STEMI: Timing to Reperfusion / Reperfusion Injury A Multi-Layer Challenge to Decrease Infarct Size

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CONFLICTS OF INTEREST

B Ibanez has no conflicts to declare
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.
   + β-blockers.

5) Impact of timing of intervention on infarct size reduction.
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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.

Mortality ↓↓

Heart Failure ↑↑↑

Adapted from Roger VL et al. Circulation 2011;123:e18-e209
• 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.

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.

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

No reperfusion

Time

Reperfusion

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 Mitinder S. Gurm, M.B., B.S.

A Overall (N=96,739)

Median door-to-balloon time (P<0.001)

Mortality (P=0.43)

Year of Procedure

<table>
<thead>
<tr>
<th>Year</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>

No. of Patients

<table>
<thead>
<tr>
<th>Year</th>
<th>All patients</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005-2006</td>
<td>19,964</td>
<td>938</td>
</tr>
<tr>
<td>2006-2007</td>
<td>24,101</td>
<td>1,108</td>
</tr>
<tr>
<td>2007-2008</td>
<td>25,728</td>
<td>1,190</td>
</tr>
<tr>
<td>2008-2009</td>
<td>27,245</td>
<td>1,268</td>
</tr>
</tbody>
</table>
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Microvascular Obstruction
Myocardial Healing
: critical players

Ibanez, Heusch, Ovize Van de Werf.
J Am Coll Cardiol 2015;65:1454-71
Reperfusion injury by CMR

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

STIR

120 ms

30 ms

T2 (ms)

Water content

T2 relaxation times

INITIAL wave

DEFERRED wave

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Conditioning example of (reverse) translational research

**BASIC RESEARCH:**
Demonstration of infarct size reduction by pre-conditioning

**PATIENT:** Clinical observation: pre-infarction angina confers good prognosis upon infarction

**J Am Coll Cardiol 2014;64:223-5**
Ischemic Conditioning

LOCAL (coronary artery) or REMOTE (peripheral organ)

Ibanez, Fuster et al.: Hurst’s the Heart 2017 (chapter 38)
Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomised trial

Hans Erik Bøtker, Rajesh Kharbanda, Michael R Schmidt, Morten Bøttcher, Anne K Kaltoft, Christian J Terkelsen, Kim Munk, Niels H Andersen, Tørls M Hansen, Sven Trautner, Jens Flensted Lassen, Evald Høj Christiansen, Lars R Krusell, Steen D Kristensen, Leif Thuesen, Søren S Nielsen, Michael Rehling, Henrik Toft Sørensen, Andrew N Redington, Torsten T Nielsen

**RIC:**
Interminent ischemia in a remote organ DURING ongoing ischemia in the index organ

333 patients with first STEMI underwent RIC protocol (4 cycles arm cuff inflation) or regular care

*Lancet* 2010;375:727-734
Remote Ischemic Conditioning in STEMI

CONDI trial

Salvage Index (median [IQR])

PCI only
p = 0.033

0.55
0.75
RIC large trial

CONDI-2 trial, Denmark, Spain, Serbia.

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

ONGOING TRIAL
The effect of early i.v. β-blocker on infarct size (and long term LV function is unclear. SCARCE DATA IN REPERFUSED PATIENTS.

→ 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.

→ Two recent trials in the pPCI era (METOCARD-CNIC and EARLY BAMI)
i.v. metoprolol before pPCI $\rightarrow$ ↓↓↓ infarct size

P = 0.012

$\downarrow$ 25%

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

Fisher’s exact test (p=0.026)
Linear-by-Linear Association test (p=0.006)
METOCARD-CNIC: long-term events

Kaplan-Meier HF admission curves

All follow-up Adjusted HR: 0.32 (95% CI 0.02-0.95)  
P=0.046

Cumulative HF admission hazard (%)

Follow-up (months)

Number at risk
Control 131
i.v. metoprolol 139

Control  
i.v. metoprolol

G Pizarro, V Fuster, B Ibanez et al.  
*J Am Coll Cardiol* 2014; 63: 2356-62.
Metoprolol reduces MVO, even normalizing to infarct size.
Early Intravenous Beta-Blockers in Patients With ST-Segment Elevation Myocardial Infarction Before Primary Percutaneous Coronary Intervention

Vincent Roolvink, MD, Borja Ibáñez, MD, PhD, Jan Paul Ottervanger, MD, PhD, Gonzalo Pizarro, MD, Niels van Royen, MD, PhD, Alonso Mateos, MD, Jan-Henk E.Dambrink, MD, PhD, Noemi Escalera, BPT, Erik Lipsic, MD, PhD, Agustin Albarran, MD, PhD, Antonio Fernández-Ortiz, MD, PhD, Francisco Fernández-Avilés, MD, PhD, Javier Goicolea, MD, PhD, Javier Botas, MD, PhD, Wouter Remkes, MD, Victoria Hernandez-Jarés, PharmD, Elvin Kedhi, MD, PhD, José L. Zamorano, MD, PhD, Felipe Navarro, MD, PhD, Fernando Alfonso, MD, PhD, Alberto García-Lledó, MD, PhD, Joaquin Alonso, MD, PhD, Maarten van Leeuwen, MD, Robin Nijveldt, MD, PhD, Sonja Postma, PhD, Evelien Kolkmann, MSc, Marcel Gosselink, MD, PhD, Bart de Smet, MD, PhD, Saman Rasoul, MD, PhD, Jan J. Piek, MD, PhD, Valentin Fuster, MD, PhD, Arnoud W.J. van 't Hof, MD, PhD, on behalf of the EARLY-BAMI Investigators

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Timing of metoprolol administration in METOCARD-CNIC

STEMI diagnosis

Reperfusion

Arterial access

Window metoprolol administration in METOCARD-CNIC

Median (53min)
The longer the “on board” metoprolol duration at reperfusion, the higher the cardioprotection

Garcia-Ruiz et al J Am Coll Cardiol 2016;67:2093-104
Timing of metoprolol admin

Window β-blk admin in trials

STEMI diagnosis

METOCARD-CNIC
(-53 min to PCI)
15mg metoprolol

EARLY BAMI
(-54 & -14 min to PCI)
10mg metoprolol

STEMI diagnosis

PCI (reperfusion)

Lytic therapy
---- reperfusion

COMMIT
(+? min from Urokinase)

TIMI IIB
(+45 min from rtPA)

Van de Werf
(immed before rtPA)
10mg atenolol
Remote ischaemic conditioning and healthcare system delay in patients with ST-segment elevation myocardial infarction

Kasper Pryds,1,2 Christian Juhl Terkelsen,1 Astrid Drivsholm Sloth,1,2 Kim Munk,1 Søren Steen Nielsen,3 Michael Rahbek Schmidt,1 Hans Erik Bøtker,1 CONDI Investigators

Events-powered trial

MOVE ON!
Trial 2017-2021

PIs: B Ibanez / V Fuster

1250 anterior STEMI patients, <6 hr from symptoms onset, undergoing pPCI, Metoprolol (15mg) vs. Placebo out-of-hospital setting (long before reperfusion)

Primary outcome (win ratio approach):
- CV death
- HF readmission
- ICD implant
- LVEF <35% on 6 months CMR

Median follow-up 3 years
1) **Timely** reperfusion widespread use has resulted in a massive reduction of acute mortality during STEMI.

2) The next goal is to reduce infarct size to reduce chronic post-MI HF.

3) Reperfusion injury reduction is a relevant target. Preserve microvascular integrity!

4) Metoprolol and remote ischemic conditioning are promising therapies.

5) **Timing** of administration of therapies to reduce infarct size seem to play a critical role in its ability to protect from ischemia/reperfusion.