Transfers, Facilitated, and Rescue PCI for AMI

Timothy D. Henry, MD
Director of Cardiology
Cedars-Sinai Heart Institute
56 yr old riverboat captain from LA

54 miles from Lock and Dam #3 to MHI
56-yr old riverboat captain from LA

- 1:30am - Onset of SOB and diaphoresis. Ship stops at lock and dam #3 in Red Wing, MN
- 02:26 - Red Wing fire department on scene
- 02:38 - 12 lead ECG shows STEMI. Called Helicopter and gave ASA and NTG
Treatment Times

- 03:09 – Helicopter on scene
- 03:20 – Helicopter leaves. Cath team activated
- 03:38 – Helicopter arrives at MHI
- 04:02 – Patient in cath lab
- 04:19 – Artery open

Door-to-balloon: 41 minutes
Prehospital EKG to balloon: 101 minutes
Summary

• D-B: 41 mins; Prehosp EKG-B: 101 mins
• 56 y.o. male without chest pain
• Middle of the night
• 3 competing health care systems
• From a riverboat in the Mississippi river 54 miles from the closest cath lab
Introduction

- **Primary PCI is superior to fibrinolysis**
  - In high volume PCI centers
  - If performed in a timely manner:
    - $<120$ min, possibly longer
Primary PCI vs Lysis for STEMI – Meta-analysis of 23 trials

Short Term Events

- Death: 5 (PTCA) vs 7 (Thrombolytic) with P = 0.0003
- Re-MI: 3 (PTCA) vs 7 (Thrombolytic) with P < 0.0001
- Total CVA: 1 (PTCA) vs 2 (Thrombolytic) with p = 0.0004
- ICH: 0.05 (PTCA) vs 1 (Thrombolytic) with P < 0.0001
- Death + Re-MI + CVA: 8 (PTCA) vs 14 (Thrombolytic) with P < 0.0001

Keeley, Lancet Jan 2003
Age Adjusted Mortality by Time

Stenestrand et al. JAMA 2006;296:1749-56
Introduction

- *Primary PCI is superior to fibrinolysis*

- **Major limitation is availability**
  - <25% of US hospital have cath labs
  - 2/3 of 1.5 million AMI patients present to hospitals without cath labs
Introduction

• *Primary PCI is superior to fibrinolysis*
• *Major limitation is availability*
• *Transfer for primary PCI is superior to fibrinolysis in European trials*
Relative Risks of Transfer for Primary PCI vs Fibrinolysis

Death/Reinfarction/Stroke

<table>
<thead>
<tr>
<th>Study</th>
<th>PCI No events / No randomised</th>
<th>Lysis No events / No randomised</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maastricht</td>
<td>8/75</td>
<td>14/75</td>
</tr>
<tr>
<td>PRAGUE</td>
<td>8/101</td>
<td>23/99</td>
</tr>
<tr>
<td>Air-Pami</td>
<td>6/71</td>
<td>9/66</td>
</tr>
<tr>
<td>CAPTIM</td>
<td>26/421</td>
<td>34/419</td>
</tr>
<tr>
<td>DANAMI 2</td>
<td>63/790</td>
<td>107/782</td>
</tr>
<tr>
<td>PRAGUE 2</td>
<td>36/429</td>
<td>64/421</td>
</tr>
<tr>
<td>Total</td>
<td>147/1887</td>
<td>251/1863</td>
</tr>
</tbody>
</table>

Relative Risk 0.1 0.2 0.3 0.5 0.7 1.0 1.4

Dalby et al. Circ 2003;108:1809-14
5.4 mill. inhabitants
5 PCI centers
24 referral hospitals
62% of Danish population
Transport distance up to 95 US miles (mean 35 miles)
Primary end point within 30 Days
Referral hospitals: 1,129 patients

Fibrinolysis (front loaded tPA) 14.2%
PCI 8.5%
Log rank: p=0.002

NNT=18

Primary end point: Death or reinfarction or stroke

Transfer for PCI is better than LYSIS! (In a timely manner)
Conclusion

- Transfer for Primary PCI is the best strategy if door-balloon times < 120 minutes (ideally < 90 minutes)
- Excellent Safety

• Can it be done outside Europe?
Transfer for Primary PCI in US
Door to Balloon Times

- **Air PAMI**
  - Median: 155 minutes

- **NRMI – 3/4**
  - Median: 180 minutes
  - 15% <120 minutes
  - 4% <90 minutes
“When I present the DANAMI-2 experience to a US audience, the most frequent comment is that in the US system it is very, very difficult to implement such a strategy.”

Henning Anderson
(DANAMI-2 PI)
Even in Denmark!

• “For field-triaged, transferred, and all EMS-transported patients, the proportion treated with a system delay <120 min was 72%, 35%, 48% respectively”

Terkelsen et al, JAMA 304:2010
What is the Optimal Reperfusion Strategy for STEMI Patients with expected delays?
Real Life!

- 70 year old Lawyer presents to ED 120 miles from a PCI center with acute onset of 9/10 chest pain at 09:15 pm called 911.
- Arrived at the community ED at 9:36 EKG obtained at 9:43
Options for Patients with Prolonged Transfer Times

1. Full dose fibrinolytic with elective transfer or for rescue
2. Full dose fibrinolytic with routine transfer and rescue as needed
3. Pharmaco-invasive PCI
4. Primary PCI (no matter how long it takes)
5. All of the above: Depending on the time of day and which cardiologist is on call!
Rescue PCI is better than LYSIS!
REACT:

6 month Primary composite
(Death, MI, CVA, or severe heart failure)

The primary composite endpoint of death, MI, CVA or severe heart failure at 6 months was significantly lower in the rescue PCI group compared with either the repeat thrombolysis group or the conservative management group.

Presented at AHA 2004
Immediate PCI after Lysis is better than LYSIS +/- Delayed PCI!
Routine Early PCI after Fibrinolysis

Cantor WJ et al, CMAJ 2005

Mortality at 1 Year

Pre-Stent Era Trials

Stent Era Trials

All Trials

Favors Early PCI  Favors Conservative

0.1 0.2 0.5 1 2 5 10
Routine Early PCI vs Selective Invasive Approach

<table>
<thead>
<tr>
<th>Study</th>
<th>Ischemic Event Rate (%)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPITAL-AMI</td>
<td>11.6</td>
<td>170</td>
</tr>
<tr>
<td>CARESS-in-AMI</td>
<td>24.4</td>
<td>598</td>
</tr>
<tr>
<td>SIAM-III</td>
<td>50.6</td>
<td>163</td>
</tr>
<tr>
<td>GRACIA-1</td>
<td>20.3</td>
<td>499</td>
</tr>
<tr>
<td>TRANSFER-AMI</td>
<td>11.0</td>
<td>1059</td>
</tr>
<tr>
<td>NORDISTEMI</td>
<td>16.0</td>
<td>266</td>
</tr>
</tbody>
</table>

N refers to the number of participants in each study.
Meta-Analysis Contemporary Trials

### Table: Death-Reinfarction, 6-12 months

<table>
<thead>
<tr>
<th>Study</th>
<th>Early PCI</th>
<th>Standard therapy</th>
<th>Odds ratio [M-H, Random, 95% CI]</th>
<th>Odds ratio [M-H, Random, 95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>CARESS-IN-AMI</td>
<td>30</td>
<td>299</td>
<td>28</td>
<td>301</td>
</tr>
<tr>
<td>GRACIA-1</td>
<td>17</td>
<td>248</td>
<td>29</td>
<td>251</td>
</tr>
<tr>
<td>CAPITAL-AMI</td>
<td>8</td>
<td>86</td>
<td>15</td>
<td>84</td>
</tr>
<tr>
<td>SIAM-III</td>
<td>6</td>
<td>82</td>
<td>11</td>
<td>81</td>
</tr>
<tr>
<td>TRANSFER-AMI</td>
<td>51</td>
<td>537</td>
<td>56</td>
<td>522</td>
</tr>
<tr>
<td>NORDISTEMI</td>
<td>7</td>
<td>134</td>
<td>16</td>
<td>132</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>119/1386</strong></td>
<td><strong>155/1371</strong></td>
<td><strong>100.0</strong></td>
<td><strong>NNT 37 [20-206]</strong></td>
</tr>
</tbody>
</table>

- Heterogeneity: $\tau^2 = 0.04$; $\chi^2 = 6.49$, df = 5 ($P = 0.26$); $I^2 = 23\%$
- Test for overall effect: $Z = 2.19$ ($P = 0.03$)
- Egger's regression test: $P$ value 0.03

Piscione F et al, Eur Heart J 2010
PCI is better than Facilitated PCI
Facilitated PCI

Dauerman and Sobel. JACC 2003
Facilitated percutaneous coronary intervention offers no benefit over primary percutaneous coronary intervention in STEMI and should not be used....
Limitations of Keeley Meta-analysis

- 17 trials with tremendous variation:
  - 9: IIb/IIIa only
  - 6: lytic only
  - 2: \(\frac{1}{2}\) dose + IIb/IIIa

- No trials in Pts with transfer delay
- 50% of Lytic data from Assent 4
- Relatively low risk pts in PCI hospitals or with short transfer distances
- Pre clopidogrel
Primary Endpoint at 90 Days

Death / CHF / Shock (% Pts)

Facilitated PCI
Primary PCI

Logrank test: p=0.0042

Time since randomisation (days)

Lancet 2006
Limitations of ASSENT-4

- Full dose Lytic: Focus on bleeding not patency
- Inadequate antiplatelet (No IIb/IIIa / delayed clopidogrel)
- Inadequate antithrombin (bolus only)
- Lower patency than expected
- 15% of deaths were CVA
- 45% in PCI hospital
- < 5% US
- Limited transfer delays (excluded long delays)
FINESSE: Study Design

Acute ST-elevation MI (or new LBBB) within 6h pain onset
Presenting at Hub or Spoke with estimated time to PCI between 1 and 4 hours

Randomize 1:1:1
N=3000

Placebo
Placebo

Placebo
Abciximab

Reteplase (5U+5U)*
Abciximab

*Only 5U if ≥ 75

Transfer To Cath Lab
ASA, unfractionated heparin 40U/kg (max 3000 U)
or enoxaparin (0.5 mg/kg IV + 0.3 mg/kg SC) – substudy only

Abciximab

Placebo

Placebo

Primary PCI with Abciximab Infusion (12 h)

Primary endpoint at 90 days: All-cause mortality, resuscitated VF occurring > 48h, cardiogenic shock, or readmission/ED visit for CHF
TIMI Flow in IRA Pre-PCI

% Subjects with TIMI 2/3 (Patency) Pre-PCI

Primary PCI (in lab Abciximab) (n=790)
Abciximab Facilitated PCI (n=809)
Reteplase/Abciximab Facilitated PCI (n=815)

Ave Time from First Abciximab Bolus to Angiogram In Facilitated Groups:
74min 76min

Modified ITT Population with Index PCI: ITT, PCI and any dose of study drug (active or placebo); Investigator assessment
Primary Endpoint

Subjects with Primary Composite Endpoint (%)

Days

Primary vs Reteplase/Abciximab-Facilitated PCI: p = 0.551
Primary vs Abciximab-Facilitated PCI: p = 0.858
Abciximab-Facilitated vs Reteplase/Abciximab-Facilitated PCI: p = 0.676

Primary PCI
Abciximab-Facilitated PCI
Reteplase/Abciximab-Facilitated PCI

10.7%
10.5%
9.8%
FINESSE

- Best trial available
- Slow enrollment, therefore underpowered
- 40% spoke hospitals with D-B 155 min
- Increase bleeding (are all regimens =?)
- Signals in Ant MI, High Risk, < 3 hrs
Benefit of Facilitated Percutaneous Coronary Intervention in High-Risk ST-Segment Elevation Myocardial Infarction Patients Presenting to Nonpercutaneous Coronary Intervention Hospitals

Howard C. Herrmann, MD,* Jiandong Lu, MD,† Bruce R. Brodie, MD,‡
Paul W. Armstrong, MD,§ Gilles Montalescot, MD, PhD,‖ Amadeo Betriu, MD,¶
Franz-Joseph Neuman, MD,§ Mark B. Efron, MD,‖ Elliot S. Barnathan, MD,†
Eric J. Topol, MD,†† Stephen G. Ellis, MD,‡‡ for the FINESSE Investigators

Philadelphia and Malvern, Pennsylvania; Greensboro, North Carolina;
Edmonton, Alberta, Canada; Paris, France; Barcelona, Spain; Bad Krozingen, Germany;
Indianapolis, Indiana; La Jolla, California; and Cleveland, Ohio

TIMI RS ≥ 3, Spoke site

TIMI RS ≥ 3, Spoke site, and symptom ≤ 4hr
Clopidogrel for STEMI

- Odds Ratio 0.80 (95% CI 0.65-0.97) P=0.026
- No difference in major bleeding (1.3% vs. 1.1%, p=NS)

Comparison of Placebo vs. Clopidogrel:
- CV Death, MI, RI: Placebo vs. Clopidogrel 20%
- No difference in major bleeding (0.58% vs. 0.55%, p=NS)

7% (SE 3) RRR p=0.03
8.1
7.5

Placebo (n=22923) Clopidogrel (n=22928)
Pharmacoinvasive (Facilitated) PCI is better than Lytic + Rescue PCI
# Pharmaco-invasive vs. facilitated PCI - what is the difference?

<table>
<thead>
<tr>
<th></th>
<th>Facilitated</th>
<th>Pharmaco-invasive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial design</strong></td>
<td>Fibrinolytic + PCI vs PCI alone</td>
<td>Fibrinolytic + PCI vs Conservative therapy (Ischaemia-guided PCI)</td>
</tr>
<tr>
<td><strong>Enrollment</strong></td>
<td>PCI hospitals</td>
<td>Non-PCI hospitals</td>
</tr>
<tr>
<td><strong>Time to PCI</strong></td>
<td>Shorter</td>
<td>Longer</td>
</tr>
</tbody>
</table>

Various regimens including: full vs. reduced dose fibrinolytic, +/- clopidogrel, +/-IIb/IIIa GP inhibitor, enoxaparin vs. UFH
# Pharmaco-invasive trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Pharmacologic regimen</th>
<th>Time to PCI (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARESS-in-AMI N=600 DiMario, Lancet 2008</td>
<td>$\frac{1}{2}$ dose reteplase Abciximab Heparin, ASA</td>
<td>135 minutes</td>
</tr>
<tr>
<td>TRANSFER-AMI N=1,059 Cantor, NEJM 2009</td>
<td>Full-dose tenecteplase Heparin or enoxaparin Clopidogrel, ASA</td>
<td>192 minutes</td>
</tr>
<tr>
<td>NORDISTEMI N=266 Bohmer, JACC 2009</td>
<td>Full-dose tenecteplase Enoxaparin Clopidogrel, ASA</td>
<td>163 minutes</td>
</tr>
</tbody>
</table>
Pharmaco-invasive trials

No significant differences in bleeding

Death, Re-MI, CS, CHF 30 days

P=0.004

TRANSFER-AMI

Death, Re-MI, refractory ischemia 30 days

CARESS-in-AMI

Death, Re-MI, stroke 30 days

My Problems with a Lytic + Rescue Strategy

- How do you decide when to go?
- Who decides when to go?
- Guaranteed delays!!!
- And cath lab unhappiness

- CARESS, TRANSFER AMI, NORDISTEMI !!!!
Options for Patients with Prolonged Transfer Times

• Full dose fibrinolytic with elective transfer or for rescue
• Full dose fibrinolytic with routine transfer and rescue as needed
• Primary PCI (no matter how long it takes)
• Pharmacoinvasive PCI
• All of the above: Depending on the time of day and which cardiologist is on call!
Problems with PCI no matter how long it takes!

- Time may be less critical with PCI but TIME STILL MATTERS!
- Delays still occur especially with Transfer Pts (<15% treated <2hours)
- When your mother has a large Anterior STEMI do you want them waiting 3 hours for Reperfusion?
Red– Zone II (90-120 mins)
Blue– Zone I (< 90 mins)

Zone1 Protocol
Aspirin 325 mg
Clopidogrel 600mg
UFH
Beta-blocker
PCI
Protocol focus:
- Simple
- Fast
- Reduce variability

Red – Zone II (90-120 mins)
Blue – Zone I (< 90 mins)

Zone 2 Protocol
- Aspirin 325 mg
- Clopidogrel 600mg
- UFH
- TNK ½ dose
- Beta-blocker
- PCI
Total STEMI
N=2,634

PCI Hosp
N=600

Zone 1 Hosp
N=1,195

Zone 2 Hosp
N=839

PPCI
N=600

PPCI
N=1,163

Ph-Inv
N=32

Ph-Inv
N=660

Ph-Inv
N=692

PPCI
N=1,763

PPCI
N=179
# Time to reperfusion segments (min)

<table>
<thead>
<tr>
<th></th>
<th>PCI Hosp</th>
<th>Zone 1 (&lt;60 miles)</th>
<th>Zone 2 (60-210 miles)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms to hospital</td>
<td>103 (60, 232)</td>
<td>88 (47, 195)</td>
<td>88 (44, 185)</td>
<td>0.008/0.002</td>
</tr>
<tr>
<td>In door – out door</td>
<td>NA</td>
<td>49 (36, 67)</td>
<td>61 (48, 83)</td>
<td></td>
</tr>
<tr>
<td>Door to fibrinolytic</td>
<td>NA</td>
<td>NA</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Transport</td>
<td>NA</td>
<td>22 (16, 31)</td>
<td>35 (26, 48)</td>
<td></td>
</tr>
<tr>
<td>Door to balloon</td>
<td>64 (44, 84)</td>
<td>95 (81, 117)</td>
<td>121 (101, 151)</td>
<td>&lt;0.001/&lt;0.001</td>
</tr>
<tr>
<td>Total reperfusion</td>
<td>171 (118, 318)</td>
<td>195 (142, 305)</td>
<td>218 (165, 329)</td>
<td>&lt;0.001/&lt;0.001</td>
</tr>
</tbody>
</table>
## Results

<table>
<thead>
<tr>
<th></th>
<th>PCI Hosp PPCI N=496</th>
<th>Zone 1 (&lt;60) PPCI N=1,005</th>
<th>Zone 2 (60-210) Ph-Inv N=606</th>
<th>P value PCI Hosp vs. Zone 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>D2B time</strong></td>
<td>64 (44, 84)</td>
<td>95 (81, 117)</td>
<td>123 (102, 151)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Mortality hospital</strong></td>
<td>5.0%</td>
<td>4.4%</td>
<td>5.5%</td>
<td>0.76</td>
</tr>
<tr>
<td><strong>Mortality 30 day</strong></td>
<td>5.7%</td>
<td>5.2%</td>
<td>5.8%</td>
<td>0.93</td>
</tr>
<tr>
<td><strong>Re-ischaemia 30 days</strong></td>
<td>3.0%</td>
<td>0.9%</td>
<td>1.0%</td>
<td>0.014</td>
</tr>
<tr>
<td><strong>Major Bleeding</strong></td>
<td>1.4%</td>
<td>0.7%</td>
<td>1.2%</td>
<td>0.71</td>
</tr>
<tr>
<td><strong>Stroke 30 days</strong></td>
<td>1.2%</td>
<td>0.5%</td>
<td>1.0%</td>
<td>0.73</td>
</tr>
</tbody>
</table>
Pre-PCI patency

Percentage of patients

Pre-PCI patency

TIMI 2/3

PPCI

Ph-Inv

37.1

72.7

P<0.001
**Death, re-MI, Heart Failure, Severe Recurrent Ischemia, Cardiogenic Shock in 1st 24 Hours**

- **Standard Treatment (n=522)**
  - 0 hours: 489
  - 2 hours: 484
  - 4 hours: 481
  - 6 hours: 477
  - 8 hours: 467
  - 10 hours: 465

- **Routine Early PCI (n=537)**
  - 0 hours: 518
  - 2 hours: 513
  - 4 hours: 511
  - 6 hours: 509
  - 8 hours: 501
  - 10 hours: 499

*P-values:*
- 0.027
- 0.046
- 0.029
“… there is currently no justification to pretreat any patient in whom primary angioplasty is intended with thrombolytic therapy”

In other words…

If PCI can be performed quickly, fibrinolytics should not be given en route to cath lab

Lancet 2006
EDITORIAL COMMENT

The Ideal Reperfusion Strategy for the ST-Segment Elevation Myocardial Infarction Patient With Expected Delay to Percutaneous Coronary Intervention

Paradise Lost or Paradise Renamed?*

Timothy D. Henry, MD, David M. Larson, MD

Minneapolis, Minnesota
Minneapolis Heart Institute
ACUTE CARDIOVASCULAR CARE
STANDARDIZED SYSTEMS

- Out of Hospital Cardiac Arrest
  - Cooling protocol
- Aortic Dissection
- Critical Limb Ischemia
- NSTEMI
- AAA
- Stroke
Cooling Outcomes

Alive at hospital discharge with favourable neurological recovery

Abbott Northwestern Hospital 53/96 55.2%

- Survival by diagnosis
  - STEMI: 33/50 66.0%
  - Other: 20/46 43.5%

- Survival by initial rhythm
  - VF/VT: 47/75 62.6%
  - PEA/Asystole: 5/19 26.3%

Transfer Outcomes
Transfer = Blue line, ANW = Red line

What Happened in Real Life

- MHI Level 1 MI protocol activated
- ASA, Clopidogrel 600mg, IV heparin, IV metoprolol
- ½ dose lytic at 10:03 (door to needle time 27 minutes)
- Repeat EKG while waiting for helicopter
What conclusions can we make!

• **PCI centers should do PCI (in a timely manner <90 min)**
• **Short Distance Transfer Pts should have PCI (in a timely manner <120?)**
• **Pharmcoinvasive PCI is an excellent choice for Pts with expected delay!!**
• **The ideal regimen and timing of PCI remain unclear!**