ON-TIME-2
Ongoing-Tirofiban In Myocardial Infarction Evaluation
1 Year Follow-Up
Trial Design
(Registration: ISRCTN 06195297)

Multicenter, prospective, randomized, international

Analysis: ITT
End-points adjudicated (CEC)

Investigator initiated and driven
Unrestricted grant from Merck and Iroko
Trial Leadership

Co-Principle Investigators
Arnoud van t´Hof
Christian W. Hamm
Jurriën M. ten Berg

Steering Committee
P. Stella
L. van den Merckhoff
T. Dill (Germany, MRI)
G. Giannitsis (biomarker)
J. Brachmann
S. Guptha

CRO
Diagram B.V., J. Klijn
Ongoing Tirofiban In Myocardial Infarction Evaluation

Study Phases

**Open Label**
- June 2004 – June 2006
- N=414
- 2 centres
- Netherlands
- HBD Tirofiban or no Tirofiban
- 600 mg Clopidogrel, heparine, ASA

**Double Blind**
- June 2006 – Nov 2007
- N=984
- 24 centres
- Netherlands, Germany, Belgium
- HBD Tirofiban or Placebo
- 600 mg Clopidogrel, heparine, ASA
**Inclusion criteria**
- Chest pain > 30 min but less than 24 hours
- ST ↑ in 2 contiguous leads: > 0.2 mV (anterior MI) or 0.1 mV (non-anterior MI)

**Exclusion criteria**
- Age > 85 yrs
- Women < 50 yrs
- Lytic therapy < 24 hrs
- Coumadin < 7 days
- C.I to 2b/3a blockade
- Killip IV
- Hemodialysis
Acute myocardial infarction diagnosed in ambulance or referral center
ASA+600 mg Clopidogrel

**Placebo**
- Transportation
  - Angiogram
  - Tirofiban provisional

**Tirofiban**
- Transportation
  - PCI centre
    - Angiogram
  - PCI
    - Tirofiban cont’d

*Bolus: 25 µg/kg & 0.15 µg/kg/min infusion*
Endpoints

**Primary**
- Residual ST segment deviation (>3mm) 1 hour after PCI

**Key Clinical Secondary**
- Combined occurrence of death, recurrent MI, urgent TVR or thrombotic bailout at 30 days follow-up
- Safety (major bleeding)
- Death at 1 year follow-up
## Baseline Data

<table>
<thead>
<tr>
<th></th>
<th>Open Label</th>
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<tbody>
<tr>
<td></td>
<td><em>(n=414)</em></td>
</tr>
<tr>
<td>Age (mean, yr)</td>
<td>62</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>77</td>
</tr>
<tr>
<td>Prev MI (%)</td>
<td>11</td>
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<tr>
<td>Diabetes (%)</td>
<td>11</td>
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<tr>
<td>Hypertension (%)</td>
<td>34</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>48</td>
</tr>
<tr>
<td>Anterior MI (%)</td>
<td>45</td>
</tr>
<tr>
<td>Killip &gt; 1 (%)</td>
<td>13</td>
</tr>
<tr>
<td>Ambulance RX (%)</td>
<td>98</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Double Blind</th>
</tr>
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<tbody>
<tr>
<td></td>
<td><em>(n=984)</em></td>
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<tr>
<td>Age (mean, yr)</td>
<td>62</td>
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<tr>
<td>Male gender (%)</td>
<td>76</td>
</tr>
<tr>
<td>Prev MI (%)</td>
<td>9</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>12</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>34</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>47</td>
</tr>
<tr>
<td>Anterior MI (%)</td>
<td>42</td>
</tr>
<tr>
<td>Killip &gt; 1 (%)</td>
<td>12</td>
</tr>
<tr>
<td>Ambulance RX (%)</td>
<td>95</td>
</tr>
</tbody>
</table>
Ischemic Time

Open Label
- 77 minutes
- 65 minutes
- 17 minutes

Double Blind
- 76 minutes
- 69 minutes
- 16 minutes

Ischemic Time (min)

- SO-Diagnosis
- Diagnosis-Angio
- Angio-Balloon
Prehospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (On-TIME 2): a multicentre, double-blind, randomised controlled trial

Amoud WJ van’t Hof, Jurrien ten Berg, Ton Heestermans, Thorsten Dill, Reinhard C Funck, Wouter van Werkum, Jan-Henk E Dambrink, Harry Suryapranata, Gert van Houwelingen, Jan Paul Ottervanger, Pieter Stella, Evangelos Giannitsis, Christian Hamm, on behalf of the Ongoing Tirofiban In Myocardial infarction Evaluation (On-TIME) 2 study group*

Summary
Background: The most effective magnitude and timing of antiplatelet therapy is important in patients with acute...
Residual ST Deviation after PCI

Open Label

- Tirofiban: 18% (3.9±6.5 mm, p=0.097)
- No Tirofiban: 27% (4.6±5.4 mm)

Double Blind

- Tirofiban: 19% (3.6±4.6 mm, p=0.003)
- No Tirofiban: 25% (4.8±6.3 mm)

The graph shows the percentage of patients with different levels of residual ST deviation after PCI, comparing Tirofiban and no Tirofiban treatments in both open label and double blind studies.
All-Cause Mortality 30 Days

- **Ongoing Tirofiban In Myocardial Infarction Evaluation**
- **Open label & double-blind, n = 1398**
- **p-value = 0.051**
All-Cause Mortality 1-Year

open label & double-blind, n = 1398

P = 0.077
Ongoing Tirofiban In Myocardial Infarction Evaluation

**All cause Mortality 1 Year**

**Double Blind**

- Placebo: 5.3
- Tirofiban: 3.4

RR: 0.78 (95% CI: 0.53-1.14, p=0.157)  
N=984

**Open Label**

- Placebo: 7.0
- Tirofiban: 4.4

RR: 0.77 (95% CI: 0.46-1.29, p=0.276)  
N=414
All cause Mortality and AMI 1 Year

Double Blind
N=984

Placebo: 8.1
Tirofiban: 6.6

-19%

Open Label
N=414

Placebo: 9.1
Tirofiban: 5.4

-41%
1 Year Survival: Patients with Primary PCI

100%

95%

90%

85%

80%

Event free survival

Days after randomization

open label & double-blind, n = 1.155

P = 0.007
### Ongoing Tirofiban In Myocardial Infarction Evaluation

<table>
<thead>
<tr>
<th></th>
<th>Tirofiban</th>
<th>Placebo</th>
<th>Death within One Year</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>no./total no.</td>
<td></td>
<td>Risk Ratio, 95% Confidence Interval</td>
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<tr>
<td>All patients</td>
<td>25/670</td>
<td>38/656</td>
<td>0.64 (0.39 - 1.05)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>9/154</td>
<td>12/164</td>
<td>0.80 (0.35 - 1.84)</td>
</tr>
<tr>
<td>Male</td>
<td>16/516</td>
<td>26/492</td>
<td>0.59 (0.32 - 1.08)</td>
</tr>
<tr>
<td>Age(years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;= 61.6</td>
<td>7/337</td>
<td>6/327</td>
<td>1.13 (0.38 - 3.33)</td>
</tr>
<tr>
<td>&gt; 61.6</td>
<td>18/333</td>
<td>32/329</td>
<td>0.56 (0.32 - 0.97)</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>20/595</td>
<td>29/585</td>
<td>0.68 (0.39 - 1.18)</td>
</tr>
<tr>
<td>Yes</td>
<td>5/75</td>
<td>9/69</td>
<td>0.51 (0.18 - 1.45)</td>
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<tr>
<td>Location</td>
<td></td>
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<tr>
<td>Anterior MI</td>
<td>12/253</td>
<td>20/259</td>
<td>0.61 (0.31 - 1.23)</td>
</tr>
<tr>
<td>Non anterior MI</td>
<td>11/343</td>
<td>14/331</td>
<td>0.76 (0.35 - 1.65)</td>
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<tr>
<td>Killip &gt; 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>15/587</td>
<td>19/554</td>
<td>0.75 (0.38 - 1.45)</td>
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<tr>
<td>Yes</td>
<td>6/69</td>
<td>18/87</td>
<td>0.42 (0.18 - 0.96)</td>
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<tr>
<td>Timi flow grade before PCI</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0-2</td>
<td>16/473</td>
<td>30/491</td>
<td>0.55 (0.31 - 0.99)</td>
</tr>
<tr>
<td>3</td>
<td>2/134</td>
<td>3/116</td>
<td>0.58 (0.10 - 3.39)</td>
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<tr>
<td>Time start study drug to balloon inflation/angiography</td>
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<tr>
<td>&lt;= 55</td>
<td>7/331</td>
<td>14/331</td>
<td>0.50 (0.20 - 1.22)</td>
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<tr>
<td>&gt; 55</td>
<td>13/326</td>
<td>22/314</td>
<td>0.57 (0.29 - 1.11)</td>
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<td>Time symptom onset to diagnosis</td>
<td></td>
<td></td>
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<tr>
<td>&lt;= 75</td>
<td>6/340</td>
<td>13/303</td>
<td>0.41 (0.16 - 1.07)</td>
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<tr>
<td>&gt; 75</td>
<td>18/315</td>
<td>21/340</td>
<td>0.93 (0.50 - 1.70)</td>
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<td>Primary PCI</td>
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<tr>
<td>No</td>
<td>11/93</td>
<td>6/78</td>
<td>1.54 (0.60 - 3.97)</td>
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<tr>
<td>Yes</td>
<td>14/577</td>
<td>32/578</td>
<td>0.44 (0.24 - 0.81)</td>
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</tbody>
</table>
Summary: HD Tirofiban in the Ambulance

- Strong trend to reduced mortality continues over 1 year follow-up in open label and double blind cohorts.
- In patients undergoing primary PCI (84%) mortality is significantly lower.
- Highest efficacy in elderly (> 65 yrs), in Killip class ≥ 2 and in early presenters.
Conclusion

Prehospital HD Tirofiban:
A Promising Option for AMI Networks