STREAM TRIAL

WHY A PHARMACO-INVASIVE APPROACH IS ESSENTIAL
Fibrinolysis or Primary PCI in ST-Segment Elevation Myocardial Infarction


PCI = Percutaneous Coronary Intervention
ESC GUIDELINES
ON ACUTE STEMI MANAGEMENT

ORGANISATION OF STEMI PATIENT DISPOSAL DESCRIBING
PRE- AND IN-HOSPITAL MANAGEMENT, AND REPERFUSION
STRATEGIES WITHIN 24H OF FMC†

Adapted from:

* * Cath = Catheterisation Laboratory; ** EMS = Emergency Medical System; † FMC = First Medical Contact; †† PCI = Percutaneous Coronary Intervention; ††† ICU = Intensive Care Unit

 Coronary angiography preferably 3 to 24 h after FMC - Delayed PCI as required

Symptoms of STEMI

EMS**
Pre-hospital diagnosis & care
Ambulance to Cath Lab
Primary PCI capable centre
Preferably < 60 mins
Primary PCI"
Rescue PCI
Immediately
No
Yes
Coronary angiography preferably 3 to 24 h after FMC - Delayed PCI as required

Successful fibrinolysis?

Transfer to ICU" of PCI-capable center
Immediate fibrinolysis

Non-primary PCI capable centre
PCI possible <2 hrs
Yes
No
Preferably ≤ 30 mins

Self referral
Private Transportation

GP / Cardiologist
STREAM (STRATEGIC REPERFUSION EARLY AFTER MYOCARDIAL INFARCTION)

Investigated whether prompt thrombolysis at first medical contact (FMC), followed by timely angiography or rescue PCI in patients with acute STEMI presenting within 3 hr not able to undergo PPCI within 60 min, is an appropriate and effective reperfusion treatment (pharmaco-invasive strategy) to PPCI

PRIMARY ENDPOINT:
composite of death, shock, congestive heart failure (CHF) or re-infarction at 30 days

SAFETY ENDPOINTS INCLUDE: all-cause mortality, cardiogenic shock, CHF, re-infarction, rehospitalisation for cardiac reasons and rehospitalisation for non-cardiac reasons

FMC = First Medical Contact; PCI = Percutaneous Coronary Intervention; PPCI = Primary Percutaneous Coronary Intervention

STREAM TRIAL AIM

To compare the outcome of early fibrinolysis with Tenecteplase followed by coronary angiography within 6-24 hours with standard primary PCI in STEMI patients presenting within 3 hours of symptom onset and unable to undergo primary PCI within 1 hour.

PCI = Percutaneous Coronary Intervention

AIM OF STUDY

Are there other therapies we can use in STEMI patients who cannot receive a primary PCI < 1 hr?

Therefore the STREAM investigators asked:

How does early thrombolysis with anti-platelet and anticoagulant therapy compare to primary PCI in STEMI patients who present <3 hours of symptom onset?

PCI = Percutaneous Coronary Intervention

Comparing Outcomes of Fibrinolysis versus PPCI

The NEW ENGLAND JOURNAL of MEDICINE

Established in 1812

April 11, 2013

Vol. 368 No. 15

Fibrinolysis or Primary PCI in ST-Segment Elevation Myocardial Infarction

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 Bluemki, 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

STREAM TRIAL STUDY ARMS

**ARM 1:**

Tenecteplase (Metalyse®) followed by angiography after 6-24 hours unless rescue is needed

**ARM 2:**

Primary PCI according to local standards

---

PCI = Percutaneous Coronary Intervention

END POINTS

PRIMARY END POINT (30 DAY COMPOSITE):

Death from any cause, shock, congestive HF, or re-infarction

SINGLE EFFICACY OR SAFETY END POINTS INCLUDED:

- Ischaemic stroke
- ICH
- Non-intracranial bleeding

HF = Heart Failure
STREAM STUDY DESIGN

PATIENTS PRESENTING WITH STEMI <3HRS FROM ONSET OF SYMPTOMS THAT CANNOT RELIABLY UNDERGO PRIMARY PCI <60 MIN

<table>
<thead>
<tr>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 75 yrs: TNK</td>
<td>ASA, No lytic</td>
</tr>
<tr>
<td>Routine ASA</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel: LD 300 mg +</td>
<td>Antiplatelet and</td>
</tr>
<tr>
<td>75 mg QD</td>
<td>anticoagulation treatment</td>
</tr>
<tr>
<td>Enoxaparin: 30 mg IV +</td>
<td>according to local standards</td>
</tr>
<tr>
<td>1 mg/kg SC Q 12 h</td>
<td></td>
</tr>
<tr>
<td>ECG at 90 min: ST resolution ≥ 50 %</td>
<td></td>
</tr>
<tr>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>NO</td>
<td></td>
</tr>
<tr>
<td>Diagnostic angiography</td>
<td>Standard angiography</td>
</tr>
<tr>
<td>+ PCI / stent, if indicated</td>
<td>+ PCI / stent immediately</td>
</tr>
<tr>
<td>&gt; 6 hrs / &lt; 24 hrs</td>
<td></td>
</tr>
<tr>
<td>n = 944</td>
<td></td>
</tr>
</tbody>
</table>

# RESULTS

<table>
<thead>
<tr>
<th></th>
<th>Fibronolysis</th>
<th>Primary PCI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point</td>
<td>12.4%</td>
<td>14.3%</td>
<td>0.21</td>
</tr>
<tr>
<td>Symptom onset to start of reperfusion treatment: tenecteplase or arterial sheath insertion (min)</td>
<td>100</td>
<td>178</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Open vessels on first angiography (before PCI)</td>
<td>58.5%</td>
<td>20.7%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PCI after angiography</td>
<td>80.4%</td>
<td>89.8%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CABG after angiography/PCI</td>
<td>4.7%</td>
<td>2.1%</td>
<td>0.002</td>
</tr>
<tr>
<td>Stent placement</td>
<td>95.7%</td>
<td>95.6%</td>
<td>0.95</td>
</tr>
</tbody>
</table>

- No difference in primary end point i.e. mortality and morbidity
- Shorter delay for patients receiving treatment in fibronolysis
- Better initial revascularization in patients receiving fibronolysis
- Less patients required a PCI after thrombolysis in arm 1 vs arm 2
- Increased number of patients needed CABG in the fibronolysis — due to longer time to angiography where revascularization decisions would be made

PCI = Percutaneous Coronary Intervention;

STREAM: INCIDENCE & INDIVIDUAL COMPONENTS OF THE PRIMARY ENDPOINT AT 30 DAYS

Pharmaco-invasive (N=944) | PPCI (N=948)

% of patients

16

12

8

4

0

12.4

4.6

3.3

6.1

4.4

2.5

4.4

14.3

4.4

3.4

7.6

5.9

2.2

p=0.24

p=0.88

p=0.92

p=0.18

p=0.13

p=0.74

Primary endpoint*

All cause death

Cardiac death

Congestive heart failure

Cardiogenic shock

Reinfarction

* death from any cause, shock, congestive heart failure, or reinfarction up to 30 days

PPCI: Primary Percutaneous Coronary Intervention

## STROKE INCIDENCE

<table>
<thead>
<tr>
<th>Event</th>
<th>Fibronolysis (N = 944)</th>
<th>Primary PCI (N = 948)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total stroke</td>
<td>15/939 (1.6)</td>
<td>5/946 (0.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>9/939 (1.0)</td>
<td>2/946 (0.2)</td>
<td>0.04</td>
</tr>
<tr>
<td>After protocol amendment*</td>
<td>4/747 (0.5)</td>
<td>2/756 (0.3)</td>
<td>0.45</td>
</tr>
</tbody>
</table>

After amendment: No difference is incidence of intracranial haemorrhage between 2 treatment groups

PCI = Percutaneous Coronary Intervention

TIMI FLOW RATES


PPCI = primary percutaneous coronary intervention
FAST-AML COHORT CONFIRMS OUTCOMES LONG TERM

Adjusted HR [95% CI] (reference no reperfusion)
- Primary PCI: 0.57 [0.43 - 0.74]
- IV Fibrinolysis: 0.48 [0.35 - 0.68]

Adjusted HR [95% CI] fibrinolysis vs pPCI
0.73 [0.50 - 1.06]

Numbers at risk

<table>
<thead>
<tr>
<th></th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>No reperfusion</td>
<td>462</td>
</tr>
<tr>
<td>Lysis</td>
<td>447</td>
</tr>
<tr>
<td>PPCI</td>
<td>583</td>
</tr>
</tbody>
</table>

PPCI = primary percutaneous coronary intervention

Adapted from:
Cardiac mortality cumulative incidence STREAM trial

<table>
<thead>
<tr>
<th>Number at Risk</th>
<th>Tenecteplase</th>
<th>Primary PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>944</td>
<td>948</td>
</tr>
<tr>
<td></td>
<td>896</td>
<td>903</td>
</tr>
<tr>
<td></td>
<td>888</td>
<td>898</td>
</tr>
<tr>
<td></td>
<td>886</td>
<td>897</td>
</tr>
<tr>
<td></td>
<td>884</td>
<td>893</td>
</tr>
<tr>
<td></td>
<td>881</td>
<td>890</td>
</tr>
<tr>
<td></td>
<td>880</td>
<td>890</td>
</tr>
<tr>
<td></td>
<td>879</td>
<td>889</td>
</tr>
<tr>
<td></td>
<td>878</td>
<td>888</td>
</tr>
<tr>
<td></td>
<td>875</td>
<td>887</td>
</tr>
<tr>
<td></td>
<td>875</td>
<td>886</td>
</tr>
<tr>
<td></td>
<td>874</td>
<td>885</td>
</tr>
<tr>
<td></td>
<td>873</td>
<td>885</td>
</tr>
</tbody>
</table>

PCI = Percutaneous Coronary Intervention

FIBRINOLYSIS WITH BOLUS TENECTEPLASE AND CONTEMPORARY ANTITHROMBOTIC THERAPY GIVEN BEFORE TRANSPORT TO A PCL-CAPABLE HOSPITAL:

- Circumvents the need for urgent PCI in about two thirds of fibrinolytic treated STEMI patients
- Is associated with small increased risk of intracranial bleeding
- Is as effective as PPCI in STEMI patients within 3 hours symptom onset who cannot undergo PCI within 1 hour of first medical contact

1. (Cantor et al., STREAM study, NEJM 2009)
SUBGROUP ANALYSIS

No difference in treatment effect of fibrinolysis vs. primary PCI in patients regardless of:

- Age
- Gender
- Blood Pressure
- Presence of diabetes mellitus
- Weight

The results are similar in different population groups

PCI = Percutaneous Coronary Intervention

IMPORTANT TAKE HOME POINTS

- Fibrinolysis provides clinicians with additional time **BUT** 80% of patients will still require a PCI

- A greater incidence of ICH was seen in patients before the protocol was amended, after which there was **no significant difference** between groups

- Blood pressure, age, gender, diabetes etc **do not** influence impact of fibrinolysis on primary outcome

*PCI = Percutaneous Coronary Intervention*

WHAT DOES THIS MEAN?

- Clinicians can “buy time” by administering tenecteplase to STEM I patients if primary PCI cannot be performed within 1 hour.

- Of importance in SA setting:
  - Traffic, patients living in outlying areas
  - Not all hospitals have PCI facilities

- Provide additional time for patient to receive PCI with similar outcomes

PCI = Percutaneous Coronary Intervention
STREAM: NEW APPROACH IN ACUTE STEMI MANAGEMENT

Fibrinolytics, administered by needle

PCI Balloon and Stent

PCI = Percutaneous Coronary Intervention

STREAM: UPDATES

1. STREAM Time Delay
2. STREAM Aborted MI
3. ECG Insights into Strategic Reperfusion
4. STREAM Elderly Patients
5. STREAM 1-Year Mortality Follow-Up
6. STREAM Cardiac Results
STREAM: TIME DELAY

- Assessed the impact of increasing time delay on outcomes in patients randomised to pharmaco-invasive strategy or PPCI
- Composite* endpoint according to time delay:

<table>
<thead>
<tr>
<th>PCI-related delay</th>
<th>Pharmaco-invasive</th>
<th>PPCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤55 min (n=583)</td>
<td>10.6%</td>
<td>10.3%</td>
</tr>
<tr>
<td>&gt;55-97 min (n=711)</td>
<td>13.9%</td>
<td>17.9%</td>
</tr>
<tr>
<td>&gt;97 min (n=359)</td>
<td>13.5%</td>
<td>16.2%</td>
</tr>
</tbody>
</table>

*p Value: 0.910, 0.148, 0.470

*Death, congestive heart failure, cardiogenic shock, myocardial infarction
PCI = Percutaneous Coronary Intervention; PPCI = Primary Coronary Intervention

Adapted from:

- Relative association of continuous PCI-related delay (min) and pharmacoinvasive treatment with 30-day composite outcome (CHF, shock, MI)

PI: Pharmaco-invasive; PPCI: primary percutaneous coronary intervention
CONCLUSIONS

• As **PCI-related delay (P-RD)** increased, pharmaco-invasive strategy outcomes became **superior to PPCI** when P-RD is prolonged and exceeds guideline-mandated times

• In such circumstances, a **pharmaco-invasive strategy** may provide an alternative reperfusion option

• Adverse **time delays for delivery of PPCI** should be considered when evaluating reperfusion strategies
Evaluated the pre-specified STREAM endpoint, aborted MI, to compare a pharmaco-invasive strategy with PPCI

<table>
<thead>
<tr>
<th></th>
<th>Pharmaco-invasive strategy</th>
<th>PPCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aborted MI*</td>
<td>11.1%</td>
<td>6.9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p≤0.01</td>
</tr>
<tr>
<td>Total ischaemic time**</td>
<td>90 mins</td>
<td>190 mins</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-</td>
</tr>
</tbody>
</table>

* Aborted MI is defined in the study as: “≥50% resolution in ST-elevation resolution in the ECG lead exhibiting the maximal baseline ST-elevation at either 90 min post-TNK or 30 min post- PCI in PI and primary PCI patients, respectively.” Additionally, biomarker analysis (either CK-MB ≤ 2 times the ULN or CK ≤2 times the ULN or cardiac troponin I/T (cTn) levels ≤ 5 times the ULN) was required.

** Total ischaemic time for the pharmaco-invasive arm is defined as time from symptom onset to TNK and symptom onset to sheath insertion in the PPCI arm

TNK: tenecteplase; MI: myocardial infarction; PPCI: primary percutaneous coronary intervention; CK-MB: creatinine kinase MB isoenzyme; CK: creatinine kinase; ULN: Upper limit of normal

Adapted from:
STREAM: ABORTED MI

Relative risk plot of the primary composite outcome and its components

Adapted from:

* Aborted MI is defined as “≥50% resolution in ST-segment elevation coupled with no or minimal subsequent rise in cardiac biomarkers and deemed to be an indicator of successful reperfusion therapy.”
CONCLUSIONS

• A **pharmaco-invasive strategy** of early fibrinolysis coupled with anti-thrombotic and antiplatelet therapy more frequently aborts MI than PPCI

• Such patients had more favourable outcomes compared to non-AbMIs

STREAM: ECG INSIGHTS INTO STRATEGIC REPERFUSION

Comparison of ECG metrics and clinical outcomes in three groups:

- fibrinolysis requiring rescue angiography (n=348)
- fibrinolysis with scheduled angiography (n=516)
- PPCI (n=927)

% of patients with residual ST elevation ≥2 mm 30 minutes after angiography:

<table>
<thead>
<tr>
<th>Rescue patients</th>
<th>Scheduled patients</th>
<th>Primary PCI patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>27.9%</td>
<td>7.9%</td>
<td>24.8%</td>
</tr>
</tbody>
</table>

Adapted from:
STREAM: ECG INSIGHTS INTO STRATEGIC REPERFUSION

REPERFUSION STRATEGY AND 30-DAY COMPOSITE ENDPOINT AND INDIVIDUAL CLINICAL EVENTS:

Adapted from:
CONCLUSIONS

- Fibrinolytic-treated patients not requiring rescue angiography had ECG evidence of superior reperfusion and lower clinical event rates than PPCI.

- Patients requiring rescue angiography had higher risk with more baseline co-morbidities and worse 30-day outcomes.

ECG: Electrocardiography; PPCI: primary percutaneous coronary intervention

Adapted from:
Baseline characteristics, clinical outcomes, and relationship of TNK dose reduction to the efficacy, safety, and electrocardiographic indicators of reperfusion efficacy were evaluated in STEMI patients ≥ 75 years

<table>
<thead>
<tr>
<th></th>
<th>Pre-dose amendment patients (%)</th>
<th>Post-dose amendment patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median extent of ST-segment resolution (≥50%)</td>
<td>63.2</td>
<td>56.0</td>
</tr>
<tr>
<td>≥2 mm in ECG lead with greatest ST-segment elevation</td>
<td>43.6</td>
<td>40.0</td>
</tr>
<tr>
<td>Rescue coronary intervention after TNK</td>
<td>42.9</td>
<td>44.1</td>
</tr>
<tr>
<td>Primary composite endpoint</td>
<td>31.0</td>
<td>24.7</td>
</tr>
</tbody>
</table>

TNK: tenecteplase; MI: myocardial infarction; ECG: Electrocardiography; STEMI: ST-Elevation Myocardial Infarction

Stream: Elderly Patients

Relative Association of Amendment and Study Treatment with 30-Day Primary Composite End Point:

30-day primary composite endpoint*

* 30-day all-cause death, cardiogenic shock, congestive heart failure, and re-infarction; PPCI: primary percutaneous coronary intervention;

CONCLUSIONS

- Half-dose TNK reduces likelihood of **intracerebral haemorrhage** (ICH) without compromising reperfusion efficacy

- Observations are **hypothesis generating** and warrant further confirmation in randomised clinical trials in the elderly

TNK: tenecteplase

### STREAM: 1-YEAR MORTALITY FOLLOW-UP

**ALL-CAUSE AND CARDIAC MORTALITY RATES:**

<table>
<thead>
<tr>
<th>All-cause Mortality Rate</th>
<th>Cardiac Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmacoinvasive</strong></td>
<td><strong>PPCI</strong></td>
</tr>
<tr>
<td>6.7%</td>
<td>5.9%</td>
</tr>
<tr>
<td>4.0%</td>
<td>4.1%</td>
</tr>
</tbody>
</table>

*30-day primary composite endpoint*

- *P = 0.49; risk ratio, 1.13; 95% confidence interval, 0.79-1.62*
- *P = 0.93; risk ratio, 0.98; 95% confidence interval, 0.62-1.54*

---

* 30-day all-cause death, cardiogenic shock, congestive heart failure, and re-infarction; PPCI: primary percutaneous coronary intervention;

---

CONCLUSIONS

At 1 year, mortality rates in the pharmaco-invasive strategy and PPCI arms were similar in STEMI patients presenting within 3h after symptom onset and unable to undergo PPCI within 1h.

STEMI= ST segment elevation myocardial infarction; PPCI: primary percutaneous coronary intervention;

1. **Pharmaco-invasive strategy** for early presenting STEMI nominally reduced 30-day cardiogenic shock and congestive heart failure compared with PPCI

2. Evaluated whether this effect was associated with infarct size

- Small (≤ 2 times the upper limit normal [ULN])
- Medium (> 2 to ≤ 5 times the ULN)
- Large (> 5 times the ULN)

---

STEMI= ST segment elevation myocardial infarction; PPCI: primary percutaneous coronary intervention; ULN: Upper limit of normal


**STREAM: CARDIAC RESULTS**

Relative risk plot of the 30-day composite endpoint of shock/congestive heart failure (CHF)

* Adjusted for thrombolysis in myocardial infarction risk score


STREAM: CARDIAC RESULTS

CONCLUSIONS

• A **pharmacoinvasive strategy** appears to alter the pattern of infarct size after STEMI, resulting in **more medium and fewer large infarcts** compared with PPCI.

• Despite a comparable number of small infarcts, pharmacoinvasive strategy patients in this group had **more aborted myocardial infarctions** and less 30-day shock and congestive heart failure.

PPCI = Primary Percutaneous Coronary Intervention; STEMI = ST segment elevation myocardial infarction


STREAM-2 (STRATEGIC REPERFUSION IN ELDERLY PATIENTS AFTER MYOCARDIAL INFARCTION)

THE AIM IS TO COMPARE THE EFFICACY AND SAFETY OF

• EARLY FIBRINOLYTIC TREATMENT (half-dose TNK and antiplatelet therapy) followed by catheterisation within 6-24 hours or rescue PCI if indicated versus

• PPCI in elderly patients (≥70 years) with STEMI treated within 3h of symptom onset

COMPOSITE ENDPOINT:
death, shock, heart failure, recurrent MI at 30 days

TRIAL STATUS:
Using a study design similar to STREAM, STREAM 2 started 01 August 2017 with an estimated completion date of June 2020

_PCI = Percutaneous Coronary Intervention; STEMI = ST segment elevation myocardial infarction_

Clinicaltrials.gov identifier: NCT02777580.