

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

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- Hospital Clínico San Carlos.



Disclosures:

Borja Ibanez has nothing to disclose



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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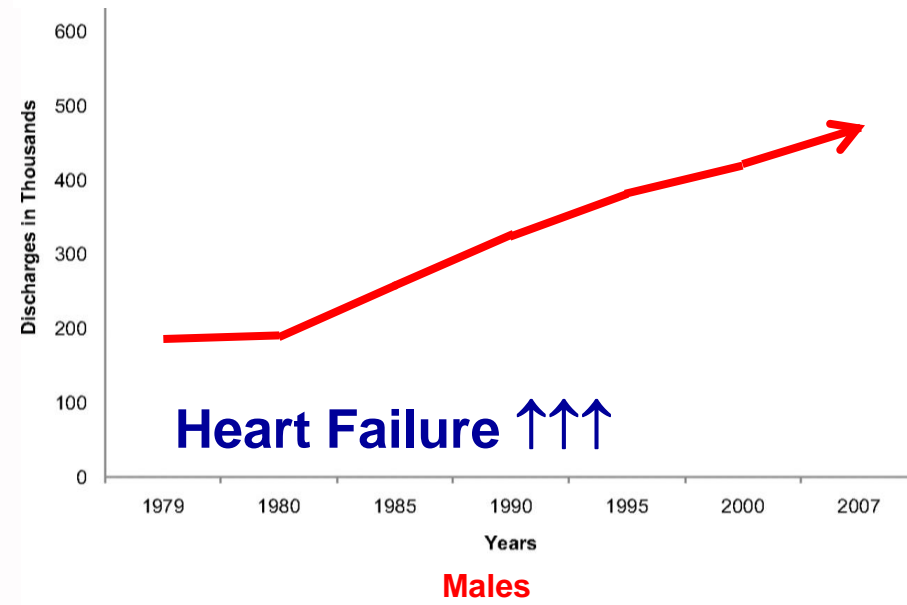
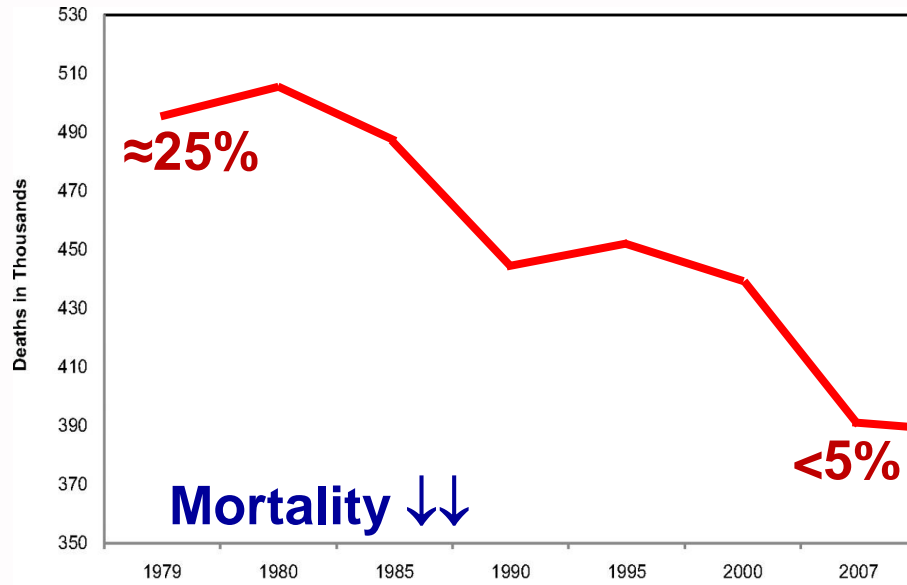
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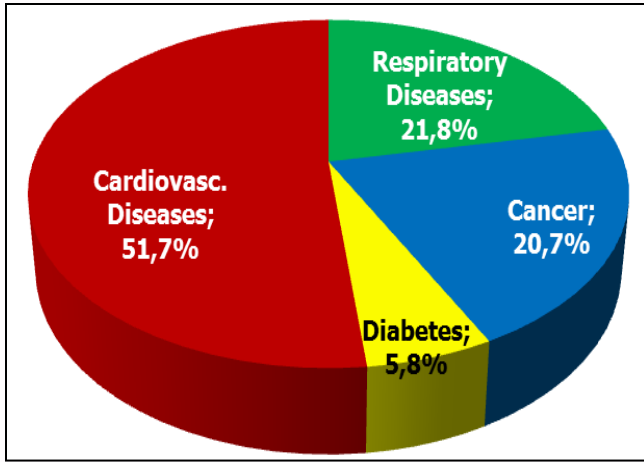
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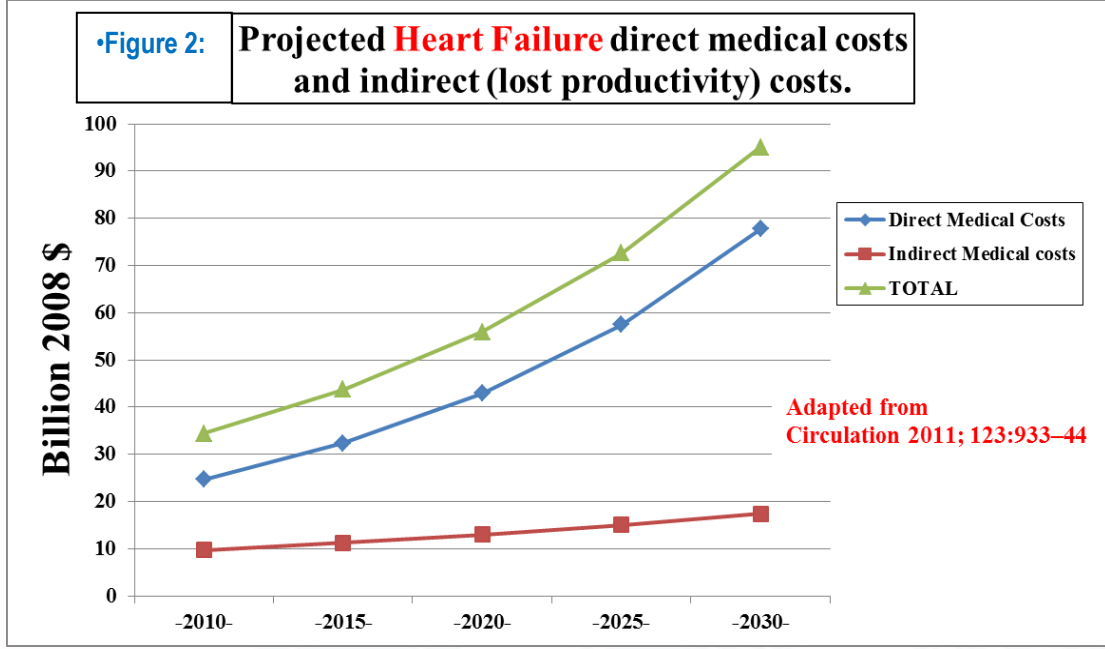


The great success of **reperfusion** therapies has resulted in a **paradigm shift** in STEMI: attention has moved from reducing **mortality** (already low) to **tackling** the downstream consequences of survival: **post-infarction heart failure**.

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



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



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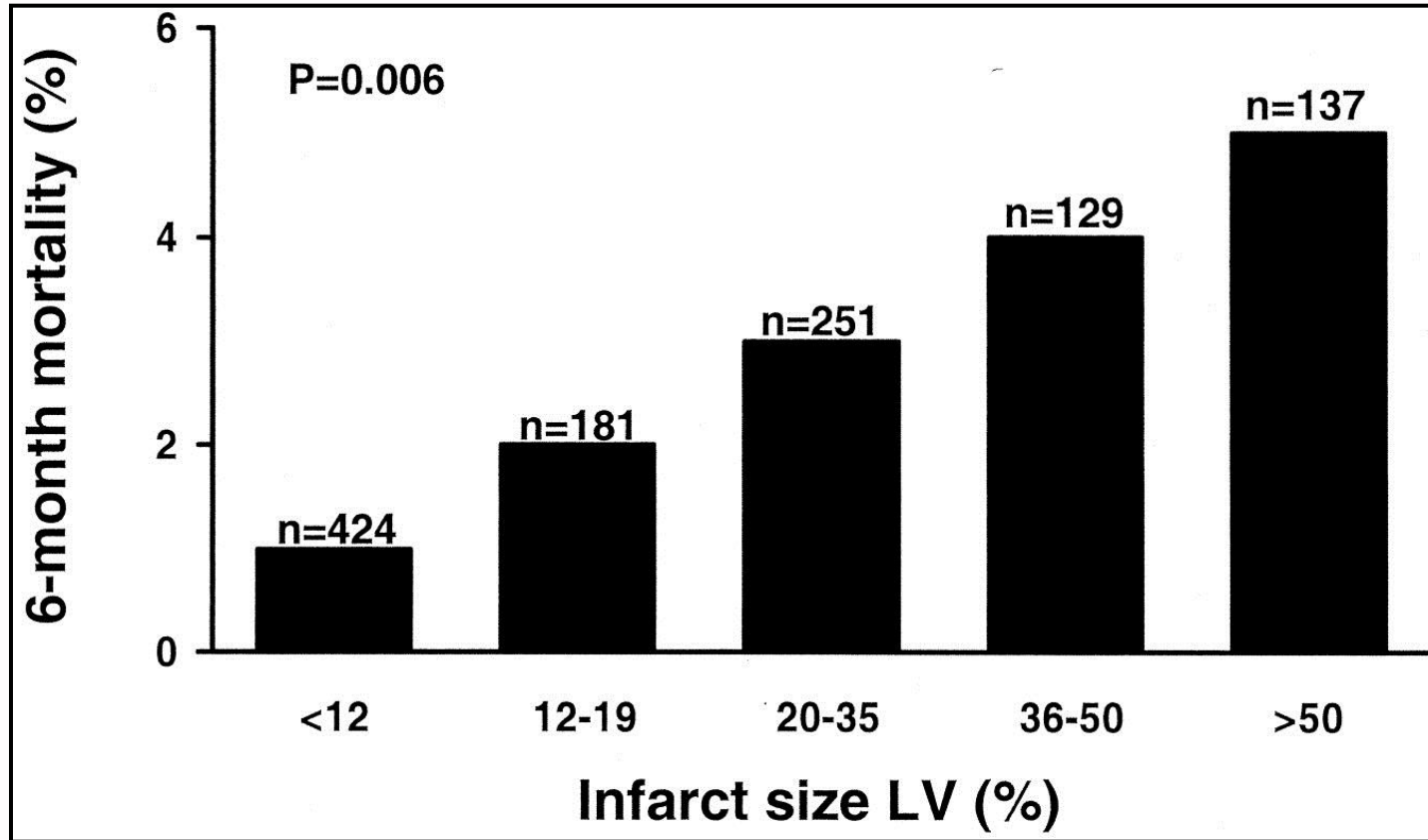
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Gibbons et al.: J Am Coll Cardiol 2004

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.

2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction : A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

Patrick T. O'Gara, Frederick G. Kushner, Deborah D. Ascheim, Donald E. Casey, Jr, Mina K. Chung, James A. de Lemos, Steven M. Ettinger, James C. Fang, Francis M. Fesmire, Barry A. Franklin, Christopher B. Granger, Harlan M. Krumholz, Jane A. Linderbaum, David A. Morrow, L. Kristin Newby, Joseph P. Ornato, Narith Ou, Martha J. Radford, Jacqueline E. Tamis-Holland, Carl L. Tommaso, Cynthia M. Tracy, Y. Joseph Woo and David X. Zhao

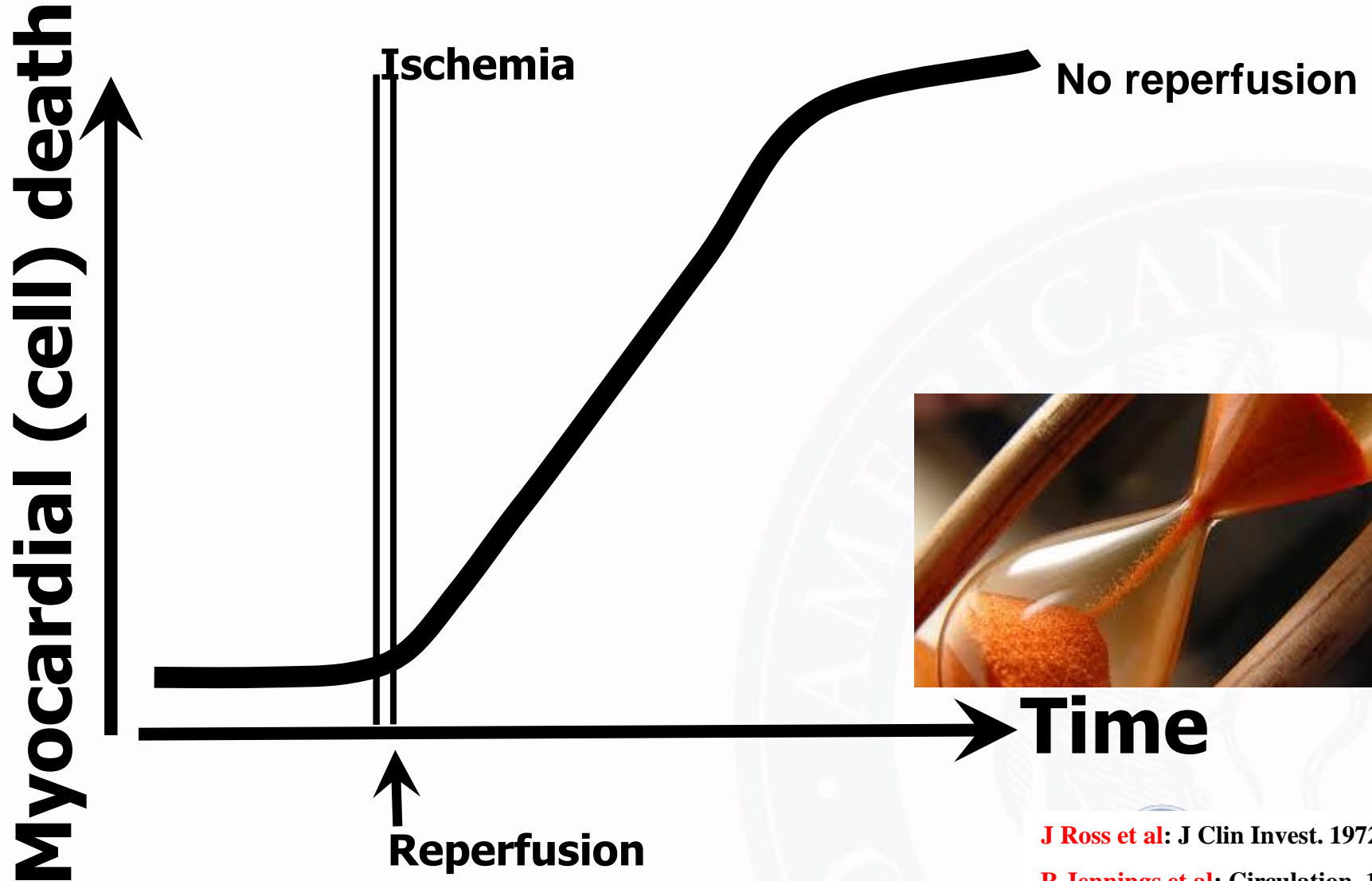
**ACC/AHA
guidelines
2013**



Unmet clinical need!



Is all about time?



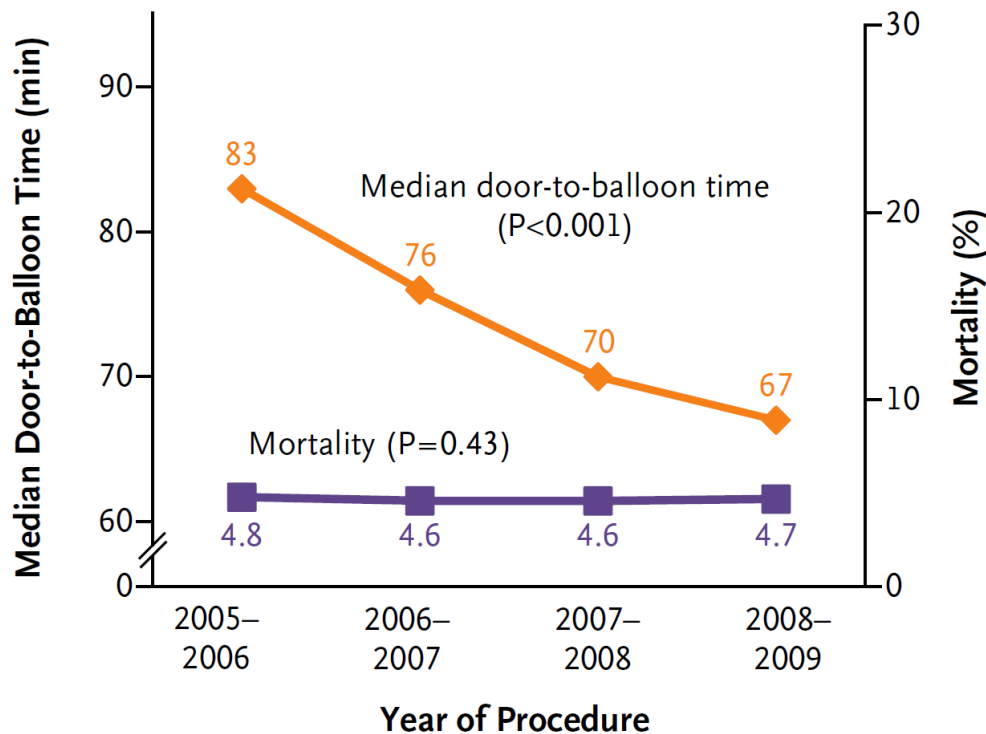
J Ross et al: J Clin Invest. 1972.

R Jennings et al: Circulation. 1977.

**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., Jephtha P. Curtis, M.D., John C. Messenger, M.D.,
 John S. Rumsfeld, M.D., Ph.D., and Hitinder S. Gurm, M.B., B.S.

A Overall (N=96,739)



No. of Patients

All patients	19,964	24,101	25,728	27,245
Deaths	938	1,108	1,190	1,268

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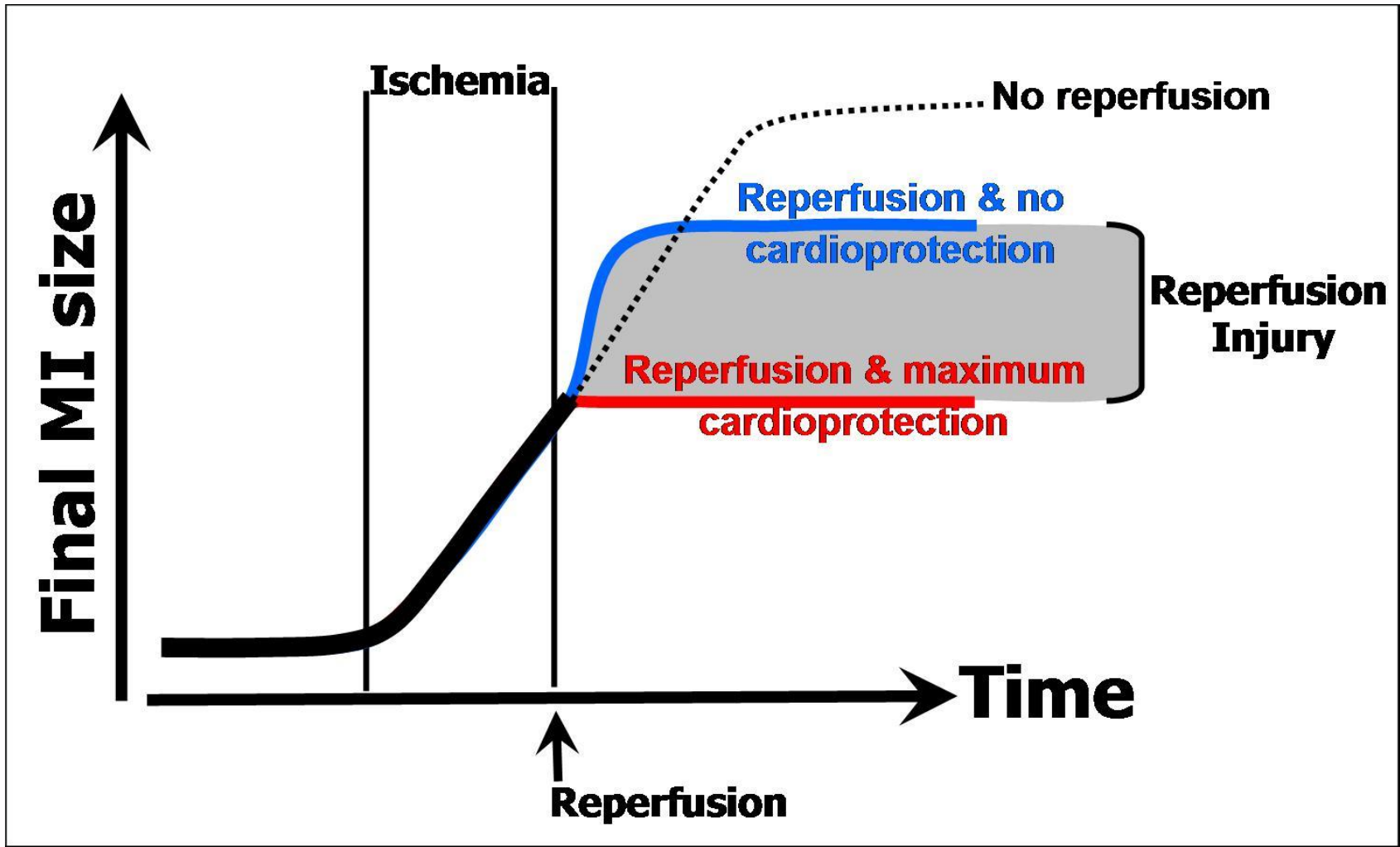
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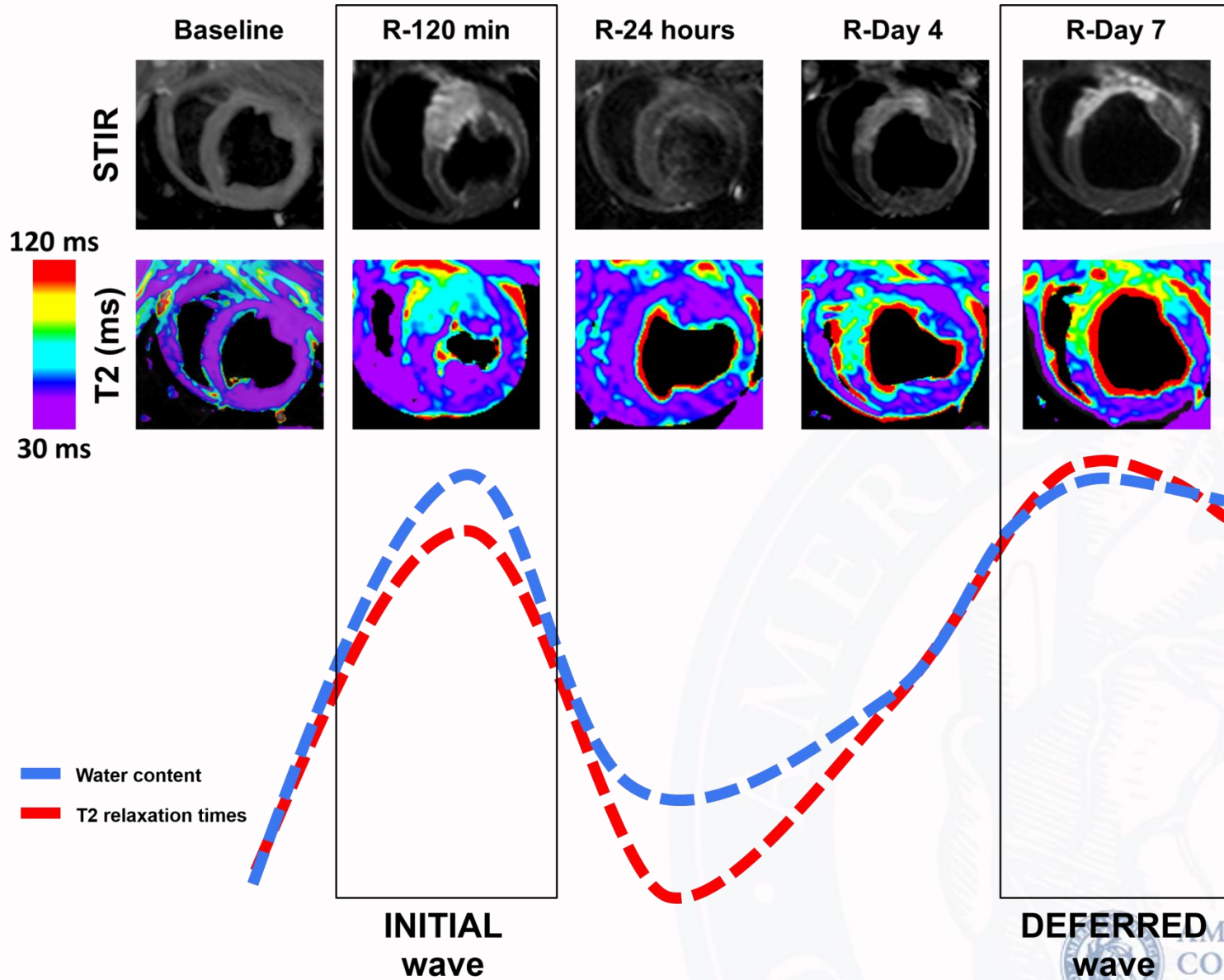


Heusch.: Lancet 2013 (REVIEW)

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



Reperfusion injury



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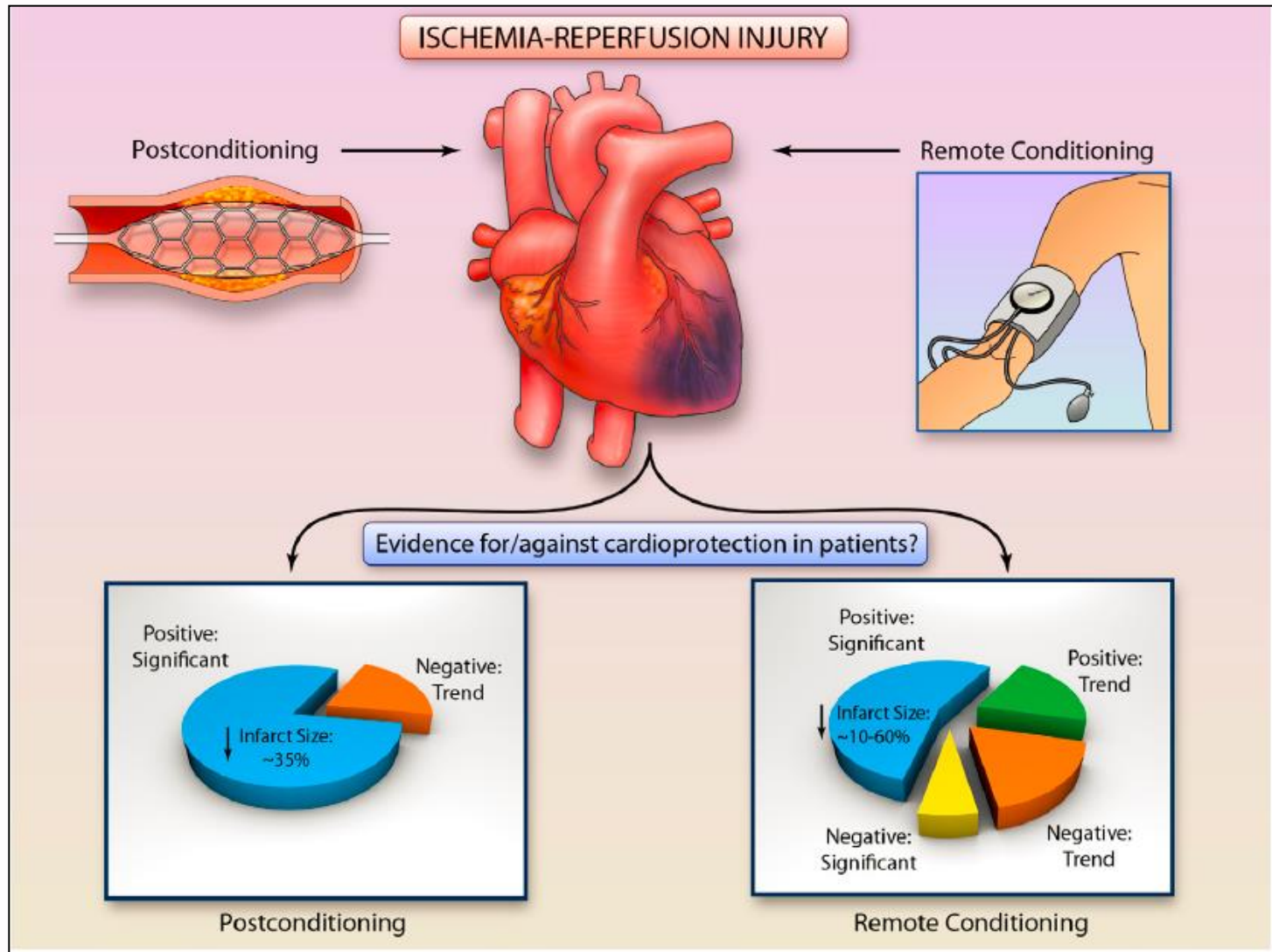
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Ovize et al.: Circ Res 2013 (REVIEW)

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

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



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

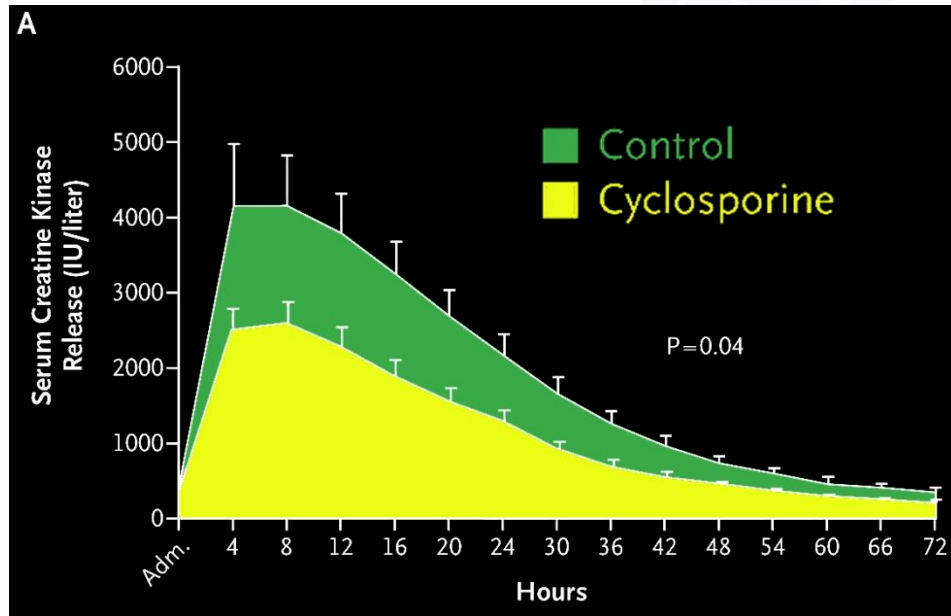


ORIGINAL ARTICLE

Effect of Cyclosporine on Reperfusion Injury in Acute Myocardial Infarction

Ovize et al.: New Engl J Med 2008

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.

ONGOING TRIAL





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.

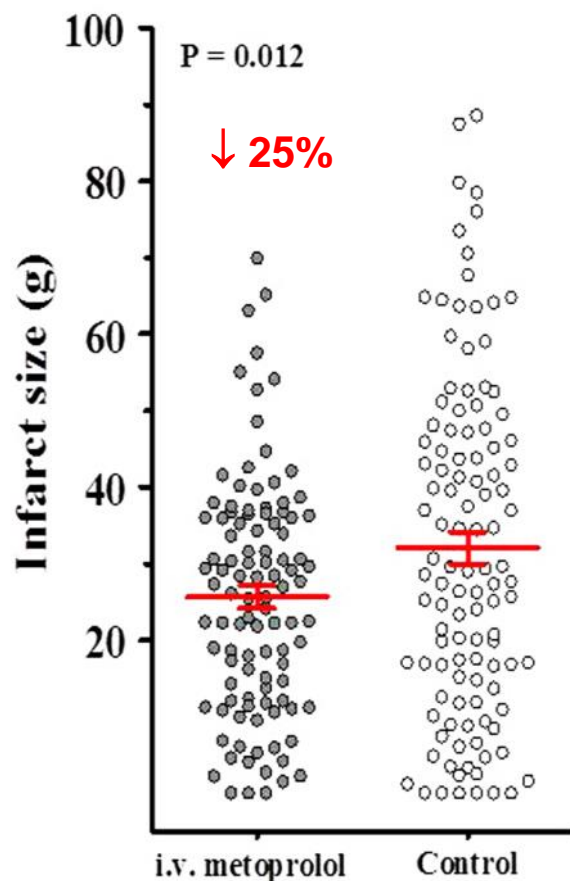
van de Werf et al *J Am Coll Cardiol* 1993.



i.v. metoprolol before pPCI → ↓↓↓ infarct size

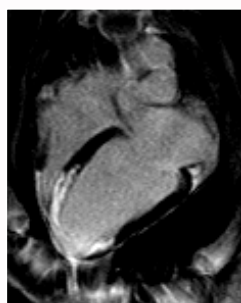
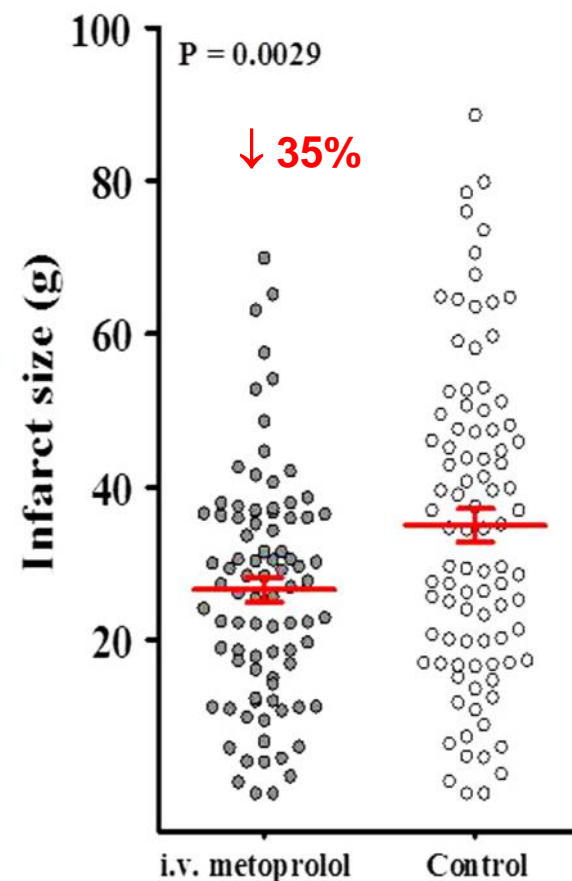
A

Patients undergoing MRI

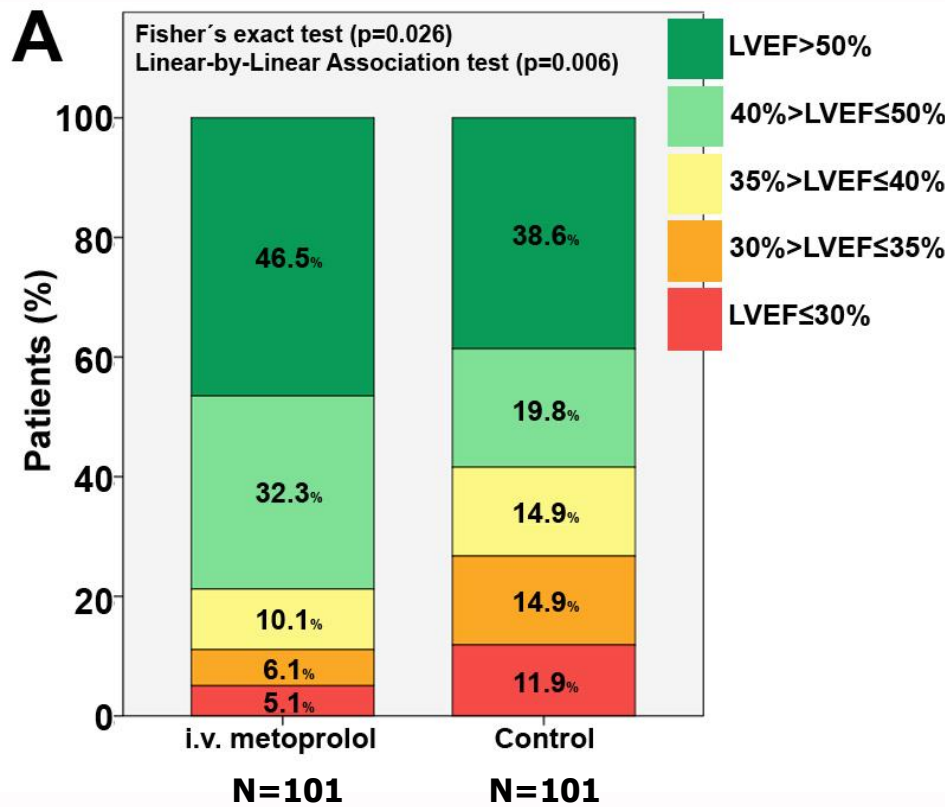


B

Subset of patients with pre-PCI TIMI 0/1



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.

cnic The future: Move on!



Pls:
V Fuster / B Ibáñez.

MOVE ON! Trial 2015-2019



AMERICAN
COLLEGE of
CARDIOLOGY

- ➔ 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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cnic

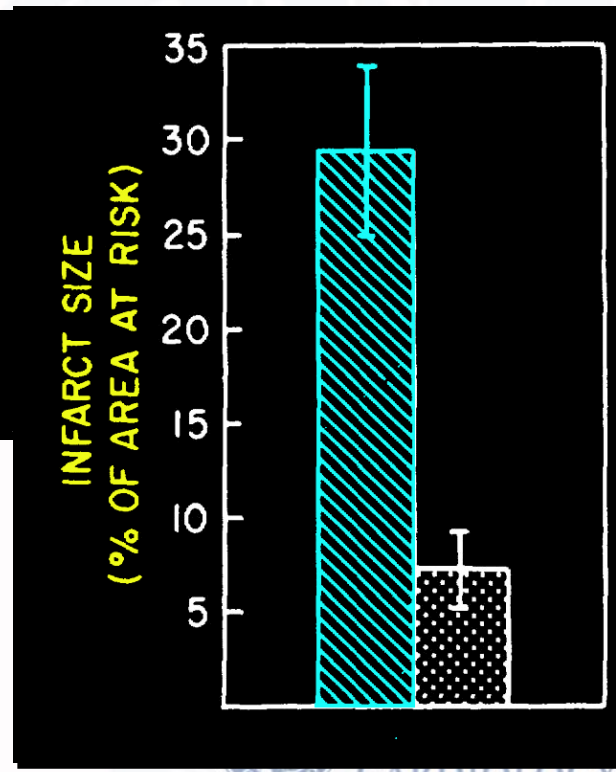
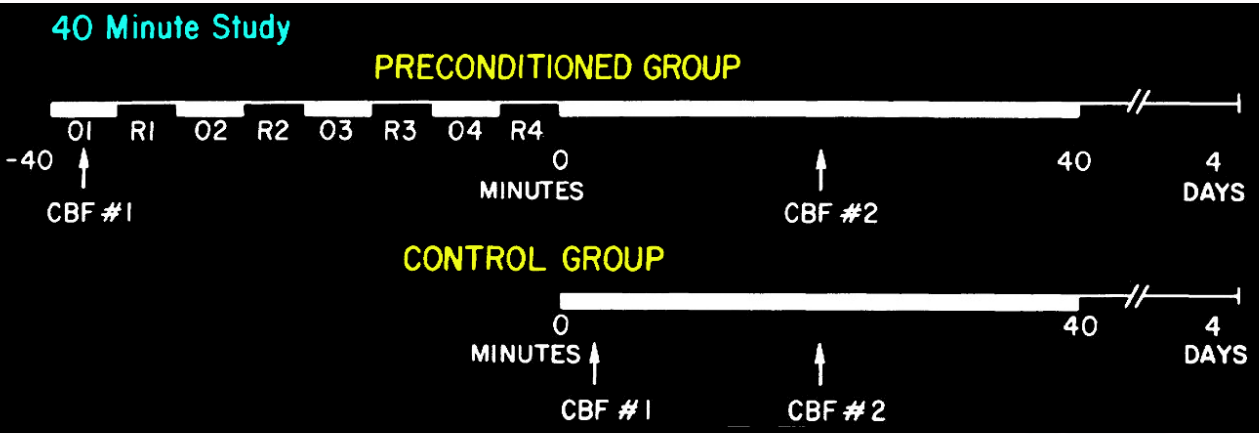
Fundación **procnic**



Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium

Circulation 1986;74:1124-1136

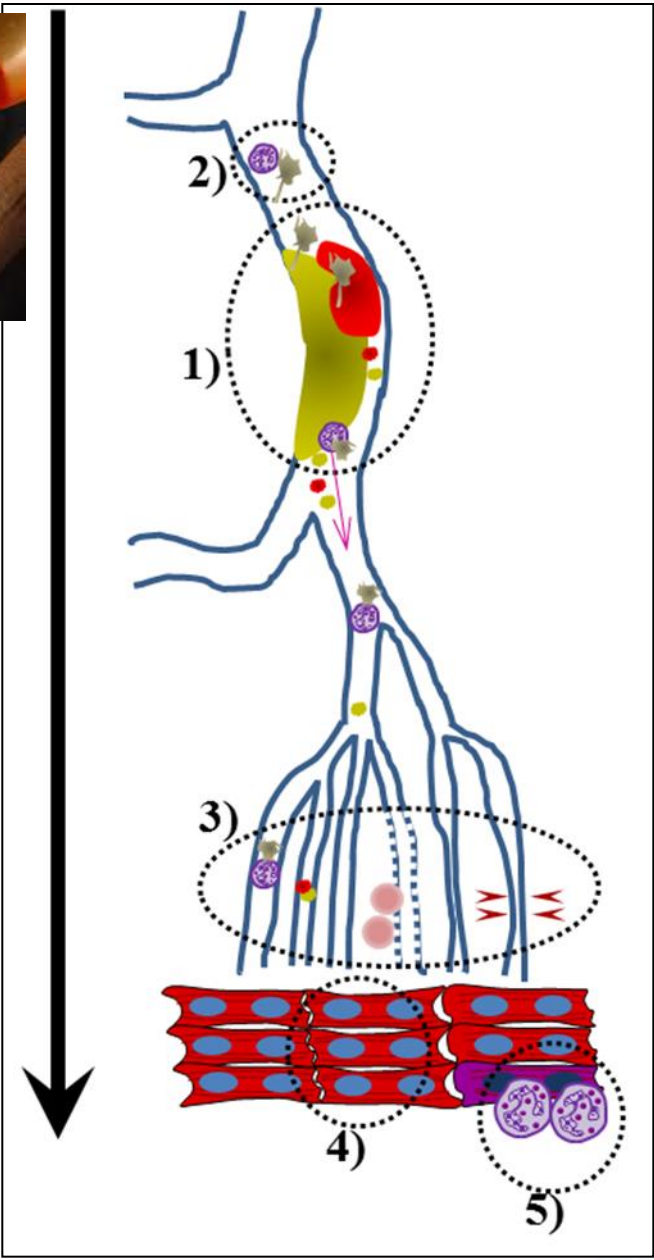
CHARLES E. MURRY, B.S., ROBERT B. JENNINGS, M.D., AND KEITH A. REIMER, M.D., PH.D.

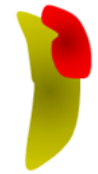









This study suggested that there was more than just duration of ischemia



Damage gradient

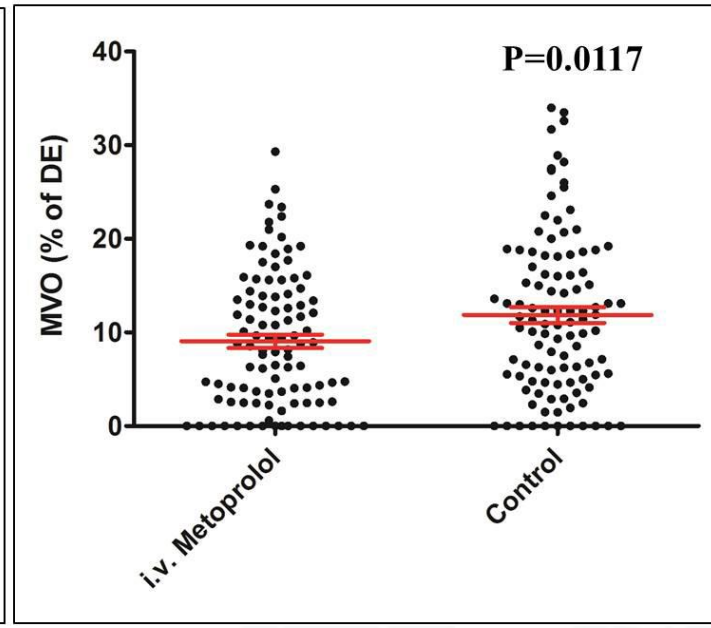
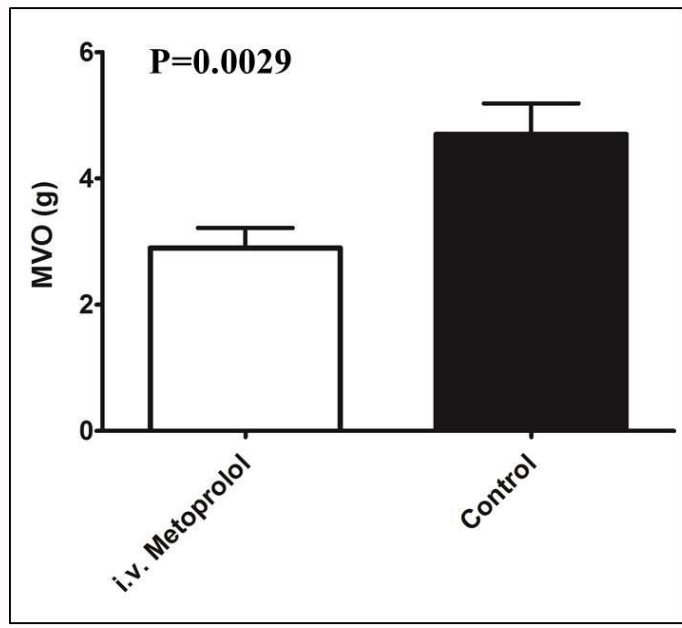


 Atherosclerotic plaque with superimposed Thrombus.	 Microemboli (plaque, thrombi,...).
 Red blood cells (hemorrhage).	 Cardiomyocyte.

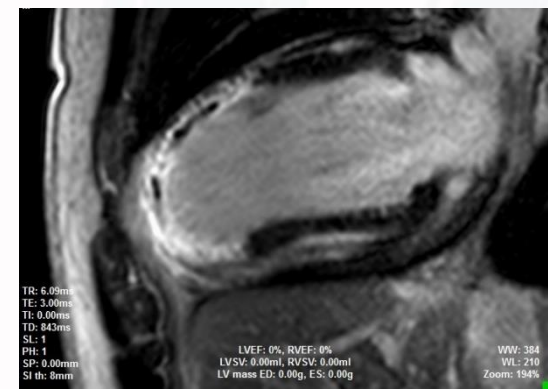
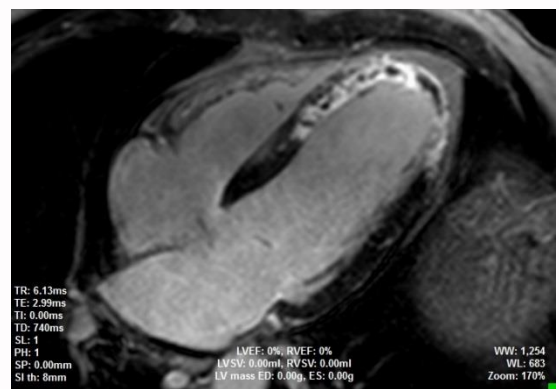
 Inflammatory cells (Leukocyte, ..).	 Platelet/leukocyte Aggregates.
 External compression (edema).	 Activated platelets.



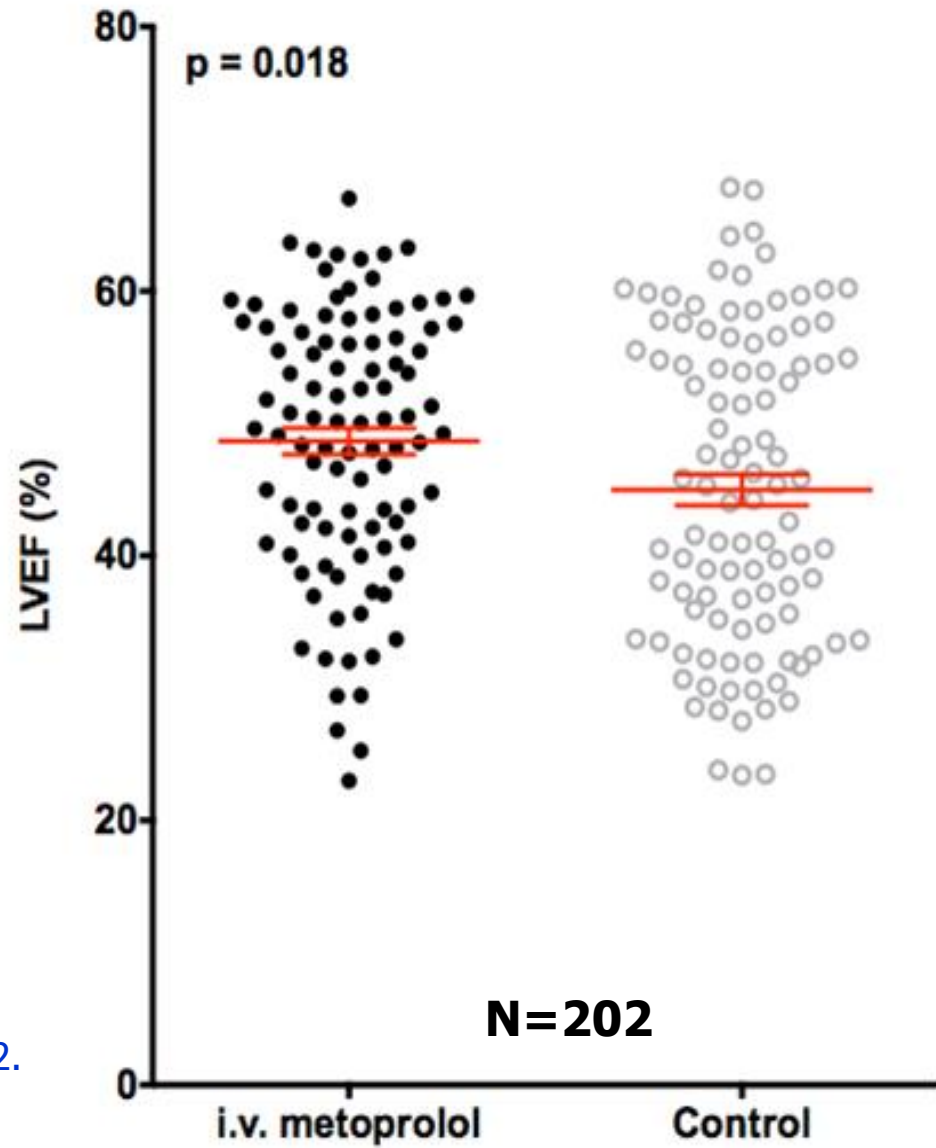
i.v. metoprolol pre-reperfusion reduces Microvascular Obstruction (even after adjusting for infarct size). N=220.



García-Lunar, Pizarro, Fernandez-Friera et al **ACC 2014** (ORAL Presentation).



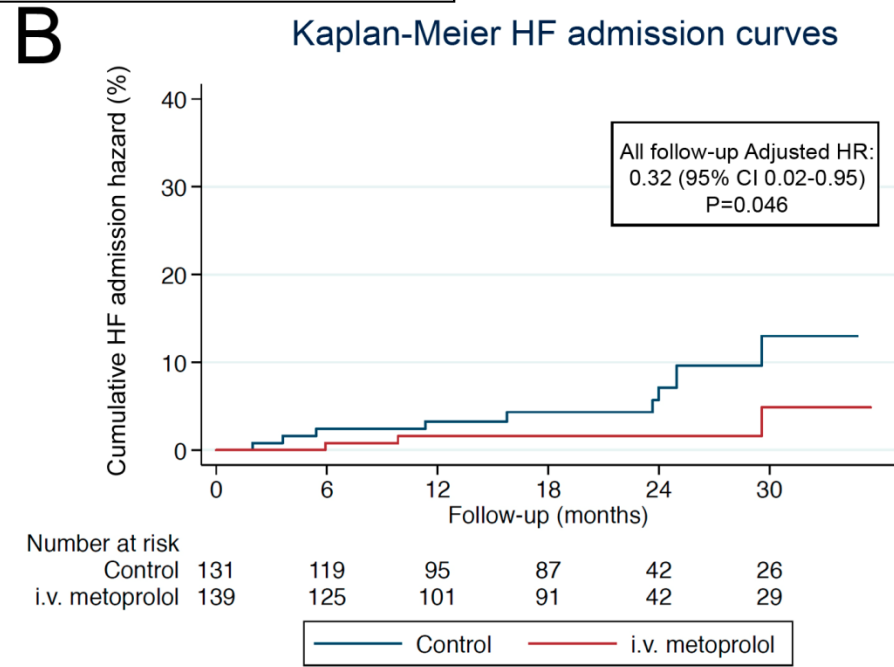
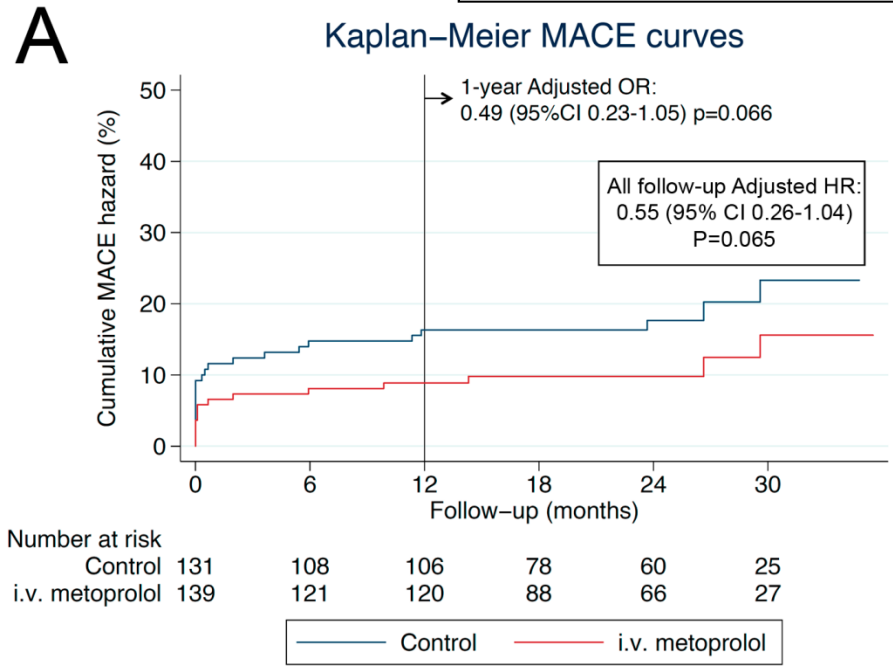
Patients undergoing MRI at 6-month follow-up



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

Table 2: Clinical Events

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



Landmarks in therapies to reduce ischemic injury

1972: First evidence that reperfusion limits extent of necrosis.

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

1986: GISSI trial: thrombolysis reduces mortality in STEMI.

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

1976: *First-in-man* intracoronary thrombolysis in STEMI.

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

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

1980: Unequivocal demonstration: coronary thrombosis cause STEMI.

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

1970s

1980s

1990s

2000s

2010s

1986: First evidence that ischemic pre-conditioning reduces infarct size.

1993: First evidence that RIC reduces infarct size.

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

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

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

2008 *Proof-of-concept:* CsA reduces infarct size in STEMI.

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

Landmarks in therapies to reduce reperfusion injury