Early Glycoprotein IIb/IIIa Inhibition in Non-ST-segment Elevation Acute Coronary Syndrome: A Randomized, Double-blind, Placebo-Controlled Trial Evaluating the Clinical Benefits of Early Front-loaded Eptifibatide in the Treatment of Patients with Non-ST-segment Elevation Acute Coronary Syndromes
Study Structure

Study Chairman: E. Braunwald
Study Co-Chairmen: R. Califf, F. Van de Werf

DCRI:
K. Newby, L. Berdan, R. Harrington
TIMI:
R. Giugliano
CVC:
P. Armstrong, C. Sorochuk
Helpline:
P. Tricoci, P. Sinnaeve

Sponsor:
Schering Plough
Physician Lead: J. Strony
Ops leaders: A. Kilian, L. Layton

440 sites
29 countries

Steering Committee

Executive Committee

Coordinating Centers

DSMB

CEC

Sites

35 Investigators
24 Countries represented
Cardiology and Emergency Medicine

Chairman:
D. Weaver
Members:
J. Alpert, E. Cohen, D. Faxon, L. Fisher, F. Verheugt

Physician Lead:
M. Roe
Lead Coordinator:
D. Montgomery
Angio Core:
M. Gibson

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Primary Goal

To compare the effect of 2 strategies for eptifibatide administration in high-risk NSTE ACS patients managed with an invasive diagnostic assessment:

- A strategy of routine, early administration of eptifibatide to all patients shortly after presentation
- A strategy of delayed, provisional eptifibatide administration at the physician’s discretion after coronary angiography and prior to PCI
do we need a bullet that says something about the
DCRI, 2009-03-28
Study Design

High-risk NSTE ACS
n = 10,500

2 of 3 high-risk criteria:
1. Age ≥ 60 years
2. + CKMB or TnT/I
3. ST ↓ or transient ST ↑
   (Or age 50-59, h/o CVD and + CKMB or TnT/I)

Routine, early eptifibatide (180/2/180)

Placebo / delayed provisional eptifibatide pre-PCI

Randomize within 12 hours of presentation

Invasive strategy: 12 to 96 hours after randomization

Safety Endpoints at 120 hrs: Bleeding (GUSTO and TIMI scales), Transfusions, Stroke, Non-hemorrhagic SAEs
Key Exclusion Criteria

- Increased bleeding risk
  - active bleeding or recent bleed
  - Recent surgery or trauma
- Prior ICH or recent ischemic stroke
- Serious concomitant illness or pregnancy
- ESRD with dialysis ≤ 30 days
- Recent or planned use of direct thrombin inhibitor, fXa inhibitor, abciximab/tirofiban
  - amendment 1: allowed bivalirudin at PCI
  - amendment 2: allowed acute fondaparinux or bivalirudin
### Blinded Study Drug Administration

- **Investigational double bolus and infusion regimen**
  - 180 ug/Kg / 2 ug/kg/min / 180 ug/Kg IV eptifibatide (or matching placebo)
    - Infusion decreased to 1 ug/Kg/min if CrCl <50 mL/min)
- Provisional, blinded cross over to open label eptifibatide at time of PCI using blinded bolus kit

---

**Diagram:**
- Eptifibatide
- Placebo
- Coronary Angio
- PCI
- Bolus kit = Provisional use
- Bolus Kit = Bailout use
- Open label Eptifibatide
- Eptifibatide
- Placebo
- Open label Eptifibatide
- Eptifibatide
Statistical Methods

- Power at original sample size (10,500 patients)
  - Primary quadruple composite at 96 hours
    - 85% Power for RRR 22.5% at alpha = 0.048
  - Death or MI at 30 days
    - 85% Power for RRR 15% at alpha = 0.048
- Sample size reduced to 9500 patients when pooled primary event rate greater than expected late in trial
  - 98% power for primary endpoint, 81% power for secondary endpoint

* Adjusted for single interim efficacy analysis
Enrollment (N = 9492)

Follow-up 99.9% complete worldwide
Enrollment

Top 20 Enrolling Sites

1/ Austria  Franz Leisch  (304)
2/ Netherlands  A W J  van 't Hof  (301)
3/ USA  Kristin Newby  (231)
4/ India  Keyur Parikh  (224)
5/ USA  Amir Malik  (209)
6/ Israel  Basil Lewis  (198)
7/ Israel  Arie Roth  (174)
8/ Germany  Peter Schuster  (156)
9/ Germany  Martin Desaga  (151)
10/ Poland  Maria Trusz-Gluza  (138)
11/ Germany  Michael Gross  (138)
12/ Germany  Uwe Zeymer  (133)
13/ USA  Yale Cohen  (119)
14/ Portugal  Luis Providencia  (112)
15/ Israel  Uri Rosenshein  (107)
16/ Poland  Piotr Ponikowski  (95)
17/ France  Khalife Khalife  (94)
18/ Israel  Eugenia Nikolsky  (92)
19/ Switzerland  Michael Pieper  (90)
20/ Canada  Manohara Senaratne  (88)
<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Routine Early Eptifibatide (n=4722)</th>
<th>Delayed Provisional Eptifibatide (n=4684)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>67 (60, 75)</td>
<td>68 (60, 75)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>32</td>
<td>31</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>71</td>
<td>72</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>58</td>
<td>58</td>
</tr>
<tr>
<td>Prior MI (%)</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td>Creatinine Clearance &lt;50 mL/min (%)</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Troponin positive (%)</td>
<td>84</td>
<td>84</td>
</tr>
<tr>
<td>ST-segment shifts (%)</td>
<td>62</td>
<td>62</td>
</tr>
<tr>
<td>Symptoms to presentation (hrs)</td>
<td>3.3 (1.4, 8.0)</td>
<td>3.2 (1.5, 7.8)</td>
</tr>
<tr>
<td>Presentation to randomization (hrs)</td>
<td>5.4 (3.3, 8.8)</td>
<td>5.7 (3.4, 8.8)</td>
</tr>
</tbody>
</table>
## In-hospital Management

<table>
<thead>
<tr>
<th></th>
<th>Routine Early Eptifibatide (n=4722)</th>
<th>Delayed Provisional Eptifibatide (n=4684)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Catheterization (%)</td>
<td>98</td>
<td>98</td>
</tr>
<tr>
<td>Randomization to cath (hrs)</td>
<td>21.4 (16.9, 34.2)</td>
<td>21.4 (16.7, 31.0)</td>
</tr>
<tr>
<td>In-hospital Management (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Medically Treated only</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td>PCI</td>
<td>59</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Provisional (before wire)</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Bailout (after wire)</td>
<td>11</td>
</tr>
<tr>
<td>Use of Established Rx (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>88</td>
<td>88</td>
</tr>
<tr>
<td>Statin</td>
<td>86</td>
<td>87</td>
</tr>
<tr>
<td>ACEI / ARB</td>
<td>78</td>
<td>79</td>
</tr>
<tr>
<td>Clopidogrel (intended early)</td>
<td>75</td>
<td>75</td>
</tr>
</tbody>
</table>
## 96-Hour Primary Efficacy Results

<table>
<thead>
<tr>
<th></th>
<th>Routine Early Eptifibatide (n=4722)</th>
<th>Delayed Provisional Eptifibatide (n=4684)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, MI, RIUR, TBO</td>
<td>9.3%</td>
<td>10.0%</td>
<td>0.92</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.80-1.06)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0.8%</td>
<td>0.9%</td>
<td>0.96</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.62-1.50)</td>
<td></td>
</tr>
<tr>
<td>Death or MI</td>
<td>7.5%</td>
<td>8.3%</td>
<td>0.89</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.77-1.04)</td>
<td></td>
</tr>
<tr>
<td>Death, MI, RIUR</td>
<td>8.4%</td>
<td>9.4%</td>
<td>0.89</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.77-1.03)</td>
<td></td>
</tr>
</tbody>
</table>

MI, myocardial infarction; RIUR, recurrent ischemia requiring urgent revascularization; TBO, thrombotic bailout
Kaplan-Meier Curves for Primary Endpoint

Death, MI, RIUR or TBO (%)

Time Since Randomization (Hours)

Delayed provisional eptifibatide

Routine early eptifibatide

P = 0.23
(stratified for intended early clopidogrel use)
## 30-Day Secondary Efficacy Results

<table>
<thead>
<tr>
<th></th>
<th>Routine Early Eptifibatide (n=4722)</th>
<th>Delayed Provisional Eptifibatide (n=4684)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or MI</td>
<td>11.2%</td>
<td>12.3%</td>
<td>0.89</td>
<td>0.079</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.79-1.01)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>2.8%</td>
<td>2.6%</td>
<td>1.10</td>
<td>0.46</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.86-1.41)</td>
<td></td>
</tr>
<tr>
<td>Death, MI, RIUR</td>
<td>12.5%</td>
<td>13.8%</td>
<td>0.89</td>
<td>0.065</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.79-1.01)</td>
<td></td>
</tr>
</tbody>
</table>

MI, myocardial infarction; RIUR, recurrent ischemia requiring urgent revascularization
Kaplan-Meier Curves for 30-day Death or MI

Death or MI (%)

Time Since Randomization (Days)

- Delayed provisional eptifibatide
  - 12.4%
- Routine early eptifibatide
  - 11.2%

P = 0.079
(stratified for intended early clopidogrel use)
96-hour Primary Efficacy Results
Prespecified Subgroups

Baseline Characteristic | 95% CI | Routine Early Eptifibatide, % | Delayed Provisional Eptifibatide, %
--- | --- | --- | ---
Overall | 0.70 0.80 0.50 0.60 0.90 1 2 | 9.3 9.1 9.7 8.6 11.4 9.5 7.7 8.9 9.5 10.8 10.0 9.8 11.4 10.6 9.5 11.5
Men | | | 
Women | | | 
Age < 75 yr | | | 
Age > 75 yr | | | 
Troponin positive | | | 
Troponin negative | | | 
Diabetes | | | 
No Diabetes | | | 
Early clopidogrel intended | | | 
No early clopidogrel intended | | | 

Delayed Provisional Eptifibatide Better
30-day Death or MI
Prespecified Subgroups

Baseline Characteristic

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<tr>
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<th>Odds Ratio for Upstream Eptifibatide (95% CI)</th>
<th>Routine Early Eptifibatide, %</th>
<th>Delayed Provisional Eptifibatide, %</th>
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<tr>
<td>Overall</td>
<td></td>
<td>11.2</td>
<td>12.3</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td>11.4</td>
<td>12.0</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td>10.7</td>
<td>13.0</td>
</tr>
<tr>
<td>Age &lt; 75 yr</td>
<td></td>
<td>10.2</td>
<td>11.6</td>
</tr>
<tr>
<td>Age &gt; 75 yr</td>
<td></td>
<td>14.0</td>
<td>14.6</td>
</tr>
<tr>
<td>Troponin positive</td>
<td></td>
<td>11.6</td>
<td>13.0</td>
</tr>
<tr>
<td>Troponin negative</td>
<td></td>
<td>8.1</td>
<td>8.4</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td>11.7</td>
<td>13.8</td>
</tr>
<tr>
<td>No Diabetes</td>
<td></td>
<td>10.9</td>
<td>11.7</td>
</tr>
<tr>
<td>Early clopidogrel intended</td>
<td></td>
<td>10.3</td>
<td>12.0</td>
</tr>
<tr>
<td>No early clopidogrel intended</td>
<td></td>
<td>13.7</td>
<td>13.4</td>
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## Safety Results (through 120 hours)

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<th>Delayed Provisional Eptifibatide (n=4634)</th>
<th>OR (95% CI)</th>
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</tr>
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<tr>
<td><strong>Bleeding (all patients, %)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI major</td>
<td>2.6</td>
<td>1.8</td>
<td>1.42 (1.07-1.89)</td>
<td>0.015</td>
</tr>
<tr>
<td>TIMI major or minor</td>
<td>5.8</td>
<td>3.4</td>
<td>1.75 (1.43-2.14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GUSTO severe</td>
<td>0.8</td>
<td>0.9</td>
<td>0.99 (0.64-1.55)</td>
<td>0.97</td>
</tr>
<tr>
<td>GUSTO moderate or severe</td>
<td>7.6</td>
<td>5.1</td>
<td>1.52 (1.28-1.80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PRBC transfusion</td>
<td>8.6</td>
<td>6.7</td>
<td>1.31 (1.12-1.53)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Bleeding (CABG)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Re-operation for bleeding (%)</td>
<td>6.0</td>
<td>8.4</td>
<td>0.70 (0.39-1.27)</td>
<td>0.24</td>
</tr>
<tr>
<td>Chest tube output (mL/24 H)</td>
<td>720</td>
<td>770</td>
<td>--</td>
<td>0.41</td>
</tr>
<tr>
<td>Thrombocytopenia (&lt;100K, %)</td>
<td>3.3</td>
<td>2.8</td>
<td>1.19 (0.93-1.51)</td>
<td>0.17</td>
</tr>
<tr>
<td>Stroke (total, %)</td>
<td>0.6</td>
<td>0.8</td>
<td>0.79 (0.48-1.30)</td>
<td>0.36</td>
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Small Molecule GP IIb/IIIa Inhibition in NSTE ACS

Odds Ratio for 30-day Death or MI Relative to Control

0.89 (0.84-0.95)  COMBINED 2009 (n = 42,666)

0.88 (0.79-0.97)  COMBINED 1998 (n = 23,967)

0.92 (0.82-1.01)  EARLY ACS + ACUITY Timing

0.89 (0.84-0.95)  COMBINED 2009 (n = 42,666)

Theroux

PARAGON A

PARAGON B

PRISM PLUS

PRISM

PURSUIT

EARLY ACS
Conclusions

- Among high-risk NSTE ACS patients, a strategy of routine, early eptifibatide compared with delayed, provisional eptifibatide at PCI
  - did not significantly reduce the primary composite of death, MI, RIUR, or TBO at 96h
  - resulted in a trend toward reduction in death or MI at 30 days, but no difference in 30-day mortality
  - resulted in higher rates of non-life-threatening bleeding and transfusions
The results of EARLY ACS do not support a strategy of routine early eptifibatide use in high-risk NSTE ACS patients managed with an invasive strategy. If subgroups of patients with high likelihood of benefit and low bleeding risk could be identified, it might be reasonable to consider early eptifibatide use in selected high-risk NSTE ACS patients who are intended to undergo angiography.
Early versus Delayed, Provisional Eptifibatide in Acute Coronary Syndromes