STEMI: Evolving Early Therapies of “Myocardial Ischemia/Reperfusion Injury”.

Borja Ibanez, MD PhD FESC.
- Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC).
  - Hospital Clínico San Carlos.
1) Reperfusion: a paradigm shift → from mortality to HF.

2) Next goal: Infarct size limitation in reperfused STEMI.

3) Ischemia/Reperfusion injury.

4) Therapies to reduce infarct size: Reperfusion
   + Conditioning.
   + Cyclosporine-A.
   + Metoprolol.
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STEMI: A paradigm shift

The great success of reperfusion therapies has resulted in a paradigm shift in STEMI: attention has moved from reducing mortality (already low) to tackling the downstream consequences of survival: post-infarction heart failure.

Adapted from Roger VL et al. Circulation 2011;123:e18-e209
STEMI $\rightarrow$ Heart Failure

**Figure 1:** Projected cumulative (2011 to 2025) economic losses from all non-communicable diseases worldwide. Adapted from ref 3.

**Figure 2:** Projected Heart Failure direct medical costs and indirect (lost productivity) costs.

- Cardiovasc. Diseases; 51.7%
- Respiratory Diseases; 21.8%
- Cancer; 20.7%
- Diabetes; 5.8%

Adapted from Circulation 2011; 123:933–44
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Infarct size is a strong determinant of long-term mortality and chronic heart failure

Gibbons et al.: J Am Coll Cardiol 2004
Despite the acknowledgement of its importance, there are no therapies (besides reperfusion) approved to reduce infarct size.

Unmet clinical need!
Is all about time?

Myocardial (cell) death

Ischemia

Time

No reperfusion

Reperfusion

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


A  Overall (N=96,739)

<table>
<thead>
<tr>
<th>Year of Procedure</th>
<th>Median Door-to-Balloon Time (min)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005–2006</td>
<td>83</td>
<td>4.8</td>
</tr>
<tr>
<td>2006–2007</td>
<td>76</td>
<td>4.6</td>
</tr>
<tr>
<td>2007–2008</td>
<td>70</td>
<td>4.6</td>
</tr>
<tr>
<td>2008–2009</td>
<td>67</td>
<td>4.7</td>
</tr>
</tbody>
</table>

Median door-to-balloon time (P<0.001)
Mortality (P=0.43)

<table>
<thead>
<tr>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
</tr>
<tr>
<td>Deaths</td>
</tr>
</tbody>
</table>
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Ischemia/Reperfusion injury

Heusch.: Lancet 2013 (REVIEW)

Yellon et al.: J Clin Invest 2012 (REVIEW)
Reperfusion injury

Baseline  R-120 min  R-24 hours  R-Day 4  R-Day 7

STIR
120 ms
30 ms

T2 (ms)

INITIAL wave

DEFERRED wave

Water content
T2 relaxation times

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Conditioning

Ovize et al.: Circ Res 2013 (REVIEW)

Heusch et al.: J Am Coll Cardiol (State-of-the-art REVIEW In Press)
Post-conditioning

**DANAMI-3 trial** (Danish Study of Optimal Acute Treatment of Patients With ST-elevation Myocardial Infarction-3, NCT01435408),

- 2,000 STEMI patients
- conventional PCI vs. postconditioning+stent vs. deferred stenting.
- Combined end-point: all-cause mortality / heart failure @ 2 years

**ONGOING TRIAL**
Remote conditioning.

**CONDI-2 trial** Denmark, Spain, Serbia. (HE Botker et al.)

- 2,000 STEMI patients
- conventional PCI vs. remote conditioning + PCI
- Combined end-point: all-cause mortality / heart failure @ 2 years

ONGOING TRIAL
Cyclosporine is a non-selective inhibitor of mitochondrial PTP.

The Cyclosporine and Prognosis in Acute Myocardial Infarction (MI) Patients CIRCUS trial

972 STEMI patients, pPCI, LAD occluded

Randomized to cyclosporine (2.5 mg/kg) vs. placebo.

Primary endpoint: composite of death; admission for heart failure; LV remodelling (increase of LV enddiastolic volume >15%) at one year post-AMI.
The effect of early i.v. β-blocker on infarct size (and long term LV function) remained unclear until recently.

→ Several trials in the pre-reperfusion era (inconclusive results).
   Roberts et al, Hjalmarson et al, Yusuf et al, MILIS,..

→ ONE single randomized trial in the thrombolytic era.
i.v. metoprolol before pPCI → ↓↓↓ infarct size

Mean LVEF (6 mo CMR):
48.7±9% vs. 45.0±11%

G Pizarro, V Fuster, B Ibanez et al.
*J Am Coll Cardiol* 2014; 63: 2356-62.
The future: Move on!

Pls: V Fuster / B Ibáñez.

MOVE ON! Trial 2015-2019
Conclusions

Infarct size reduction is the next frontier in STEMI treatment (heart failure epidemics).

Timely reperfusion has made it possible a massive reduction in mortality. It is time to tackle reperfusion injury.

Metoprolol, Cyclosporin-A, post- and remote-conditioning are the therapies closest to reach clinical evidence.
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Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium

Charles E. Murry, B.S., Robert B. Jennings, M.D., and Keith A. Reimer, M.D., Ph.D.

This study suggested that there was more than just duration of ischemia
Ischemia/reperfusion injury players

1) Atherosclerotic plaque with superimposed Thrombus.
2) Microemboli (plaque, thrombi,...).
3) Red blood cells (hemorrhage).
4) Cardiomyocyte.
5) Inflammatory cells (Leukocyte, ..).
6) Platelet/leukocyte Aggregates.
7) External compression (edema).
8) Activated platelets.

Damage gradient
i.v. metoprolol pre-reperfusion reduces Microvascular Obstruction (even after adjusting for infarct size). N=220.

G Pizarro, V Fuster, B Ibanez et al.  
*J Am Coll Cardiol* 2014; 63: 2356-62.

**METOCARD-CNIC: long-term LVEF**

*Patients undergoing MRI at 6-month follow-up*

\[ p = 0.018 \]

N=202
Table 2: Clinical Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Intravenous Metoprolol N (%)</th>
<th>Control N (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>15 (10.8)</td>
<td>24 (18.3)</td>
<td>0.065</td>
</tr>
<tr>
<td>Death</td>
<td>6 (4.3)</td>
<td>6 (4.6)</td>
<td>0.92</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>3 (2.2)</td>
<td>5 (3.8)</td>
<td></td>
</tr>
<tr>
<td>non-cardiac death</td>
<td>3 (2.2)</td>
<td>1 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Heart Failure Admission</td>
<td>3 (2.2)</td>
<td>9 (6.9)</td>
<td>0.046</td>
</tr>
<tr>
<td>ICD implantation</td>
<td>2 (1.4)</td>
<td>7 (5.3)</td>
<td></td>
</tr>
<tr>
<td>decompensation</td>
<td>1 (0.7)</td>
<td>3 (2.3)</td>
<td></td>
</tr>
<tr>
<td>Re-AMI</td>
<td>1 (0.7)</td>
<td>3 (2.3)</td>
<td>0.15</td>
</tr>
<tr>
<td>Malignant ventricular arrhythmia</td>
<td>5 (3.6)</td>
<td>10 (7.7)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Kaplan-Meier MACE curves:

- 1-year Adjusted OR: 0.49 (95% CI 0.23-1.05) \( p = 0.066 \)

Kaplan-Meier HF admission curves:

- All follow-up Adjusted HR: 0.55 (95% CI 0.26-1.04) \( p = 0.065 \)
- All follow-up Adjusted HR: 0.32 (95% CI 0.02-0.95) \( p = 0.046 \)
1972: First evidence that reperfusion limits extent of necrosis.

1977: Wavefront (endo to epi) progression of necrosis.

1980: Unequivocal demonstration: coronary thrombosis cause STEMI.

1983: First-in-man primary angioplasty in STEMI.

1986: First evidence that ischemic preconditioning reduces infarct size.

1988: ISIS-2 trial: aspirin improves outcomes in STEMI.

1993: GUSTO-I trial: tPA reduces mortality compared with SK in STEMI.

1993: First evidence that RIC reduces infarct size.

2003: First evidence that post-conditioning reduces infarct size.

2005: First-in-man post-conditioning reduces infarct size in STEMI.

2003: Metaanalysys show mortality benefits of primary angioplasty over thrombolysis in STEMI.

2008: First-in-man in STEMI.

2010 Proof-of-concept: RIC increases myocardial salvage in STEMI.

2013 Proof-of-concept: metoprolol reduces infarct size & increases LVEF in STEMI.

Landmarks in therapies to reduce ischemic injury

Landmarks in therapies to reduce reperfusion injury