td>
<td>NS</td>
</tr>
<tr>
<td>Time-to-peak</td>
<td>10.0 ± 7.1</td>
<td>11.1 ± 6.5</td>
<td>NS</td>
</tr>
<tr>
<td>30-d Composite</td>
<td>6%</td>
<td>10%</td>
<td>NS</td>
</tr>
<tr>
<td>Death</td>
<td>2%</td>
<td>2%</td>
<td>NS</td>
</tr>
<tr>
<td>Re-MI</td>
<td>0</td>
<td>2%</td>
<td>NS</td>
</tr>
<tr>
<td>Rehosp</td>
<td>4%</td>
<td>6%</td>
<td>NS</td>
</tr>
<tr>
<td>Urgent TVR</td>
<td>0%</td>
<td>2%</td>
<td>NS</td>
</tr>
</tbody>
</table>
**TIGER-PA**

*Pilot*

### Clinical Outcomes

<table>
<thead>
<tr>
<th></th>
<th>ER</th>
<th>Cath Lab</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Minor bleeding</em></td>
<td>10%</td>
<td>6%</td>
<td>NS</td>
</tr>
<tr>
<td><em>Major bleeding</em></td>
<td>2%</td>
<td>2%</td>
<td>NS</td>
</tr>
<tr>
<td>Transfusions</td>
<td>10%</td>
<td>8%</td>
<td>NS</td>
</tr>
<tr>
<td>PLT &lt; 100K</td>
<td>4%</td>
<td>0%</td>
<td>NS</td>
</tr>
</tbody>
</table>

*TIMI-defined*
GP IIb/IIIa Summary

• GP IIb/IIIa receptor inhibitors may be beneficial as an adjunct in AMI treated with primary angioplasty
• Safe and well-tolerated
• Is there a long-term benefit?
ON-TIME

Trial Design: ON-TIME was a randomized trial of early (in ambulance or referral center; n=251) vs delayed (in the catheterization lab; n=256) tirofiban therapy in patients with ST elevation myocardial infarction undergoing percutaneous coronary intervention (PCI). The primary endpoint was TIMI grade 3 flow at initial angiography.

**TIMI grade 3 flow**
- **p=0.22**

**TIMI grade 2/3 flow**
- **p=0.04**

---

**Results**
- In early therapy arm, tirofiban administered mean of 59 minutes earlier than in late therapy arm
- No difference between treatment arms in primary endpoint of TIMI grade 3 flow, but patency (TIMI 2 or 3 flow) ↑ in early tirofiban arm (Figure)
- Thrombus presence ↓ in early tirofiban arm (25% vs 32%, p=0.06)
- No difference in post-PCI TIMI flow grade 3 (89% vs 91%), TIMI frame count (27 vs 26 frames) or myocardial blush grade 3 (51% vs 53%)

**Conclusions**
- Among ST elevation MI patients undergoing PCI, early administration of tirofiban therapy was not associated with a difference in primary endpoint of TIMI flow grade 3 compared with cath lab administration of tirofiban, but early therapy was associated with ↑ in patency (TIMI flow grade 2/3) and ↓ in thrombus

Presented at ESC 2003

www.cardiosource.com
On-Time

Trends positive:
- Thrombus 60% vs 73%
- Blush before PCI 30% vs 22%
- Ambulance patients mortality 3.7% vs 4.5%
ADVANCE-MI

\[
\uparrow \text{ST / LBBB} \\
\text{n = 5640}
\]

Eptifibatide + 1/2 TNK \hspace{1cm} \text{Eptifibatide}

Primary angioplasty (LMWH or UFH)

Primary endpoint at 30 days: death or left ventricular failure
Study design

**Randomise AMI open label**

ASA UFH (bolus)
TNK (Group A)

ASA UFH (bolus)
No lytic (Group B)

n = 2000

**Cath lab**

Angiography / PCI (immediate)

Stent / clopidogrel (optional)

Heparin as routinely used

NO GP IIb/IIIa inhibitors, (only bail-out at investig. discretion)

Angiography / PCI (immediate)

Stent / clopidogrel (optional)

Heparin as routinely used

GP IIb/IIIa inhibitors can be used at investig. discretion

n = 2000
CARESS IN AMI
(Combined Abciximab RE-teplase Stent Study in Acute Myocardial Infarction)

N = 1800
AMI < 12 h

Medical Treatment
Half dosage r-PA 5 IU 30 min interval plus full dose abciximab during 12 hours
Transfer for PTCA only if Sustained ischemia < 50% ST segment resolution

Facilitated angioplasty
Half dosage r-PA 5 IU 30 min interval plus full dose abciximab during 12 hours
Direct transfer for facilitated angioplasty

Primary endpoint at 30 days
Mortality, re-infarction and refractory ischemia
FINESSE

↑ ST / LBBB

- Abciximab + 1/2 rt-PA
- Abciximab before angio
- Abciximab after angio

Primary angioplasty (LMWH or UFH)

Primary endpoint at 30 days: death or left ventricular failure
TITAN: Design Overview

N = 300

ST Elevation MI < 6 hrs

ASA, heparin

Randomize open label

Time 0

ED initiation of eptifibatide

Cath lab initiation of eptifibatide

Ascertain TIMI Flow Grade (1° Endpt)
Immediate, obligatory PCI if feasible

IC Adenosine for CFR calculation

Angiographic Flow and Perfusion Scoring

In hospital and 30 day clinical follow-up

Angiographic Flow and Perfusion Scoring
TITAN: Study Procedures

STEMI < 6 HRS

ASA 160-325 mg pO
HEPARIN 60 U/kg bolus (Max 4000U) and 7U/kg infusion (Max 800 U/hr)

N = 300

"EARLY EPTIFIBATIDE"
EPTIFIBATIDE 180/2.0/180
TRANSFER TO CATH LAB
DIAGNOSTIC ANGIO

"RANDOMIZE = TIME ZERO"

"CATH LAB EPTIFIBATIDE"
TRANSFER TO CATH LAB
DIAGNOSTIC ANGIO
EPTIFIBATIDE 180/2.0/180

ASCERTAIN PRIMARY ENDPOINT (TIMI Flow) & PERFORM PCI

ANGIOGRAPHIC PERFUSION SCORE
TITAN: 01-26-2004

TIMI FLOW AND CORONARY FLOW RESERVE

IN-HOSPITAL AND 30 DAY CLINICAL EVENTS
What are the issues in Prejunctive Therapy?

- The increase perfusion with IIbIIIa inhibitor is small but consistent so far.
- Will increase dose (different IIbIIIa) improve the results?
- Will giving it in the ambulance provides better reperfusion?
- Will use of LMWH or direct thrombin inhibitor helps?

Stay tune.....TIGER-PA 2