Pharmaco-invasive strategies for acute myocardial infarction: the CARESS-in-AMI Trial

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PHARMACOINVASIVE STRATEGIES IN ACUTE MI

STEMI

Aspirin
Clopidogrel/ Prasugrel/ AZD6140/ Cangrelor
UFH/ LMWH/ Fondaparinux/ Bivalirudin
Beta- blockers

<90min to PCI

>90min to PCI

Contraindication to lytics/ late presenters

Accelerated Alteplase
Retepase
Tenecteplase
Combo lytics+½IIb/IIIa

Rescue PCI

Delayed PCI

Primary PCI

Facilitated PCI

IIb/IIIa +/- ½dose lytics preadministered

Immediate PCI

PCI post thrombolysis

Primary PCI

failed

BRAVE-3

ASSENT 4 PCI

FINESSE

Ilb/IIa
1,345 Pts Consecutively Treated in the Regional PCI System for STEMI
Minneapolis-Minnesota Network between 2003 and 2006

73% Pts Transported by Helicopter

1,650 consecutive STEMI pts in the EUROTRANSFER Registry; 7 european countries from 2005 to 2007

Dudek, Siudak, Janzon et al. ESC 2007
Immediate (within 24h) or Deferred PCI after Lysis

- **Lytics + angio within 24 hrs**
- **Lytics + angio when clinically mandated**

**GRACIA-1  499 Pts**
- 12 m †, MI, TLR
- P<0.00008

**SIAM III 163 Pts**
- 6 m †, MI, RI, TLR
- P<0.001
- 25.6

**CAPITAL AMI 170 Pts**
- 6 m †, MI, UAP, Stroke
- P<0.04
- 21

- Fernandez-Aviles et al,
  Lancet 2004;364:1045-53

- Scheller et al,
  JACC 2003;42:634-41

- LeMay et al,
  JACC 2005;46:417-24
**Angio+/- PCI**

**Angio+Rescue PCI**

**Reteplase 5U+5U+Abciximab, UFH**

**Immediate PCI**
- Transfer to PCI Centre
  - N=299

**Standard Care/ Rescue PCI**
- N=301
  - Assess chest pain, ST↑ resolution at 90 min
  - Failed Reperfusion*
    - 35.7%
  - Successful Reperfusion
    - 64.3%

**Angio for symptoms/ischemia**
- 30.5%

**HUB PCI Centre**

**Di Mario et al. Lancet 2008;371:559-68**
• 60 Yr old man, type II DM treated with oral antidiabetic drugs; Heavy smoker (40 cigarettes); Hypertension; Dyslipidaemia; ECG evidence of previous (silent) inferior MI
Pozzuoli 22 November 2006: 16:34, Bolus given

- Aspirin 150 mg + Clopidogrel 300
- Reteplase 5 U
- Heparin 40 mg/Kg
- Abciximab 25 µg/Kg
On the Road: 55 min transfer time, arrival 17:58

Reteplase 5 U 2nd bolus after 30 m’
Heparin 7 U/Kg/hour
Abciximab 0.125 mcg/Kg/min
Chest pain disappears
18:11 First Angio Naples

Before PTCA: TIMI 3

AFTER Taxus
ECG 90 minutes after PCI

- AngioSeal 6 Fr: no haematoma
- Uneventful hospital stay
- Discharged after 4 days
PHARMACOINVASIVE STRATEGIES IN ACUTE MI

CARESS-in-AMI

Symptom Onset to Reteplase

Immediate PCI    Standard/Rescue PCI

298 Pts    300 Pts

Di Mario et al. Lancet 2008;371:559-68

Reteplase to Angiography

Immediate PCI    Standard/Rescue PCI

298 Pts    107 Pts

Di Mario et al. Lancet 2008;371:559-68
TIMI flow pre in CARESS and FINESS

Reteplase to Angio
132 mins

72 min

Di Mario et al. Lancet 2008;371:559-68
Ellis et al. NEJM 2008 in press
CARESS-in-AMI

Primary Endpoint
Death, re-MI, refractory ischaemia

Cumulative incidence of 1ary endpoint (%)

Time from randomization (days)

Standard Care / Rescue PCI
Logrank p=0.004

Immediate PCI

Di Mario et al. Lancet 2008;371:559-68

OR 0.34
(95% CI 0.17-0.68)
P=0.001

Standard/Rescue
Immediate PCI
Di Mario et al. Lancet 2008;371:559-68
PHARMACOINVASIVE STRATEGIES IN ACUTE MI

CARESS-in-AMI

Di Mario et al. Lancet 2008;371:559-68
Neither clopidogrel nor LMWH were used

- Early PCI after lytics is clearly beneficial but when: 17 hours as in GRACIA-1 or immediate?

The trial suggests a benefit but it was stopped before scheduled recruitment was completed and numbers are too low to confirm it

Combo therapy with 2b-3a inhibitors is not a recommended lytic regimen in Guidelines. An approved lytic type and dose should be tested
# Clopidogrel trials in comparison

<table>
<thead>
<tr>
<th>CLARITY</th>
<th>COMMIT/CCS-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 1ary EP: TIMI flow on angio</td>
<td>- 1ary EP: Mortality, Death/MI/CVA</td>
</tr>
<tr>
<td>- n=3500</td>
<td>- n=46000!</td>
</tr>
<tr>
<td>- MI &lt; 12 hrs</td>
<td>- MI &lt; 24 hrs</td>
</tr>
<tr>
<td>- ≤ 75 years</td>
<td>- ≤ 100 years!</td>
</tr>
<tr>
<td>- 100% Fibrinolytic</td>
<td>- ~50% Fibrinolytic (also SK)</td>
</tr>
<tr>
<td>- Loading dose 300mg</td>
<td>- No loading dose</td>
</tr>
<tr>
<td>- Angio 2-8 days</td>
<td>- Non-invasive Strategy</td>
</tr>
<tr>
<td>- Europe / North America</td>
<td>- China</td>
</tr>
</tbody>
</table>
CLARITY
n=3500

Death ReMI Stroke before discharge

OR 0.64, 95% CI 0.53-0.76, p<0.0001

COMMIT/CCS-2
n=46000

Death ReMI Stroke before discharge

Placebo: 2310 with event (9.1%)
Clopidogrel: 2121 with event (9.2%)
9% (SE 3) proportional risk reduction (p=0.002)

Bleeds ns


Lancet. 2005 Nov 5;366(9497):1607-21
LMWH in AMI: EXTRACT TIMI-25

STEMI
  Fibrinolysis with
  SK/TNK/Atleplase/Reteplase
  Clopidogrel at operators discretion

ENOXAPARIN
  Until discharge or <8 days
  n=10256
  Median treatment 7 days

UFH
  ≥48h
  n=10223
  Median treatment 2 days

1ary EP=Death/ reMI
30 days


Unfractionated heparin

Enoxaparin

Relative risk, 0.83
(95% CI, 0.77–0.90)
P < 0.001
PHARMACOINVASIVE STRATEGIES IN ACUTE MI

ASSENT 4: Facilitated PCI

STEMI ≤ 6h
PCI delay 1-3h
ASA, UFH bolus (no infusion)

PCI N=833

TNK+PCI N=829

1ary EP: 90day Death/ CHF/ Shock
Planned 4000 pts: Stopped due to ↑ in-hospital mortality

Lancet 2006; 367: 569–78
Prothrombotic effect of thrombolysis

- **GRACIA-1 (rtPA)**
  - 16h 42min.

- **ASSENT-4 PCI (TNK)**
  - 1h 44min.

↑ F1,2 fragments == ↑ prothrombin activation

GUSTO V

STEMI < 12h
No age limit

At discretion of investigator: Angiography +/- PCI

GUSTO V. Lancet 2001; 357: 1905–14

All-cause mortality at 30 days (5.9 vs 5.6%) test for superiority, p = 0.43; for non-inferiority, relative risk 0.95 [95% CI 0.84–1.08]).
GUSTO V: Bleeding

P<0.0001

P=0.27

P=0.069

P=0.79

rtPA

rtPA+Abcx
“Pharmacoinvasive Strategy”
Urgent Transfer to PCI Centre
N=522

‘High Risk’ ST Elevation MI within 12 hours of symptom onset

Randomization stratified by age (≤75 vs. > 75) and by enrolling site

TNK + ASA + Heparin / Enoxaparin + Clopidogrel

Cath / PCI within 6 hrs regardless of reperfusion

Failed Reperfusion*

Successful Reperfusion

Assess chest pain, ST↑ resolution at 60-90 minutes after randomization

Cath and Rescue PCI ± GP IIb/IIIa Inhibitor

“Pharmacoinvasive Strategy”

Cath and Rescue PCI ± GP IIb/IIIa Inhibitor

Elective Cath ± PCI ➢24 hrs later

Repatriation of stable patients within 24 hrs of PCI

PCI within 12h from thrombolysis=47%
CARESS-in-AMI vs TRANSFER-MI

In TRANSFER-AMI endpoint included CHF + shock at 30 days

Cantor, ACC 2008. www.cardiosource.com
Di Mario et al. Lancet 2008;371:559-68
CARESS-in-AMI & TRANSFER-AMI

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CARESS-in-AMI & TRANSFER-AMI

Bleeding

- CARESS Immediate
- CARESS Standard
- TRANSFER Pharmacoinvasive
- TRANSFER Standard

TIMI Major

30d haemorrh CVA

P=0.066

Cantor, ACC 2008. www.cardiosource.com
Di Mario et al. Lancet 2008;371:559-68
### Pharmacologic strategies in AMI

**ANTIPLATELET**
- Aspirin
- Clopidogrel
- Prasugrel
- Cangrelor
- AZD6140
- GP IIb/IIIa Inhibitors

**ANTITHROMBOTIC**
- UFH
- LMWH
- Bivalirudin

**THROMBOLYTICS**

**COMBINATION THERAPY**
(thrombolytics+GP IIb IIIa)

<table>
<thead>
<tr>
<th>Recommended</th>
<th>Under evaluation</th>
<th>Discouraged</th>
</tr>
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</table>

- Primary PCI possible within 90 minutes
- Primary PCI NOT possible within 90 minutes

*Rescue*

Primary PCI possible within 90 minutes
Primary PCI NOT possible within 90 minutes

- Rescue Recommended
- Discouraged
**Individual 30 day outcomes**

Rescue/Medical Treatment Only Divided

<table>
<thead>
<tr>
<th>Condition</th>
<th>Facilitated PCI (n=294)</th>
<th>Med. Treatment/ Rescue (n=298)</th>
<th>Rescue PCI (n=106)</th>
<th>Med. Treatment Only (n=192)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>3.1% (n=9)</td>
<td>10.6% (n=11)</td>
<td>1.9% (n=2)</td>
<td>9.4% (n=18)</td>
</tr>
<tr>
<td>Re-MI/Refractory Ischaemia</td>
<td>4.4% (n=13)</td>
<td>1.0% (n=2)</td>
<td>1.0% (n=3)</td>
<td>6.7% (n=20)</td>
</tr>
</tbody>
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P-values:

- Death: P=0.403
- Re-MI/Refractory Ischaemia: P<0.002