The role of pre hospital thrombolysis

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Is thrombolysis still valid?
Disclosure

I am an Interventional Cardiologist
Anatomy of 60% of Fatal Myocardial Infarctions: Rupture

- Endothelium
- Thrombus
- Thin fibrous cap
- Diffuse intimal thickening (dense collagen, sparse smooth muscle cells)
- Macrophages
- Cholesterol, old hemorrhage, cell debris, calcium
Anatomy of 30% of Fatal Myocardial Infarctions: Erosion
STEMI is mainly a **thrombotic event**

- It induces ischemia
- As a consequence: myocardial damage, CHF, death

- **Our goal**: to minimize all the above with a long-lasting effect
Reperfusion-the treatment of STEMI

• **Goal:** rapidly achieving high quality perfusion at the **epicardial and microcirculatory vessels, and the myocytes** levels (which are not identical) and **preventing reocclusion** after initial success

• Is a prompt, fast, reperfusion beneficial for the patient?
Primary PCI vs Fibrinolysis
Reperfusion and Re-vascularization

• The artery does not care how reperfusion is achieved as long as it is fast and long lasting
• **Primary PCI** (PPCI): Mechanical method-first reperfusion (balloon, thrombus aspiration), then re-vascularization (stent)
• **Fibrinolysis** (FL) (Thrombolysis-TL): Pharmacological method-reperfusion only
Reperfusion Factors

- **Patient**: age, co-morbidity, pt. time delay
- **Set up**: Cath. Lab. availability, hour of day
- **Time to reperfusion**: “time is muscle, is survival”
- **Lesion**: thrombus burden, complexity
- **What can we learn from the medical literature?**
“Time is muscle, is survival”
Reperfusion: the ‘golden hour’

Absolute reduction in 35 day mortality per 1000 patients treated

Lives saved per 1000 treated patients

FTT data - closed circles
Smaller trials - open circles

Boersma, Lancet 1996;348:771
PCI delay

Time difference between PCI vs TL, from symptom onset to treatment
Time from symptom onset to treatment in recent trials

PPCI delay = door to balloon minus door to needle

Mean PCI delay: in-hospital lysis = 59 min, prehospital lysis = 114 min, Δ = 55 min

<table>
<thead>
<tr>
<th>Trial</th>
<th>Primary PCI</th>
<th>In-hospital lysis</th>
<th>Prehospital lysis</th>
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Time from symptom onset to treatment (mins)
“Time is muscle, is survival”

According to these studies, we can gain almost 2 hours by the pre-hospital TL approach compare to PPCI and theoretically save more heart muscle and improve survival
Relationship between time of day and time to reperfusion

Geometric mean door to drug or balloon times (mins)

- Regular hours
- Off hours

Thrombolysis (n=68439)
- Regular hours: 33
- Off hours: 34

Primary PCI (n=33647)
- Regular hours: 95
- Off hours: 116

Δ = 21

Off hours PCI delay vs TL = 82 min!

Regular hours = weekdays 7am to 5pm
67.9% lysis and 54.2% PPCI were treated off hours
NRMI registry 1999-2002

Magid, JAMA 2005;294:803
ACSIS: Israeli registry 2000-2010

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<tr>
<th>Method</th>
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<th>Symptoms to reperfusion (min)</th>
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<td>PPCI</td>
<td>899</td>
<td>108±38</td>
<td>179±235*</td>
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<tr>
<td>TL followed by PCI</td>
<td>383</td>
<td>106±37</td>
<td>122±45*</td>
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Mean PCI delay: 57 min

*P<0.001
23 trials of PCI versus thrombolysis (n=7419)

Mean delay 39.5 min (SD 22.1)
For every 10 min delay there is 0.94% decrease in mortality benefit, p=0.006.

No benefit if delay > 62 mins

Circles reflect trial sample size
Blue line: weighted meta-regression

Nallamothu, Am J Cardiol 2003;92:824
Lesion factor

• PPCI is performed mainly at a totally occluded artery with high thrombotic burden

The challenge:
• Lesion crossing with guide wire
• Thrombus burden reduction-mechanical (TAPAS)? Pharmacological (INFUSE AMI)?
• Distal embolization-no solution so far
• Slow or no reflow-increases MACE tenfold
• Lethal reperfusion injury-permanent myocardium damage despite and maybe because, prompt and aggressive early reperfusion by PCI with good flow

Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials

*Ellen C Keeley, Judith A Boura, Cindy L Grines*

Department of Internal Medicine, Division of Cardiology, University of Texas Southwestern Medical Center, Dallas, TX, USA (E C Keeley MD); and William Beaumont Hospital, Royal Oak, MI (J A Boura MS, C L Grines MD)

*Lancet 2003; 361: 13–20*
Primary PCI versus Thrombolysis - meta-analysis of 23 trials

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Favours PPCI
Favors Lysis
Meta-Analysis of 23 Randomized Trials of PCI vs Lysis (n=7739)

% Events at 4-6 weeks

- Death (w/shock) 7% PCI, 9% Lysis, p=.0002
- Death (shock excl.) 5% PCI, 7% Lysis, p=.0003
- Non Fatal ReMI 2.5% PCI, 6.8% Lysis, p<.0001
- Total Stroke 1% PCI, 2% Lysis, p=.0004
- Hemorrhagic CVA 0.05% PCI, 1.1% Lysis, p<.0001

Keeley, Lancet 2003
Keeley meta-analysis of 23 trials
Some limitations...

• Suboptimal lytic strategies, many late comers...
  - The criterion for time to treatment was 6 h or less in 9 of the trials, 12 h in 13 trials, and up to 36 h in the SHOCK trial
    - streptokinase in 8 trials
• Many high risk patients with shock and CHF got lytic therapy! (mainly in the SHOCK trial with 63% in the lysis group)
• Most trials (15) had fewer than 200 patients
• 2% major bleeding and 0.4–2% need for vascular repair in PPCI patients
• Development of acute renal failure in 0.5–13% of PPCI patients
• PRAGUE-2: “The study results do not show difference between thrombolysis and PCI among patients with a presentation time <3 hours”.
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Accelerated tPA trials, excluding Shock

Favours PPCI   Favours Lysis

OR 0.81, 95% CI 0.64-1.02, \( P=0.07 \)
No routine revascularization after TL reperfusion!

• Most of the trials with no reference to post TL PCI or “NA”
• PRAGUE 2: “In the TL group, angiography was performed according to routine clinical indications: post MI angina, reinfarction, rescue PCI”. No numbers
• DANAMI 2: “PCI occurred in only 2.5% of patients who got fibrinolysis”
Real scientific conclusions?

Most of the TL patients were left with no definitive re-vascularization that made them prone to re-MI and further MACE. For real scientific conclusions the comparison should have been between the PPCI patients and the TL patients that underwent early re-vascularization.
## Primary PCI in STEMI

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<th>Condition</th>
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<td>Ischemic symptoms &lt;12 h and contraindications to fibrinolytic therapy</td>
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<td>B</td>
<td>(52,53)</td>
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<td>irrespective of time delay from FMC</td>
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<td>Cardiogenic shock or acute severe HF</td>
<td>I</td>
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<td>(54–57)</td>
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<td>irrespective of time delay from MI onset</td>
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<td>Evidence of ongoing ischemia 12 to 24 h after symptom onset</td>
<td>Ila</td>
<td>B</td>
<td>(29,30)</td>
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<td>PCI of a noninfarct artery at the time of primary PCI in patients</td>
<td>III: Harm</td>
<td>B</td>
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<td>without hemodynamic compromise</td>
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**COR** indicates Class of Recommendation; **FMC**, first medical contact; **HF**, heart failure; **LOE**, Level of Evidence; **MI**, myocardial infarction; **PCI**, percutaneous coronary intervention; and **STEMI**, ST-elevation myocardial infarction.
Fibrinolytic Therapy When There Is an Anticipated Delay to Performing Primary PCI Within 120 Minutes of FMC

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<td>ST depression except if true posterior (inferobasal) MI suspected or when associated with ST-elevation in lead aVR</td>
<td>III: Harm</td>
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COR indicates Class of Recommendation; FMC, first medical contact; LOE, Level of Evidence; MI, myocardial infarction; N/A, not available; and PCI, percutaneous coronary intervention.
Benefit to TL in “early comers”? 

PPCI was accepted as superior to fibrinolytic therapy (TL) for STEMI, but there are more and more evidences that show otherwise in patients presenting soon after the onset of symptoms treated with TL.
Smokers With ST-Segment Elevation Myocardial Infarction and Short Time to Treatment Have Equal Effects of PCI and Fibrinolysis


• 1572 patients with STEMI were randomized to either fibrinolysis or PCI for DANAMI-2
• 895 (57%) were identified as smokers
• Smokers with short time to treatment (<3 hours) benefited equally from PCI and fibrinolysis $P=0.82$
• There was a trend toward higher mortality in the PCI group
Comparison of primary PCI and prehospital thrombolysis in acute MI (CAPTIM n=840)

Events at 30 days

- **Primary PCI**
- **Pre-hospital alteplase (rescue PCI 26%)**

**Death**
- Primary PCI: 4.8%
- Pre-hospital alteplase (rescue PCI 26%): 3.8%
- P=0.61

**Death, re-MI, CVA**
- Primary PCI: 6.2%
- Pre-hospital alteplase (rescue PCI 26%): 8.2%
- P=0.29

Planned 1200 patients
Symptoms to lysis 130 min
Symptoms to balloon 190 min

Bonnefoy, Lancet 2002;360:825
Fibrinolysis or Primary PCI in ST-Segment Elevation Myocardial Infarction-STREAM

Paul W. Armstrong, M.D., Anthony H. Gershlick, M.D., Patrick Goldstein, M.D., Robert Wilcox, M.D., Thierry Danays, M.D., Yves Lambert, M.D., Vitaly Sulimov, M.D., Ph.D., Fernando Rosell Ortiz, M.D., Ph.D., Miodrag Ostojic, M.D., Ph.D., Robert C. Welsh, M.D., Antonio C. Carvalho, M.D., Ph.D., John Nanas, M.D., Ph.D., Hans-Richard Arntz, M.D., Ph.D., Sigrun Halvorsen, M.D., Ph.D., Kurt Huber, M.D., Stefan Grajek, M.D., Ph.D., Claudio Fresco, M.D., Erich Bluhmki, M.D., Ph.D., Anne Regelin, Ph.D., Katleen Vandenberghe, Ph.D., Kris Bogaerts, Ph.D., and Frans Van de Werf, M.D., Ph.D. for the STREAM Investigative Team

March 10, 2013, at NEJM.org
Methods

- 1892 patients with STEMI, presented within 3 hours after symptom onset
- Randomly assigned to undergo either PPCI or TL by TNK
- Emergency coronary angiography (Rescue) was performed if fibrinolysis failed
- Angiography and PCI was performed 6 to 24 hours after randomization
- Primary end point: death, shock, congestive heart failure, or reinfarction up to 30 days
Total primary end point: death, shock, CHF, reinfarction-up to 30 days

P=0.21

14.3%

12.4%

FL: Fibrinolysis, PPCI: Primary PCI

TL patients underwent angiography at a **median of 17 hours** after randomization.

**Lower rates of shock and heart failure**, as well as **more complete surgical coronary revascularization**, among the patients undergoing fibrinolysis.
Conclusion

“Prehospital fibrinolysis with timely coronary angiography resulted in effective reperfusion in patients with early STEMI who could not undergo primary PCI within 1 hour after the first medical contact”
French FAST AMI registry:
One-year survival according to use and type of reperfusion therapy

Lysis: 2/3 pre hospital, 70% treated <3h

# at risk
No reperfusion 581 562 552 534
Thrombolysis 440 437 434 433
PPCI 529 522 518 512

Pre-hospital lysis is as good as primary PCI, provided “rescue” procedures are available.

“In early comers, pre hospital lysis is probably better than primary PCI”
Cumulative Survival among 1050 Patients in the Primary-Angioplasty Group and 2095 Patients in the Thrombolytic-Therapy Group.


MITI trial
ACSIS: Israeli registry 2000-2010

1-YEAR SURVIVAL STRATIFIED BY TYPE OF REPERFUSION

LOG RANK TEST, P = 0.098

TIME (DAYS)
<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Level&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinolytic therapy is recommended within 12 h of symptom onset in patients without contraindications if primary PCI cannot be performed by an experienced team within 120 min of FMC.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>In patients presenting early (&lt;2 h after symptom onset) with a large infarct and low bleeding risk, fibrinolysis should be considered if time from FMC to balloon inflation is &gt;90 min.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>If possible, fibrinolysis should start in the prehospital setting.</td>
<td>IIa</td>
<td>A</td>
</tr>
<tr>
<td>A fibrin-specific agent (tenecteplase, alteplase, reteplase) is recommended (over non-fibrin specific agents).</td>
<td>I</td>
<td>B</td>
</tr>
</tbody>
</table>
Factors that increase the long term beneficial effect of TL in STEMI patients

• Patients presenting early (2-3 hr) after symptom onset
• Patients with no hemodynamic compromise
• Early definitive revascularization (6-24 hr after successful TL reperfusion) is obligatory
The PRER strategy

**PRER:** Prompt Reperfusion (TL) Followed by Early Revascularization (PCI) in Selected STEMI Patients

Early-arriving STEMI patients (2-3 hr after onset), with no signs of hemodynamic compromise, that come during off hour period, can benefit from prompt reperfusion by thrombolytic therapy, ASAP (pre hospital) followed by early IRA revascularization 6 to 24 hours after TL using TRA.

All the rest will be treated as PPCI.

We call for a multi-center, prospective study, to substantiate the validity of this strategy.

Prompt Pharmacological Reperfusion Followed by Early Mechanical Revascularization in Selected STEMI Patients  *Frimerman et al*
• 48 y.o. male, heavy smoker, admitted to ICCU at 02:30 with anterior STEMI.
• Symptoms begun one and a half hour prior to admission.
• 17 months ago he had lateral MI and a BMS was implanted in LCX.
• 10 minutes after arrival he got SK infusion.
• In 20 minutes the pain subsided and the ECG normalized.
• 10 hours later he was in the Cath. Lab.
“The reports of my death are greatly exaggerated.”

Mark Twain, 1897, cable from London to the Associated Press
Thank You
Our experience in 2010-2012

Early-arriving STEMI patients (2-3 hr after onset), with no signs of hemodynamic compromise, were treated by SK followed by PCI at 6-24 hr using trans-radial approach.

In hospital, 1 month and 1 year mortality was compared to PPCI patients

Results

In-hospital, 1 month, and 1-year mortality of the PPCI patients versus the THR patients are presented in the table:

<table>
<thead>
<tr>
<th></th>
<th>Patient number (%)</th>
<th>In-hospital mortality</th>
<th>1-month mortality</th>
<th>1-year mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPCI</td>
<td>183 (58%)</td>
<td>5 (2.7%)</td>
<td>11 (6%)</td>
<td>17 (9.3%)</td>
</tr>
<tr>
<td>THR</td>
<td>133 (42%)</td>
<td>1 (0.7%)</td>
<td>1 (0.7%)</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>p-value</td>
<td>ns</td>
<td>0.016</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

PPCI: Primary PCI, THR: Thrombolysis

No intra-cranial hemorrhage occurred in the THR group.

Prompt Pharmacological Reperfusion Followed by Early Mechanical Revascularization in Selected STEMI Patients  Frimerman et al
Thrombus causes complications during intervention

- 3X higher MACE – ischemic complications
- Lower procedural success (<75%): Type C lesions
- Higher distal embolization leading to slow flow or no re-flow
- High mortality (3-5%)
- ST-elevation
- Longer hospital stays

# Benefit of an Open Artery on Arrival at the Cath Lab

<table>
<thead>
<tr>
<th></th>
<th>Closed Artery TIMI 0-1 (n = 1,214)</th>
<th>Open Artery TIMI 2-3 (n = 272)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Procedural Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedural Success</td>
<td>94%</td>
<td>97%</td>
<td>.02</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>13.1%</td>
<td>5.0%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Hospital Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 Day Mortality</td>
<td>8.9%</td>
<td>4.8%</td>
<td>.02</td>
</tr>
<tr>
<td>Peak CK(U/L)</td>
<td>2,790</td>
<td>1,328</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>LV Function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute EF</td>
<td>51.6%</td>
<td>54.3%</td>
<td>.05</td>
</tr>
<tr>
<td>6 Month EF</td>
<td>54.9%</td>
<td>59.2%</td>
<td>.004</td>
</tr>
</tbody>
</table>

Brodie AJC 2000; 25:13
Survival as a Function of ST-Segment Resolution

- In 403 patients with TIMI-3 flow after primary PTCA

Survival (%)

- Complete (51%)
- Partial (35%)
- None (14%)

MV risk of death = 3.5 [1.5, 8.0] 16%
MV risk of death = 6.4 [2.7, 15.3] 31%

P < 0.001

Time (months)

Van’t Hof et al. Lancet 1997;350:615
TIMI-3 Flow & ST-Segment Resolution

- In 403 consecutive patients with ST-segment elevation AMI achieving TIMI-3 flow after primary PTCA with ECGs before and after

- Partial ST-segment resolution (30-70%)
- Complete ST-segment Resolution (>70%)
- No ST-segment resolution (<30%)

Reperfusion injury?