
Christopher B. Granger
Duke University
Disclosures

- Research contracts: Armetheon, AstraZeneca, Bayer, Novartis, GSK, BMS, Pfizer, The Medicines Company, and Boehringer Ingelheim

- Consulting/Honoraria: AstraZeneca, GSK, BMS, Pfizer, Lilly, Daiichi Sankyo, Novartis, Boehringer Ingelheim, The Medicines Company, and Sanofi-Aventis

- For full listing see www.dcri.duke.edu/research/coi.jsp
Time is a critical element in care of ACS

- Time to reperfusion for STEMI
- Time to cath following fibrinolytics
- Timing of non-culprit artery PCI
- Time to cath for ACS according to risk
- Timing of starting P2Y$_{12}$ antagonists in ACS
These results document the presence of a subepicardial zone of ischemic but viable myocardium which is available for pharmacologic or surgical salvage for at least three and perhaps six hours following circumflex occlusion.

Reimer KA, ... Jennings RB. Circulation 1977; 56:786
Rao M. J Int Cardiol 2014
Importance of Time

Mortality reduction versus treatment delay

35 day mortality

In first 1-2 hours, up to 40 lives per 1000 saved per hour of faster treatment

Presentation Delay and Outcome

Sx Onset to Presentation

Primary Angioplasty

- < 2hr: 5.1%
- 2-4hr: 6.1%
- > 4hr: 6.7%

Fibrinolysis

- < 2hr: 5.4%
- 2-4hr: 7.3%
- > 4hr: 14.6%

-- Zijlstra, EHJ, 2002
Primary PCI
Median D2B  83 min
Overall mortality  4.6%

N= 43,801 NCDR STEMI Patients  
2005-2006

P <0.001 for trend
Contradictory studies from the same dataset

**Door-to-Balloon Time and Mortality among Patients Undergoing Primary PCI**

Daniel S. Menees, M.D., Eric D. Peterson, M.D., Yongfei Wang, M.S., Jeptha P. Curtis, M.D., John C. Messenger, M.D., John S. Rumsfeld, M.D., Ph.D., and Hitinder S. Gurm, M.B., B.S.

**Relation between door-to-balloon times and mortality after primary percutaneous coronary intervention over time: a retrospective study**


---

**Overall (N=96,739)**

- **Median door-to-balloon time (min):**
  - 2005-2006: 83
  - 2006-2007: 76
  - 2007-2008: 70
  - 2008-2009: 67

- **Mortality:**
  - 2005-2006: 4.8
  - 2006-2007: 4.6
  - 2007-2008: 4.6
  - 2008-2009: 4.7

System Delay (First Medical Contact to Wire) and Long-Term Mortality

Each hour of delay associated with 10% ↑ risk of death

Terkelsen JAMA. 2010;304(7):763-771
Regional Systems of STEMI Care, Reperfusion Therapy, and Time-to-Treatment Goals

All communities should create and maintain a regional system of STEMI care that includes assessment and continuous quality improvement of EMS and hospital-based activities. Performance can be facilitated by participating in programs such as Mission: Lifeline and the D2B Alliance.

Performance of a 12-lead ECG by EMS personnel at the site of FMC is recommended in patients with symptoms consistent with STEMI.
STEMI Regional Systems

Onset of symptom of STEMI

9-1-1 EMS dispatch

EMS on-scene
- Encourage 12-lead ECGs
- Consider prehospital fibrinolytic if capable and EMS-to-needle within 30 min

EMS transport

Patient self-transport:
Hospital door-to-balloon within 90 min

EMS transport:
EMS-to-balloon within 90 min

Prehospital fibrinolysis:
EMS-to-needle within 30 min

STEMI-referral hospital (non PCI-capable)

Inter-hospital transfer

STEMI-receiving hospital (PCI-capable)

EMS Triage Plan

GOALS†

Patient
5 min after symptom onset

Dispatch
1 min

EMS on scene
within 8 min

Total ischemic time: Within 120 min*

* Golden Hour = First 60 minutes

©2011, American Heart Association 11
Baseline characteristics and reperfusion strategy

<table>
<thead>
<tr>
<th>Variable</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs)*</td>
<td>60 (52,71)</td>
<td>60 (52,71)</td>
<td>60 (52,71)</td>
<td>61 (52,71)</td>
<td>61 (52,70)</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>*<em>Time symptom onset to FMC (minutes)</em></td>
<td>50 (21,120)</td>
<td>50 (23,120)</td>
<td>50 (23,120)</td>
<td>52 (24,120)</td>
<td>49 (23,115)</td>
</tr>
<tr>
<td><strong>Reperfusion strategy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary PCI for transfer-in (%)</td>
<td>62</td>
<td>68</td>
<td>72</td>
<td>85</td>
<td>90</td>
</tr>
<tr>
<td>Fibrinolytic therapy (%)</td>
<td>13.4</td>
<td>11.1</td>
<td>9.0</td>
<td>7.4</td>
<td>7.0</td>
</tr>
</tbody>
</table>

*median (25th, 75th percentile)
New York City PCI and Non-PCI Hospitals

Hospitals by Type

**PCI Hospitals**
1. Bellevue Hospital Center
2. Beth Israel Medical Center - Petrie Campus
3. Bronx Lebanon Hospital Center - Concourse Division
4. Brookdale University Hospital & Medical Center
5. Elmhurst Hospital Center
6. Jamaica Hospital Medical Center
7. Lenox Hill Hospital
8. Long Island Jewish Medical Center
9. Lutheran Medical Center
10. Maimonides Medical Center
11. Montefiore Medical Center Jack D. Weiler Division, Albert Einstein School of Medicine
12. Montefiore Medical Center, Henry & Lucy Moses Division
13. Mount Sinai Hospital
14. New York Hospital Medical Center of Queens
15. New York Methodist Hospital
16. New York Presbyterian Hospital - Columbia Presbyterian Center
17. New York Presbyterian Hospital - New York Weill Cornell Medical Center
18. NYU Langone Medical Center
19. St. Barnabas Hospital
21. Staten Island University Hospital - North
22. University Hospital of Brooklyn at Long Island College Hospital
23. University Hospital of Brooklyn at SUNY Downstate

**Non-PCI Hospitals**
24. Beth Israel Medical Center - Kings Highway Division
25. Bronx-Lebanon Hospital Center - Fulton Site
26. Brooklyn Hospital Center - Downtown Campus
27. Coney Island Hospital
28. Flushing Hospital Medical Center
29. Forest Hills Hospital
30. Harlem Hospital Center
31. Interfaith Medical Center
32. Jacobi Medical Center
33. Kings County Hospital Center
34. Kingsbrook Jewish Medical Center
35. Lincoln Medical and Mental Health Center
36. Metropolitan Hospital Center
37. Montefiore Medical Center - North Division
38. Mount Sinai Hospital of Queens
39. New York Community Hospital
40. New York Downtown Hospital
41. New York Presbyterian Hospital - Allen Hospital
42. New York Westchester Square Medical Center
43. North Central Bronx Hospital
44. Queens Hospital Center
45. Richmond University Medical Center
46. St. John's Episcopal Hospital South Shore
47. St. Luke's Roosevelt Hospital - Roosevelt Division
48. Woodhull Medical and Mental Health Center
49. Wyckoff Heights Medical Center

**Hospital by Status**

- **PCI Hospital**
- **Non-PCI Hospital**
- **VA Hospital**

VA Hospitals
50. VA: James J. Peters VA Medical Center, Bronx Campus
51. VA: NY Harbor Healthcare System, Brooklyn Campus
52. VA: NY Harbor Healthcare System, Manhattan Campus
Timing of cath after fibrinolytic therapy
Primary Outcome of 7 Trials of Routine vs Ischemia-driven Catheterization and PCI After Fibrinolytic Therapy

Time (median or average) from Fibrinolytic to PCI

- 3.5 hr
- 16.7 hr
- 1.6 hr
- 2.2 hr
- 4.9 hr
- 3.9 hr
- 2.7 hr

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Risk Follow-up</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIAM-3</td>
<td>163</td>
<td>All</td>
<td>D, MI, RI, TVR D, MI, revasc</td>
</tr>
<tr>
<td>GRACIA-1</td>
<td>500</td>
<td>All</td>
<td>High</td>
</tr>
<tr>
<td>CAPITAL-AMI</td>
<td>170</td>
<td>6 mo</td>
<td>D, MI, RI, stroke</td>
</tr>
<tr>
<td>CARESS-in-AMI</td>
<td>600</td>
<td>High</td>
<td>D, MI, RI, stroke</td>
</tr>
<tr>
<td>WEST</td>
<td>204</td>
<td>All</td>
<td>D, MI, RI, CHF, shock, arrhy</td>
</tr>
<tr>
<td>TRANSFER-AMI</td>
<td>1059</td>
<td>High</td>
<td>D, MI, RI, CHF, shock</td>
</tr>
<tr>
<td>NORDISTEMI</td>
<td>266</td>
<td>All</td>
<td>D, MI, RI, stroke</td>
</tr>
</tbody>
</table>

Composite

- 12 mo D, MI, revasc
- 6 mo D, MI, RI, stroke
- 30 d D, MI, RI, CHF, shock, arrhy
- 30 d D, MI, RI, CHF, shock
- 12 mo D, MI, RI, stroke
- 30 d D, MI, RI, stroke
Practice and timing of non-infarct vessel PCI
**PRAMI Trial**

Non-culprit vessel PCI at time of primary PCI vs only for refractory angina/ischemia (74 D/MI/RI events)


---

**CvLPRIT Trial**

Non-culprit vessel PCI at time of primary PCI vs only for refractory angina/ischemia (46 MACE events)

Non-Culprit Lesion PCI: CvLPRIT and PRAMI

FIGURE 1 Pooled Analysis of CvLPRIT and PRAMI Trial-Level Data for Cardiac Death, MI, and Revascularization

- Cardiac Death
  - CvLPRIT
  - Combined
- Repeat MI
  - CvLPRIT
  - Combined
- Revascularization
  - CvLPRIT
  - Combined

Bhatt  J Am Coll Cardiol. 2015
DANAMI 3 – PRIMULTI Trial: FFR-Guided PCI reduced revasc with no difference in death or MI

<table>
<thead>
<tr>
<th></th>
<th>IRA only (n = 313)</th>
<th>Complete revascularisation (n = 314)</th>
<th>HR [95% CI]</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>68 (22%)</td>
<td>40 (13%)</td>
<td>0.56 [0.38 – 0.83]</td>
<td>0.004</td>
</tr>
<tr>
<td>All-cause death</td>
<td>11 (4%)</td>
<td>15 (5%)</td>
<td>1.4 [0.63 – 3.0]</td>
<td>0.43</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>16 (5%)</td>
<td>15 (5%)</td>
<td>0.94 [0.47 – 1.9]</td>
<td>0.87</td>
</tr>
<tr>
<td>Ischemia-driven revascularisation*</td>
<td>52 (17%)</td>
<td>17 (5%)</td>
<td>0.31 [0.18 – 0.53]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Engstrøm, Lancet 2015
### Culprit Artery Only vs Multivessel PCI

<table>
<thead>
<tr>
<th>2013 Recommendation</th>
<th>2015 Focused Update Recommendation</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class III: Harm</strong></td>
<td><strong>Class IIb</strong></td>
<td>Modified recommendation (changed class from “III: Harm” to “IIb” and expanded time frame in which multivessel PCI could be performed).</td>
</tr>
<tr>
<td>PCI should not be performed in a noninfarct artery at the time of primary PCI in patients with STEMI who are hemodynamically stable (11-13). <em>(Level of Evidence: B)</em></td>
<td>PCI of a noninfarct artery may be considered in selected patients with STEMI and multivessel disease who are hemodynamically stable, either at the time of primary PCI or as a planned staged procedure (11-24). <em>(Level of Evidence: B-R)</em></td>
<td></td>
</tr>
</tbody>
</table>
STEMI with successful culprit lesion PCI (primary, rescue or pharmacoinvasive) + ≥ 70% stenosis or ≥ 50% with FFR < 0.80

**COMPLETE Trial: Trial Design**

**Randomized** Within 72 h of index Primary PCI

**Staged Non-culprit lesion PCI+OMT**
- Staged PCI of all suitable non-culprit lesions
- N=1950

**Optimal Medical Therapy Alone**
- No further revascularization of non-culprit lesions (OMT Alone)
- N=1950

All patients receive OMT (ASA, Ticagrelor, Statin, Beta Blocker, RF Modification)

Follow-up: Discharge, 30 Days, 6 mos, then Annually

**Primary Outcome:** CV Death / MI

**Key Secondary Outcome:** CV Death/MI/Ischemia driven revascularization

Funded by CIHR, AstraZeneca and Boston Scientific

Clinicaltrials.gov NCT0174049
Summary (of evidence to date) pending the COMPLETE trial

1. PCI is effective in reducing angina and subsequent revascularization. This is true in patients with and without ACS, including patients with STEMI who have multivessel disease (PRAMI, Cvlprit and DANAMI-3).

2. Current evidence is encouraging, but insufficient to determine whether non-culprit lesion PCI reliably reduces death or MI.

3. The COMPLETE trial is powered to detect differences in death or MI and is designed to determine whether staged PCI reliably reduces these events in patients with STEMI and multivessel disease.
Timing of cath and PCI in NSTE ACS
## Interventions and Timing

<table>
<thead>
<tr>
<th></th>
<th>Early N=1,593</th>
<th>Delayed N=1,438</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Angiography (%)</td>
<td>97.6</td>
<td>95.5</td>
</tr>
<tr>
<td>Median time (h ± iqr)</td>
<td>14 (3-21)</td>
<td>50 (41-81)</td>
</tr>
<tr>
<td>PCI (%)</td>
<td>59.6</td>
<td>55.1</td>
</tr>
<tr>
<td>Median time (h ± iqr)</td>
<td>16 (3-23)</td>
<td>52 (41-101)</td>
</tr>
<tr>
<td>CABG (%)</td>
<td>14.8</td>
<td>13.6</td>
</tr>
<tr>
<td>Median time (d ± iqr)</td>
<td>7.7 (4.7-17.4)</td>
<td>10.8 (6.7-19.8)</td>
</tr>
</tbody>
</table>

Iqr = interquartile range

## Death, MI, Stroke at 6 Months
### Pre-specified Subgroups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>Early %</th>
<th>Delayed %</th>
<th>HR (95% CI)</th>
<th>Interaction p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>3031</td>
<td>9.7</td>
<td>11.4</td>
<td>0.85 (0.68 - 1.06)</td>
<td></td>
</tr>
<tr>
<td>Age &lt; 65</td>
<td>1293</td>
<td>6.5</td>
<td>6.5</td>
<td>0.98 (0.64 - 1.52)</td>
<td></td>
</tr>
<tr>
<td>&gt;=65</td>
<td>1736</td>
<td>12.3</td>
<td>14.8</td>
<td>0.83 (0.64 - 1.07)</td>
<td>0.463</td>
</tr>
<tr>
<td>Female</td>
<td>1052</td>
<td>9.7</td>
<td>12.3</td>
<td>0.77 (0.54 - 1.12)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1976</td>
<td>9.8</td>
<td>10.9</td>
<td>0.89 (0.68 - 1.18)</td>
<td>0.540</td>
</tr>
<tr>
<td>No ST deviation</td>
<td>1523</td>
<td>7.6</td>
<td>8.7</td>
<td>0.88 (0.62 - 1.26)</td>
<td></td>
</tr>
<tr>
<td>ST deviation</td>
<td>1508</td>
<td>11.7</td>
<td>14.3</td>
<td>0.81 (0.61 - 1.07)</td>
<td>0.722</td>
</tr>
<tr>
<td>No elevated marker</td>
<td>668</td>
<td>10.5</td>
<td>10.5</td>
<td>1.00 (0.62 - 1.60)</td>
<td></td>
</tr>
<tr>
<td>Elevated Marker</td>
<td>2363</td>
<td>9.5</td>
<td>11.7</td>
<td>0.81 (0.63 - 1.04)</td>
<td>0.423</td>
</tr>
<tr>
<td>GRACE 0-140</td>
<td>2070</td>
<td>7.7</td>
<td>6.7</td>
<td>1.14 (0.82 - 1.58)</td>
<td></td>
</tr>
<tr>
<td>GRACE &gt;=141</td>
<td>961</td>
<td>14.1</td>
<td>21.6</td>
<td>0.65 (0.48 - 0.88)</td>
<td>0.0097</td>
</tr>
</tbody>
</table>

GRACE Risk Score: Primary Outcome

Death, MI or Stroke at 6 mo.

- **Low/Int Risk**
  - GRACE Score < 140
  - N=2070
  - Death, MI or Stroke at 6 mo.: 6.7%
  - HR: 1.14
  - 95% CI: 0.82-1.58
  - P=0.43

- **High Risk**
  - GRACE Score >= 140
  - N=961
  - Death, MI or Stroke at 6 mo.: 21.6%
  - HR: 0.65
  - 95% CI: 0.48-0.88
  - P=0.005

Interaction P=0.01

Which $\text{P2Y}_{12}$ antagonist in acute ACS, and when?
ACCOAST design

NSTEMI + Troponin ≥ 1.5 times ULN local lab value
Clopidogrel naive or on long term clopidogrel 75 mg

Randomize 1:1
Double-blind

Prasugrel 30 mg
Coronary Angiography
PCI
Prasugrel 30 mg

Placebo
Coronary Angiography
PCI
Prasugrel 60 mg

CABG or Medical Management (no more prasugrel)

CABG or Medical Management (no more prasugrel)

Prasugrel 10 mg or 5 mg (based on weight and age) for 30 days

1° Endpoint: CV Death, MI, Stroke, Urg Revasc, GP IIb/IIIa bailout, at 7 days

All TIMI (CABG or non-CABG) Major Bleeding (All Treated patients)

Hazard Ratio, 1.90 (95% 1.19, 3.02) P=0.006
Hazard Ratio, 1.97 (95% 1.26, 3.08) P=0.002

Pre-treatment
- Pre-treatment 2.9
- Pre-treatment 2.6
- No Pre-treatment 1.5
- No Pre-treatment 1.4
Duke ACS Algorithm: NSTE ACS

**Antithrombotic Rx**

- **Ticagrelor** 180 mg load; 90 mg twice daily
- or Clopidogrel 600 mg load

**Dynamic STΔs, pos. cardiac markers**
- GRACE > 3% death

**NSSTT Δs, neg. cardiac markers**

- Cath <24 hrs
- Cath >24 hrs
- No or delayed cath

**Anticoagulant Rx**

- UFH †
- Fondaparinux or enoxaparin
- Or bivalirudin**

†GP IIb/IIIa at time of PCI or if refractory ischemia
**Consider bivalirudin for cath <12 hours**
A common mistake in management of ACS: stopping anticoagulation prior to revascularization
FRISC II: Open + double-blind treatment period

FRISC II. Lancet, August 1999
Reperfusion is the most important way to save lives in acute STEMI, and faster reperfusion saves more lives, with regional systems as key to accomplishing this.

Non-infarct PCI, acutely or during the initial hospitalization, reduces ischemia and need for subsequent revascularization, and may reduce reMI.

Early cath and PCI results in better outcome for high risk NSTEMI.

Start P2Y₁₂ early (at first hospital), but very early (prehospital) does not help.

For NSTEMI, continue anticoagulation until planned CABG revascularization.