Pharmaco-Invasive Strategies
Current Status in STEMI Management

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Cairo University
STEMI Management

- What are the options?

  - Primary PCI
  - Primary Fibrinolytic Therapy
    - Rescue PCI (fibrinolytic failures only)
    - Immediate/Facilitated PCI (< 3 hours)
    - Pharmacoinvasive PCI (within 3-24 hours)
    - Deferred PCI (> 24 hours)
Primary PCI > Fibrinolytics

### Primary PCI
- 95% TIMI 3 Flow
- Less re-occlusion
- 2% survival benefit
- Eliminates 1% ICH


But... Fibrinolytics Still Important

- Many patients present to hospitals without PCI capability
- Even so... PCI often cannot realistically occur within 90 minutes
- In NRMI 2006 Database, 27.6% of patients received fibrinolytic therapy

Can We Count Time (of 1st Contact to Balloon) in Cairo

Enemy?   Friend?
How best to combine the two strategies?

- Can we improve on Primary PCI with concomitant (co-administered) fibrinolytics?
  - Immediate/Facilitated Approach
- Should all fibrinolytic patients go to PCI?
  - Pharmacoinvasive Approach
  - Deferred Approach
- Should only fibrinolytic “failures” get PCI?
  - Rescue Approach

**Pros and Cons**

- **Lysis before PCI**
  - + Re-opened IRA
  - + Earlier reperfusion
  - + PCI easier
  - - Thrombus burden ↓
  - - Bleeding↑
  - - Prothrombotic state
  - - Costs
  - - Stroke rate
Immediate/Facilitated PCI

- Definition: PCI immediately (< 3 hours) after fibrinolytics
- You may combine fibrinolytics with 2b/3a receptor inhibitors
  - Theory: *Both PCI And Lytics*
    
    =

    *Rapid Early Reperfusion + Sustained Reperfusion*

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**Protocol**

- STEMI < 6 hours
- High Risk ECG
- Thrombolytic Eligible

- **Randomize** (n = 4,000)
  - **TNK**
    - UFH, ASA (n = 829)
  - **UFH, ASA** (n = 838)

- **Facilitated PCI**
  - GP IIb/IIIa bailout

- **Primary PCI**
  - GP IIb/IIIa at Operator discretion

Transfer

Primary Endpoint: 90 day Composite (death/CHF/Shock)

*Lancet 2006; 367:569*
30 DAY MORTALITY

Stopped Early at 1667 Patients!

Mortality %

- Facilitated PCI: 6.0%
- Primary PCI: 3.8%

Log rank p = 0.04

Days

90 Day Outcomes

- Any Bleeding:
  - Facilitated PCI: 31%
  - Primary PCI: 23%

  p value <0.001

Lancet 2006; 367:569
**FINESSE**

**STEMI < 6 hrs**

Estimated time to Cath 1-4 hours

40% Enrolled at Non-PCI Hospitals

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Randomize
N=2452

- Placebo
- Abciximab
- Replase (5U+5U) + Abciximab

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Transfer for PCI

- Primary PCI (with abciximab)
- Facilitated PCI (abciximab)
- Facilitated PCI (combination)

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F/U 90 days and 1 year

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**TIMI 2-3 Flow Pre-PCI**

Core Lab Analysis (n=198)

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**Ellis NEJM 2008**
Primary Endpoint
(Death, VF, Shock, CHF @ 90 days)

Even in patients with the longest
door-to-balloon times (> 2.8 hrs)
there were no differences in outcomes

Ellis NEJM 2008

TIMI Major or Minor Bleeding
(Nonintracranial through discharge/day7)

Primary PCI with In Lab Abciximab (n=795)
Abciximab Facilitated PCI (n=805)
Abciximab/Reteplase Facilitated PCI (n=814)
Immediate/Facilitated PCI
Why did it fail?

- Early period post-lytics (within 3 hours) carries the highest risk of bleeding
- Early period paradoxically is also pro-thrombotic, due to degradation products
- *Immediate PCI may increase bleeding and also paradoxically increase ischemic endpoints*
- 2b/3a inhibitors may reduce the thrombotic complications but at a cost of excess bleeding

Pharmaco-Invasive Strategy

Pharmacologic reperfusion therapy *(lytics or half dose lytics + IIb/IIIa)* followed by transfer to a PCI hospital for urgent cath/PCI *(within 3-24 hours).*
Pharmacoinvasive PCI: Finding the Sweet Spot for PCI

**197 Patients STEMI Retavase < 12 hours of Symptoms**

**Conservative Management: Deferred PCI Angiography/PCI of IRA at 2 weeks**

**Early PCI < 6 hours of Retavase Mean 3.5 hours**

**Composite Outcome:**
Death, reinfarction, target lesion revascularization or other ischemic events at 30 days and 6 months

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**Table 5: End Points: Comparison of Randomization Groups**

<table>
<thead>
<tr>
<th>Event (50-day follow-up)</th>
<th>Immediate Steenting</th>
<th>Delayed Steenting</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>1.5%</td>
<td>2.5%</td>
<td>0.23</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>2.4%</td>
<td>2.8%</td>
<td>0.40</td>
</tr>
<tr>
<td>Exit reinfarction</td>
<td>13.5%</td>
<td>14.8%</td>
<td>0.34</td>
</tr>
<tr>
<td>Target lesion revascularization</td>
<td>2.4%</td>
<td>2.8%</td>
<td>0.40</td>
</tr>
<tr>
<td>Ischemic events</td>
<td>3.5%</td>
<td>3.8%</td>
<td>0.02</td>
</tr>
<tr>
<td>Death</td>
<td>5.0%</td>
<td>5.4%</td>
<td>0.3</td>
</tr>
<tr>
<td>Death or reinfarction</td>
<td>7.2%</td>
<td>7.9%</td>
<td>0.08</td>
</tr>
<tr>
<td>Death, reinfarction, target lesion revascularization</td>
<td>5.5%</td>
<td>6.1%</td>
<td>0.09</td>
</tr>
<tr>
<td>Death, reinfarction, target lesion revascularization, ischemic events</td>
<td>14.6%</td>
<td>15.7%</td>
<td>0.03</td>
</tr>
</tbody>
</table>

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**50-day Follow-up**

<table>
<thead>
<tr>
<th>Event</th>
<th>Early</th>
<th>Deferred</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up</td>
<td>7.9%</td>
<td>11.4%</td>
<td>0.02</td>
</tr>
<tr>
<td>CABG</td>
<td>7.9%</td>
<td>11.4%</td>
<td>0.02</td>
</tr>
<tr>
<td>Target lesion revascularization</td>
<td>10.5%</td>
<td>14.8%</td>
<td>0.02</td>
</tr>
<tr>
<td>Ischemic events</td>
<td>3.9%</td>
<td>4.7%</td>
<td>0.5</td>
</tr>
<tr>
<td>Death</td>
<td>5.0%</td>
<td>5.4%</td>
<td>0.3</td>
</tr>
<tr>
<td>Death or reinfarction</td>
<td>7.1%</td>
<td>8.9%</td>
<td>0.1</td>
</tr>
<tr>
<td>Death, reinfarction, target lesion revascularization</td>
<td>14.7%</td>
<td>15.9%</td>
<td>0.03</td>
</tr>
<tr>
<td>Death, reinfarction, target lesion revascularization, ischemic events</td>
<td>14.7%</td>
<td>16.2%</td>
<td>0.03</td>
</tr>
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**LV ejection fraction**

<table>
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<th>Event</th>
<th>Early</th>
<th>Deferred</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV ejection fraction acute phase</td>
<td>52.2 ± 12.6%</td>
<td>NA</td>
<td>0.0001</td>
</tr>
<tr>
<td>LV ejection fraction after two weeks</td>
<td>53.1 ± 13.38%</td>
<td>53.5 ± 13.13%</td>
<td>0.0037</td>
</tr>
<tr>
<td>LV ejection fraction after six months</td>
<td>56.5 ± 12.09%</td>
<td>56.4 ± 11.49%</td>
<td>0.0018</td>
</tr>
</tbody>
</table>
GRACIA 1 Trial

500 STEMI Patients
Alteplase

Conservative Management
Ischemia-guided PCI

Early PCI
6-24 hours
Mean 16.7 hours

Composite Outcome:
Death, nonfatal reinfarction and revascularization
at one year


GRACIA 1 - Results

WEST Trial

304 STEMI Patients in whom Primary PCI Could NOT be performed Within 1 hour

A: TNK Alone
Usual Care

B: TNK
Early PCI < 24 hours

C: Primary PCI

Composite Outcome:
Death, reinfarction, refractory ischemia
Congestive heart failure, cardiogenic shock and
Major ventricular arrhythmia at 30 days


WEST - Results

A vs. C, p=0.02
B vs. C, p=NS

P=NS

TRANSFER – AMI Trial

1059 STEMI Patients who received TNK and had at least one High Risk Characteristic: SBP < 100, HR > 100, Killip Class II-III, ST depression anterior leads, or ST elevation right sided V4

Standard Treatment: Rescue PCI or Deferred PCI > 24 hours

Mean Cath 32.5 hours

Early PCI < 6 hours

Mean Cath 2.8 hours

Composite Outcome:
Death, nonfatal reinfarction, recurrent ischemia, new or worsening heart failure or cardiogenic shock within 30 days


Primary Endpoint:
30-Day Death, re-MI, Heart Failure, Severe Recurrent Ischemia, Cardiogenic Shock

% of Patients

<table>
<thead>
<tr>
<th>Standard (n=496)</th>
<th>Pharmacoinvasive (n=508)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.6</td>
<td></td>
</tr>
<tr>
<td>(0.368, 0.783)</td>
<td></td>
</tr>
<tr>
<td>p=0.0013</td>
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</tbody>
</table>

GRACIA 2 Trial
Pharmacoinvasive vs. Primary PCI

212 STEMI Patients

Primary PCI with Abciximab within 3 hours
Mean 1 hour

Pharmacoinvasive PCI
TNK followed by
PCI within 3-12 hours
Mean 4.6 hours

Primary Outcome:
Epicardial and Myocardial Reperfusion
Infarct Size
6 week LV Function

Secondary Outcome:
Bleeding, and composite of death, reinfarction, stroke, or revascularization at 6 months

Tissue Perfusion
Pharmacoinvasive > Primary PCI


Outcomes
Pharmacoinvasive = Primary PCI


No difference in composite ischemic endpoints or LV function despite the added delay in the Pharmacoinvasive group
STUDY PROTOCOL

Fibrinolysis or Primary PCI in ST-Segment Elevation Myocardial Infarction

Primary endpoint: composite of all cause death or shock or CHF or reinfarction up to day 30

ECG at 90 min: ST resolution $\geq 50\%$

STEMI <3 hrs from onset symptoms, PPCI <60 min not possible, 2 mm ST-elevation in 2 leads

RANDOMIZATION 1:1 by IVRS, OPEN LABEL

Strategy A: pharmaco-invasive

Aspirin
Clopidogrel:
LD 300 mg + 75 mg QD
Enoxaparin:
30 mg IV + 1 mg/kg SC Q12h

<75y: full dose

≥75y: ½ dose TNK

PCI/CABG if indicated

Immediate Angio + rescue PCI if indicated

Strategy B: primary PCI

no lytic

Antiplatelet and antithrombin treatment according to local standards

>6 to 24 hrs PCI/CABG if indicated

Primary endpoint: composite of all cause death or shock or CHF or reinfarction up to day 30
TIMI FLOW RATES

SINGLE ENDPOINTS UP TO 30 DAYS

<table>
<thead>
<tr>
<th>Event</th>
<th>Pharmaco-invasive (N=944)</th>
<th>PPCI (N=948)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause death</td>
<td>(43/939) 4.6%</td>
<td>(42/946)</td>
<td>0.88</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>(31/939) 3.3%</td>
<td>4.4% (32/946)</td>
<td>0.92</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>(57/939) 6.1%</td>
<td>(72/943)</td>
<td>0.18</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>(41/939) 4.4%</td>
<td>5.9% (56/944)</td>
<td>0.13</td>
</tr>
<tr>
<td>Reinfarction</td>
<td>(23/938) 2.5%</td>
<td>(21/944)</td>
<td>0.74</td>
</tr>
</tbody>
</table>
### STROKE RATES

<table>
<thead>
<tr>
<th></th>
<th>Pharmaco-invasive</th>
<th>PPCI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TOTAL POPULATION (N=1892)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total stroke</td>
<td>15/939 (1.60%)</td>
<td>5/946 (0.53%)</td>
<td>0.03</td>
</tr>
<tr>
<td>fatal stroke</td>
<td>7/939 (0.75%)</td>
<td>4/946 (0.42%)</td>
<td>0.39</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>9/939 (0.96%)</td>
<td>2/946 (0.21%)</td>
<td>0.04</td>
</tr>
<tr>
<td>fatal haemorrhagic stroke</td>
<td>6/939 (0.64%)</td>
<td>2/946 (0.21%)</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>POST AMENDMENT POPULATION (N=1503)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total stroke</td>
<td>9/747 (1.20%)</td>
<td>5/756 (0.66%)</td>
<td>0.30</td>
</tr>
<tr>
<td>fatal stroke</td>
<td>3/747 (0.40%)</td>
<td>4/756 (0.53%)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>4/747 (0.54%)</td>
<td>2/756 (0.26%)</td>
<td>0.45</td>
</tr>
<tr>
<td>fatal haemorrhagic stroke</td>
<td>2/747 (0.27%)</td>
<td>2/756 (0.26%)</td>
<td>&gt;0.999</td>
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### IN-HOSPITAL BLEEDING COMPLICATIONS

<table>
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<tr>
<th></th>
<th>Pharmaco-invasive (N=944)</th>
<th>PPCI (N=948)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major non-ICH bleeding</td>
<td>6.5%</td>
<td>4.8%</td>
<td>0.11</td>
</tr>
<tr>
<td>Minor non-ICH bleeding</td>
<td>21.8%</td>
<td>20.2%</td>
<td>0.40</td>
</tr>
<tr>
<td>Blood transfusions</td>
<td>2.9%</td>
<td>2.3%</td>
<td>0.47</td>
</tr>
</tbody>
</table>
Options for Reperfusion Therapy at Non-PCI Hospitals

Transfer for primary PCI is better than …

Pharmacoinvasive strategy which is better than …

Fibrinolysis alone

Reperfusion Strategies in STEMI

STEMI Diagnosis*

Primary PCI capable center

Preferably <60 min.

Primary PCI

Rescue-PCI

Immediately

No

Yes

Pharmacoinvasive PCI

EMS or non-primary PCI capable center

PCI possible < 120 min.?

Yes

No

Immediate transfer to PCI-Center

Immediate Transfer PCI-Zentrum

Immediate Transfer PCI-Center

Successful Fibrinolysis?

Immediate Fibrinolysis

Preferably ≤30 min.

Steg et al. ESC STEMI Guidelines. Eur Heart J. 2012;33:2569-2619

*The timepoint the diagnosis is confirmed with patient history and ECG ideally within 10 min from the first medical contact (FMC). All delays are related to FMC (first medical contact).
Conclusion

- Pharmacoinvasive PCI with fibrinolysis is the second best option, if primary PCI is not possible within the required time limits.

- Optimize your local STEMI network so that you don’t need this second best option.

Thank you