

Papel de los β bloqueantes en el SCA en 2019

Borja Ibanez, MD PhD FESC



National Center for Cardiovascular Research, Spain



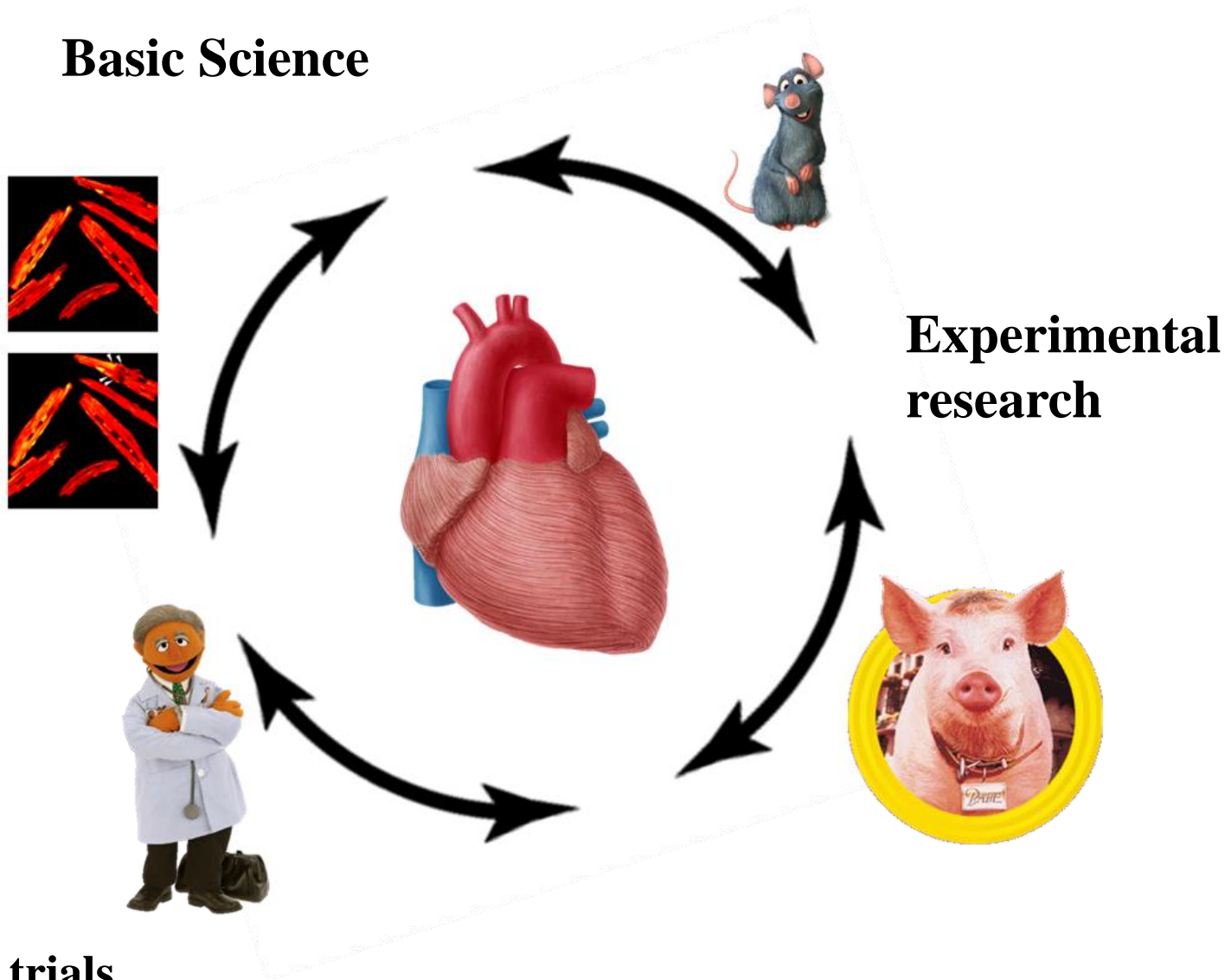
Fundación Jiménez Díaz University Hospital, Spain





B Ibanez has no conflict to declare

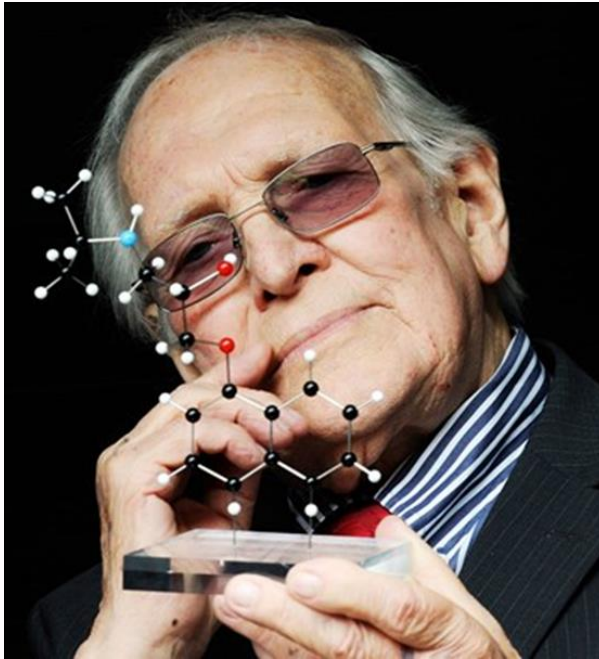




Clinical trials
Clinical Practice Guidelines



β blockers are fascinating!! *cnic*



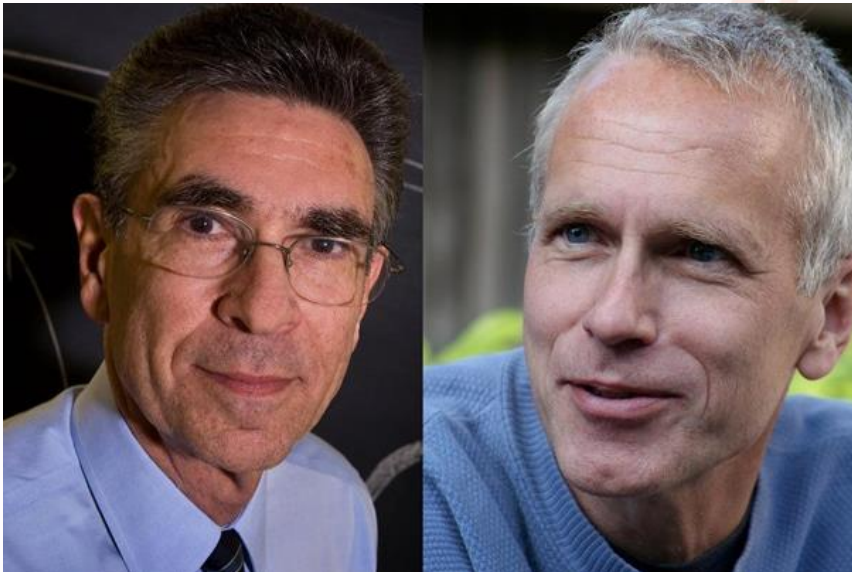
Sir James Black

1988 Nobel Prize Medicine
Development of propranolol
(and cimetidine)



Robert J. Lefkowitz **Brian K. Kobilka**

2012 Nobel Prize Chemistry
 β adrenergic receptors (GPCR)





ESC

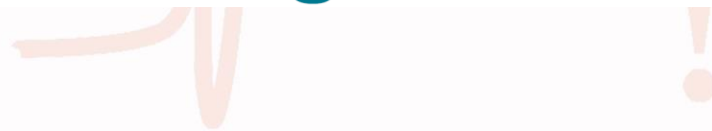
European Society
of Cardiology

European Heart Journal (2018) **39**, 119–177

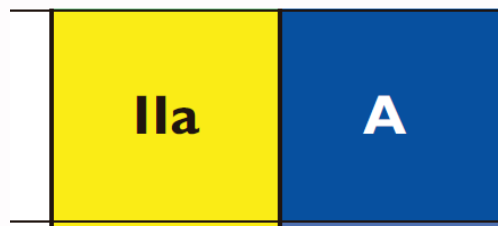
doi:10.1093/eurheartj/ehx393

ESC GUIDELINES

2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation



Intravenous beta-blockers should be considered at the time of presentation in patients undergoing primary PCI without contraindications, with no signs of acute heart failure, and with an SBP >120 mmHg.^{346–348,350,403}





ESC

European Society
of Cardiology

European Heart Journal (2018) **39**, 119–177
doi:10.1093/eurheartj/ehx393

ESC GUIDELINES

2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation

Oral β blocker

LVEF $\leq 40\%$ or HF

I A

LVEF $> 40\%$, no HF

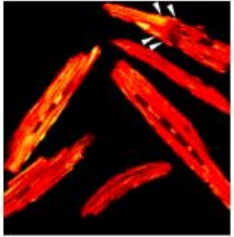
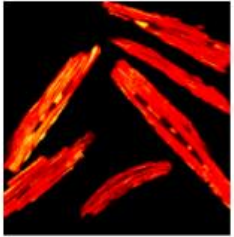
IIa B



- Early i.v. admin to reduce MI size
- Chronic oral treatment

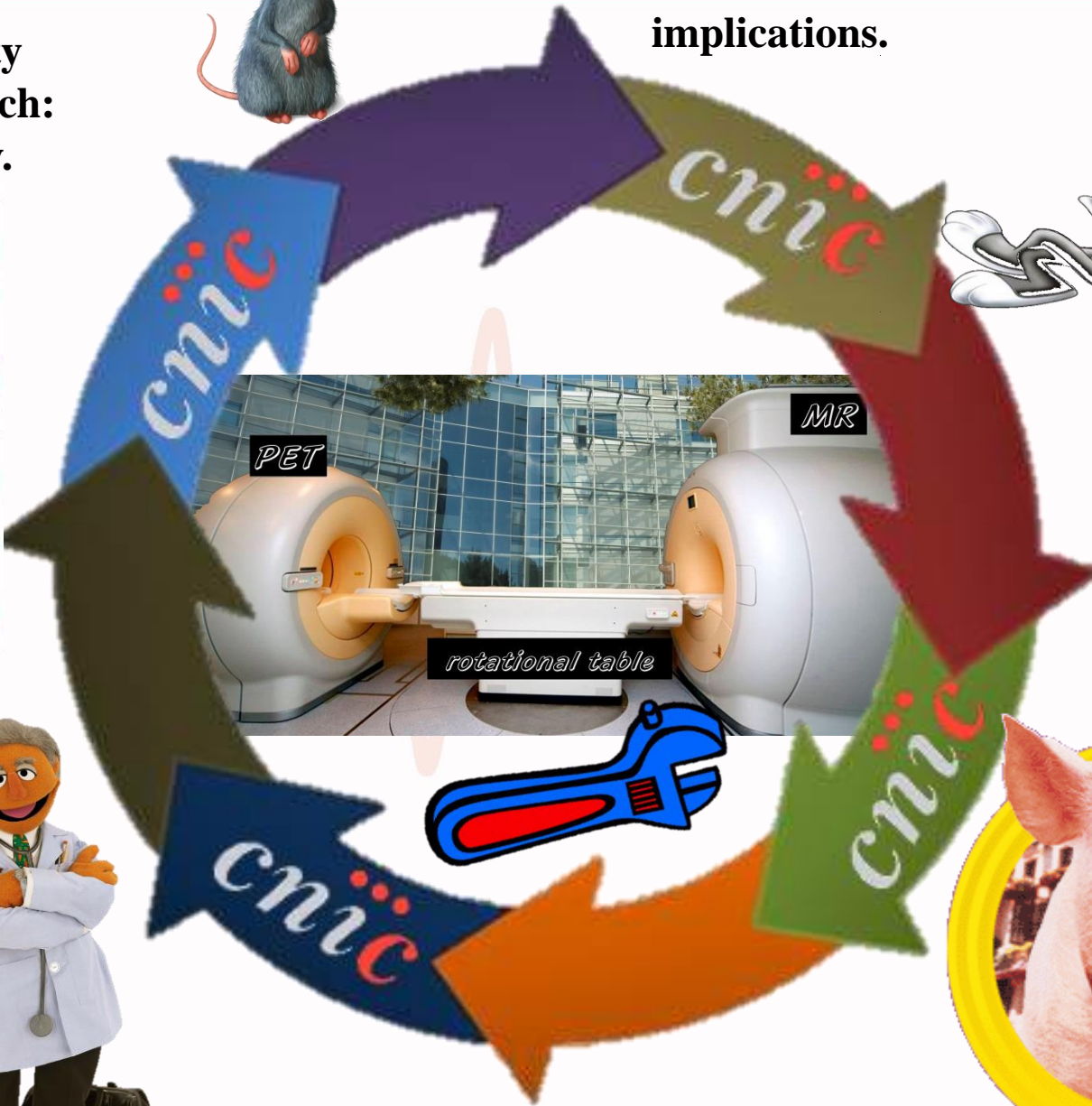
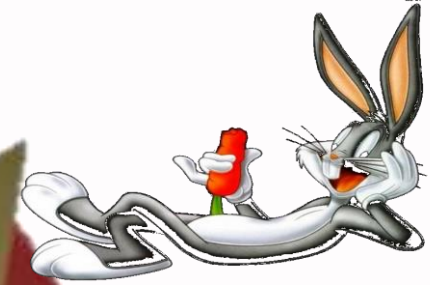


**Top quality
basic research:
Discovery.**



**Systems Biology:
in vivo
implications.**

cnic



**Large animal:
Pre-human step.**

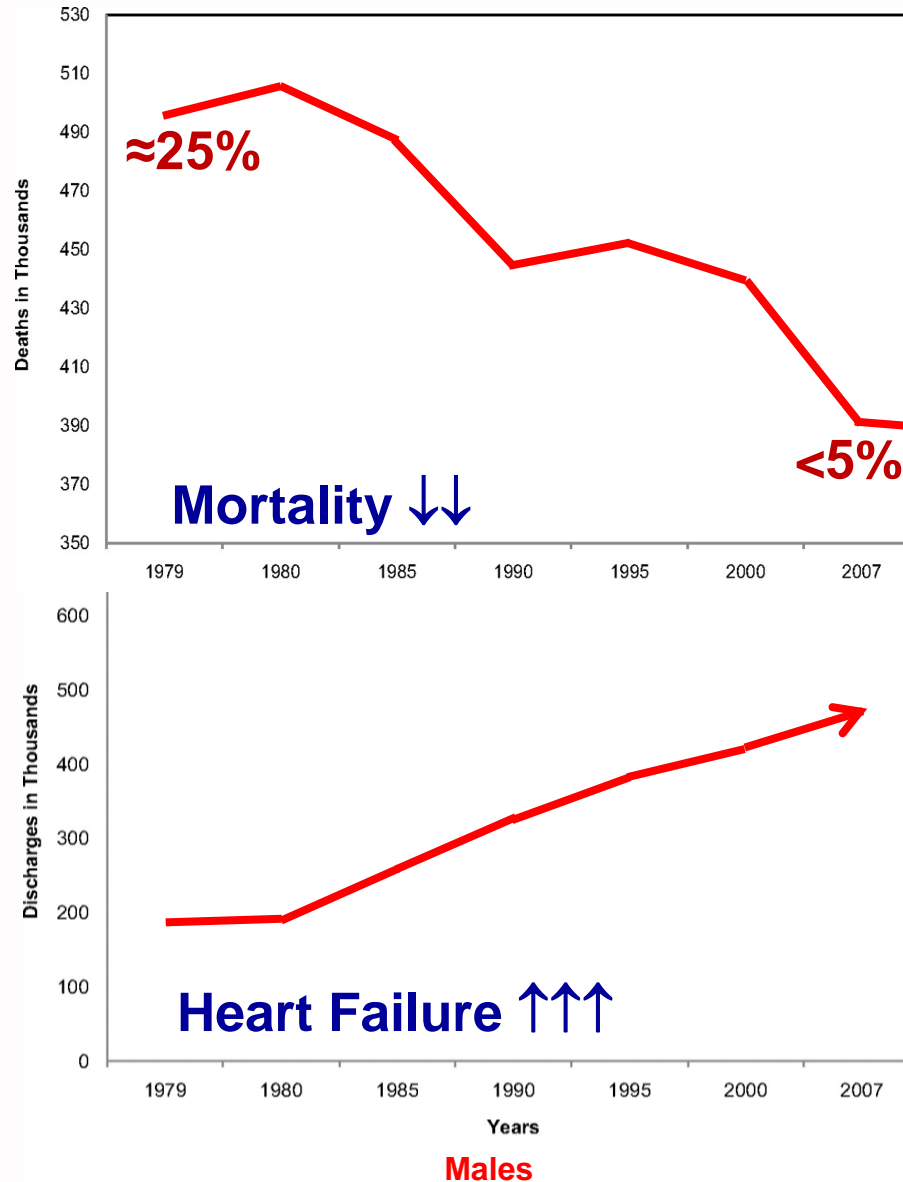


Clinical trials.





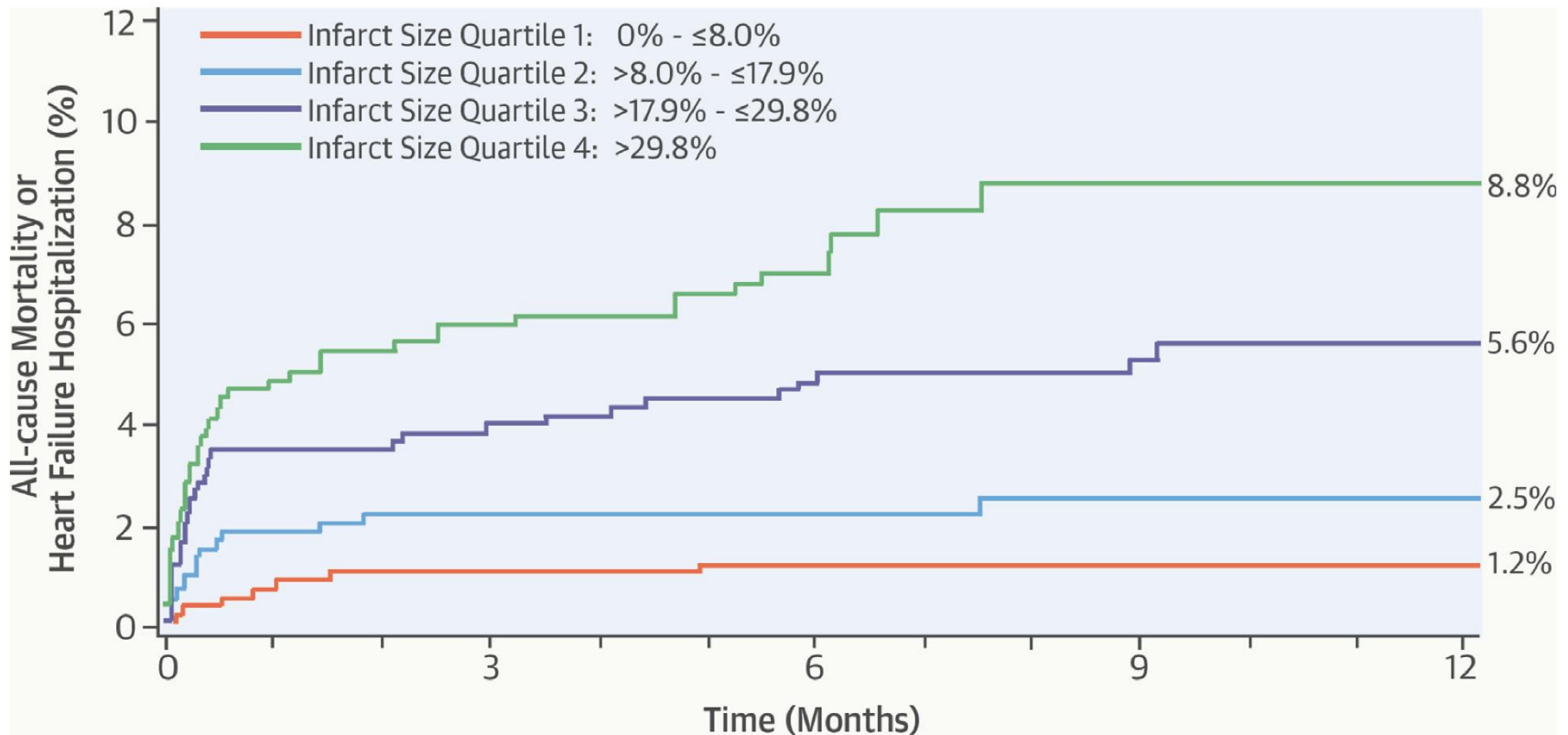
REPERFUSION: Paradigm shift *enic*



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



CENTRAL ILLUSTRATION IS and Prognosis After Primary PCI: All-Cause Mortality or HF Hospitalization



Stone, G.W. et al. J Am Coll Cardiol. 2016;67(14):1674-83.

Infarct size is a strong determinant of long-term mortality and chronic heart failure



Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



JACC
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

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



2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation

The Task Force for the management of acute myocardial infarction
in patients presenting with ST-segment elevation of the European
Society of Cardiology (ESC)

Authors/Task Force Members: Borja Ibanez* (Chairperson) (Spain), Stefan James*



ESC

European Society
of Cardiology

**No therapy to reduce MI size
→ URGENT clinical need**



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.

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



Betablockers in STEMI

cnic

2005



- Early intravenous then oral metoprolol in 45 852 patients with acute myocardial infarction: randomised placebo-controlled trial

Lancet 2005; 366: 1622–32

COMMIT (ClopIdogrel and Metoprolol in Myocardial Infarction Trial) collaborative group*

	Metoprolol (n=22 929)	Placebo (n=22 923)	Odds ratio (95% CI)	Absolute difference per 1000 (SE)	p
--	--------------------------	-----------------------	------------------------	---	---

Co-primary outcomes

Composite*	2166 (9.4%)	2261 (9.9%)	0.96 (0.90–1.01)	–4.2 (2.8)	0.10
Death	1774 (7.7%)	1797 (7.8%)	0.99 (0.92–1.05)	–1.0 (2.6)	0.69

Death, by recorded cause

Arrhythmia	388 (1.7%)	498 (2.2%)	0.78 (0.68–0.89)	–4.8 (1.3)	0.0002
Shock†	496 (2.2%)	384 (1.7%)	1.29 (1.13–1.47)	4.9 (1.3)	0.0002
Neither	890 (3.9%)	915 (4.0%)	0.97 (0.89–1.07)	–1.1 (1.8)	0.55



Data in perspective:

COMMIT

cnic

➤ Early intravenous then oral metoprolol in 45 852 patients with acute myocardial infarction: randomised placebo-controlled trial

COMMIT (ClopIdogrel and Metoprolol in Myocardial Infarction Trial) collaborative group*

Lancet 2005; 366: 1622-32

6 h. The presenting ECG showed ST elevation in 39 755 (87%) patients and bundle branch block in 2928 (6%), with the remainder having ST depression alone. Heart failure (Killip II or III) was present at entry in 11 249 (24%) patients, 15 399 (34%) had systolic blood pressure lower than 120 mm Hg, and 3244 (7%) had heart rate over 110 bpm. Previous MI was recorded in 3818 (8%) patients and hypertension in 19 838 (43%). β -blocker therapy had been used before hospital admission by 2990 (7%) patients. Fibrinolytic therapy (mainly urokinase) had been received by 22 794 (50%) patients just before randomisation, and by a total of 24 967 (54%) at some time before or after randomisation (68% in those presenting within 12 h with ST-elevation). During the hospital stay, there were no significant differences between the treatment groups in the use of fibrinolytic, anticoagulant (mainly heparin), or nitrate therapy. But somewhat fewer metoprolol-allocated patients received

Heart Failure was present in a significant % of patients

45% were NOT reperfused

Mean symptoms onset-Lysis: 10.3±6.3 hr



- **Early intravenous then oral metoprolol in 45 852 patients with acute myocardial infarction: randomised placebo-controlled trial**

*COMMIT (CLOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group**

Lancet 2005; 366: 1622-32

COMMIT does not represent current
State of the art treatment for STEMI

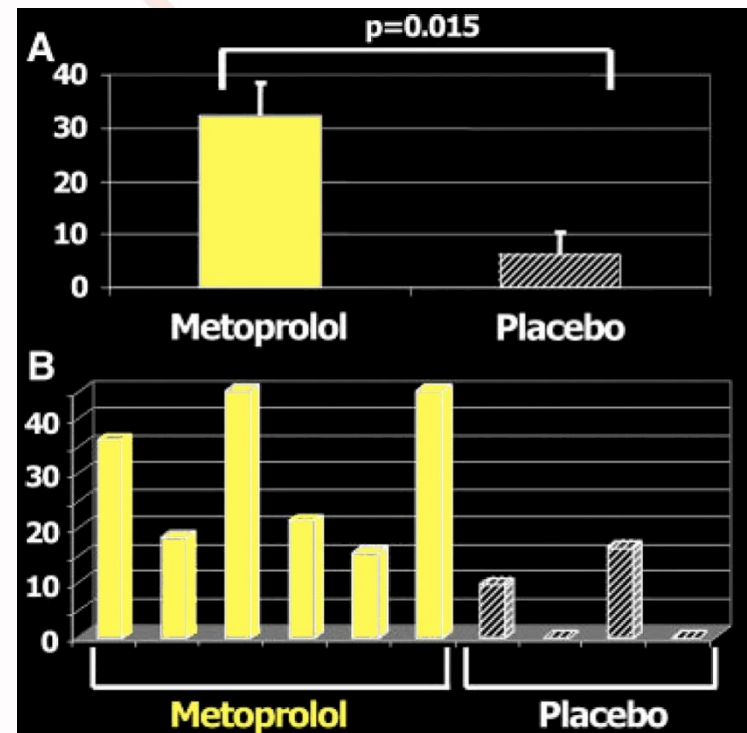
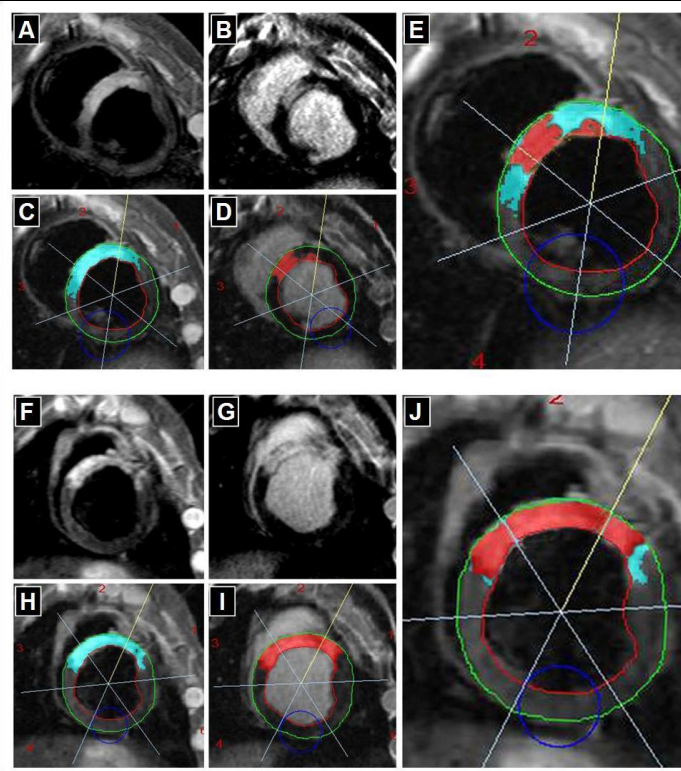


Early Metoprolol Administration Before Coronary Reperfusion Results in Increased Myocardial Salvage

Analysis of Ischemic Myocardium at Risk Using Cardiac Magnetic Resonance

Circulation 2007;115:2909-16

Borja Ibanez, MD; Susanna Prat-González, MD; Walter S. Speidl, MD; Gemma Vilahur, DVM, PhD; Antonio Pinero, MD; Giovanni Cimmino, MD; Mario J. García, MD; Valentin Fuster, MD, PhD; Javier Sanz, MD; Juan J. Badimon, PhD





METOCARD-CNIC trial

cnic



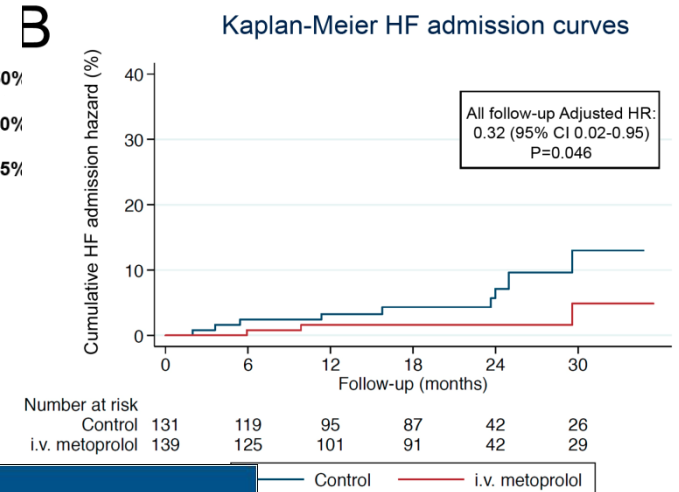
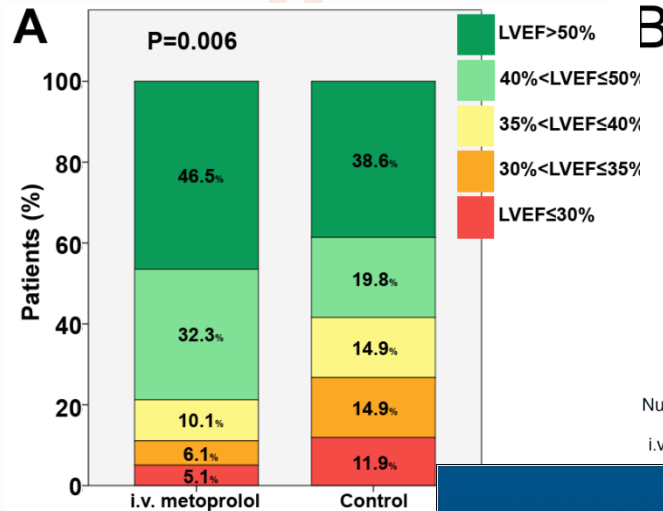
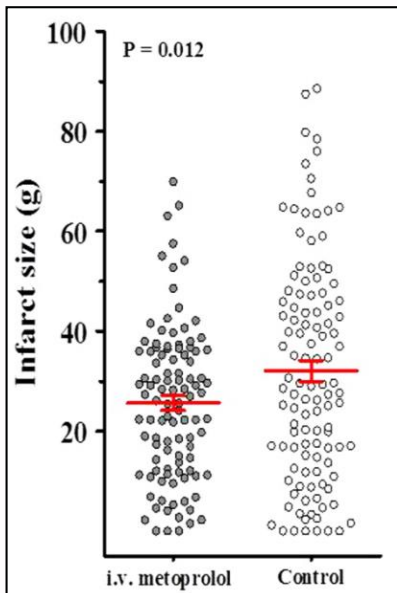


Metoprolol ↓ MI size in STEMI

cnic



Reduction of scar tissue by 20%,
Increase in short & long-term LVEF,
Reduction of Heart Failure readmission



Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

JACC
JOURNAL of the AMERICAN COLLEGE of CARDIOLOGY

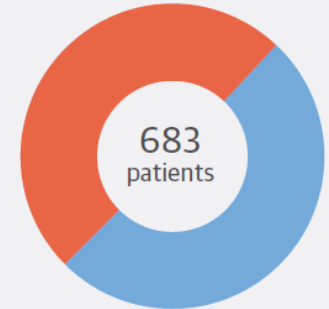
Circulation 2013 & JACC 2014 & Annals Emerg Med 2015 & JACC 2016



Early Intravenous Beta-Blockers in Patients With ST-Segment Elevation Myocardial Infarction Before Primary Percutaneous Coronary Intervention



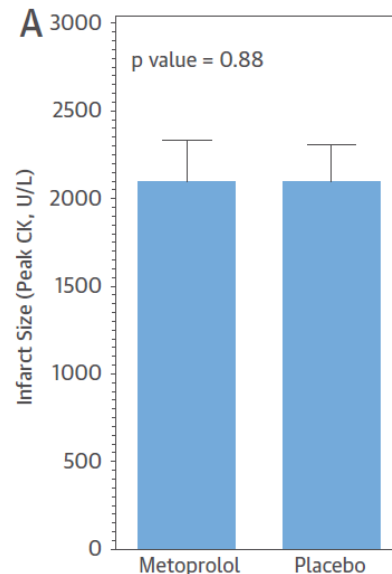
336 patients: 10 mg metoprolol



346 patients: placebo

Vincent Roolvink, MD,^a Borja Ibáñez, MD, PhD,^{b,c} Jan Paul Ottervanger, MD, PhD,^a Gonzalo Pizarro, MD,^{b,d} Niels van Royen, MD, PhD,^e Alonso Mateos, MD,^f Jan-Henk E. Dambrink, MD, PhD,^a Noemi Escalera, BPT,^b Erik Lipsic, MD, PhD,^g Agustín Albarran, MD, PhD,^{h,i} Antonio Fernández-Ortiz, MD, PhD,^{h,j} Francisco Fernández-Avilés, MD, PhD,^{h,k} Javier Goicolea, MD, PhD,^{h,l} Javier Botas, MD, PhD,^{h,m} Wouter Remkes, MD,^a Victoria Hernandez-Jaras, PHARM,^f Elvin Kedhi, MD, PhD,^a José L. Zamorano, MD, PhD,^{h,n} Felipe Navarro, MD, PhD,^{c,h} Fernando Alfonso, MD, PhD,^{h,o} Alberto García-Lledó, MD, PhD,^{h,p} Joaquin Alonso, MD, PhD,^{h,q} Maarten van Leeuwen, MD,^e Robin Nijveldt, MD, PhD,^e Sonja Postma, PhD,^r Evelien Kolkman, MSc,^r Marcel Gosselink, MD, PhD,^a Bart de Smet, MD, PhD,^s Saman Rasoul, MD, PhD,^t Jan J. Piek, MD, PhD,^u Valentin Fuster, MD, PhD,^{b,v} Arnoud W.J. van 't Hof, MD, PhD,^a
on behalf of the EARLY-BAMI Investigators

J Am Coll Cardiol. 2016;67(23):2705-15.





STEMI diagnosis



Reperfusion



Arterial access

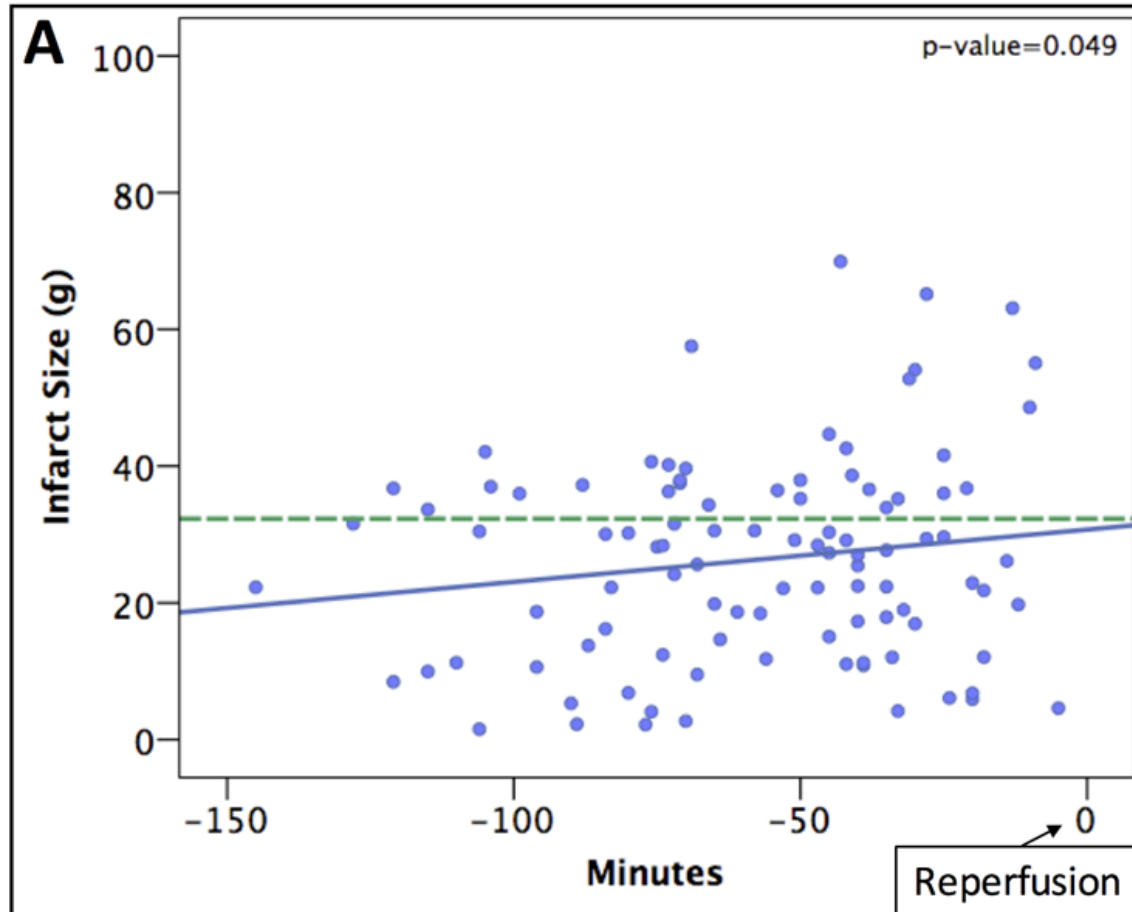


Window metoprolol administration in METOCARD-CNIC



Timing of metoprolol admin *cnic*

Time of i.v. metoprolol bolus before reperfusion



The longer the “on board” metoprolol duration at reperfusion, the higher the cardioprotection



Timing of metoprolol admin

Ad hoc animal study to test the hypothesis generated in the subanalysis of the clinical trial



LAD occlusion



Reperfusion (45 min)



Meto i.v.
@ 20 min



Meto i.v.
@ 40 min



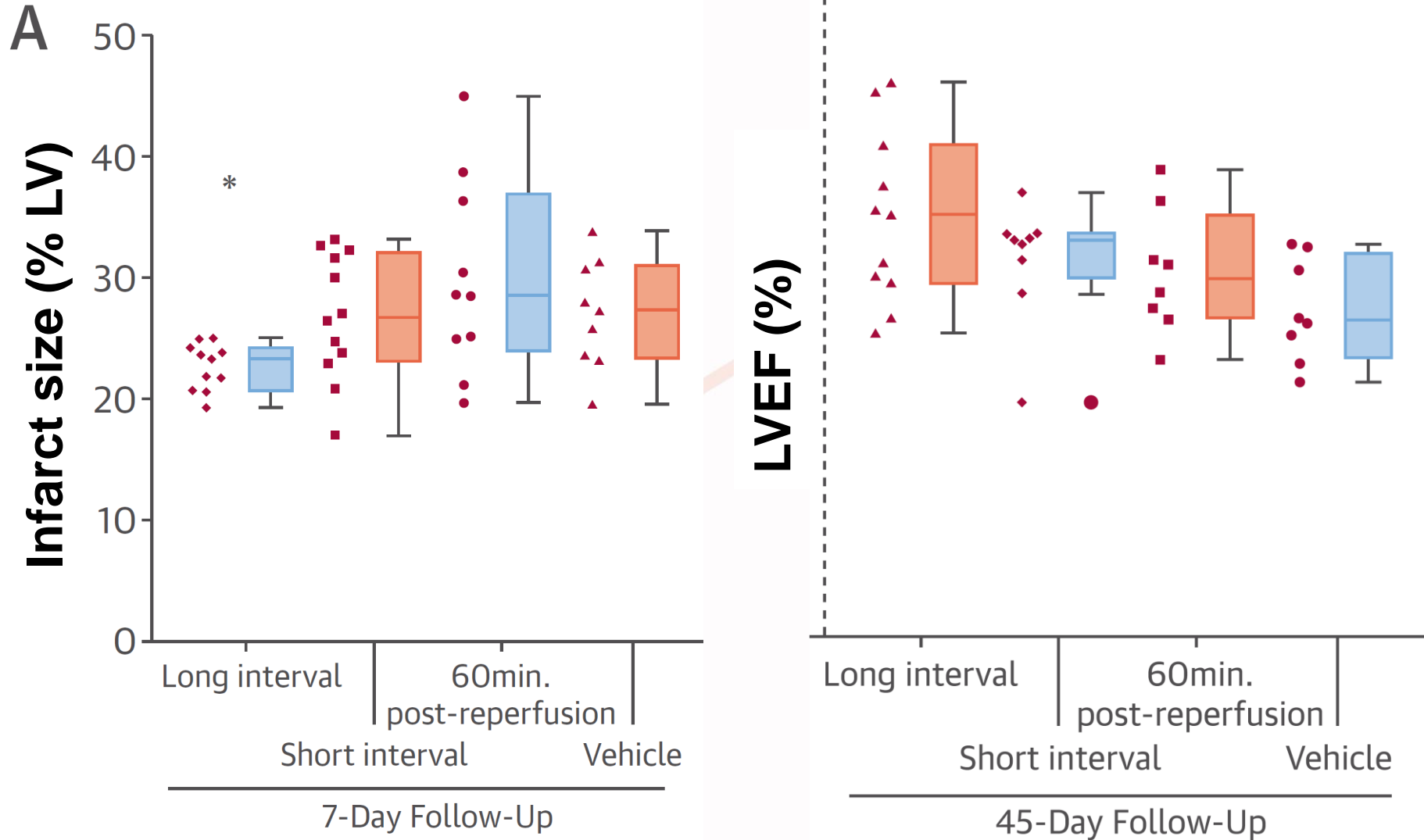
Meto i.v.
60 min
Post-reperf



Placebo

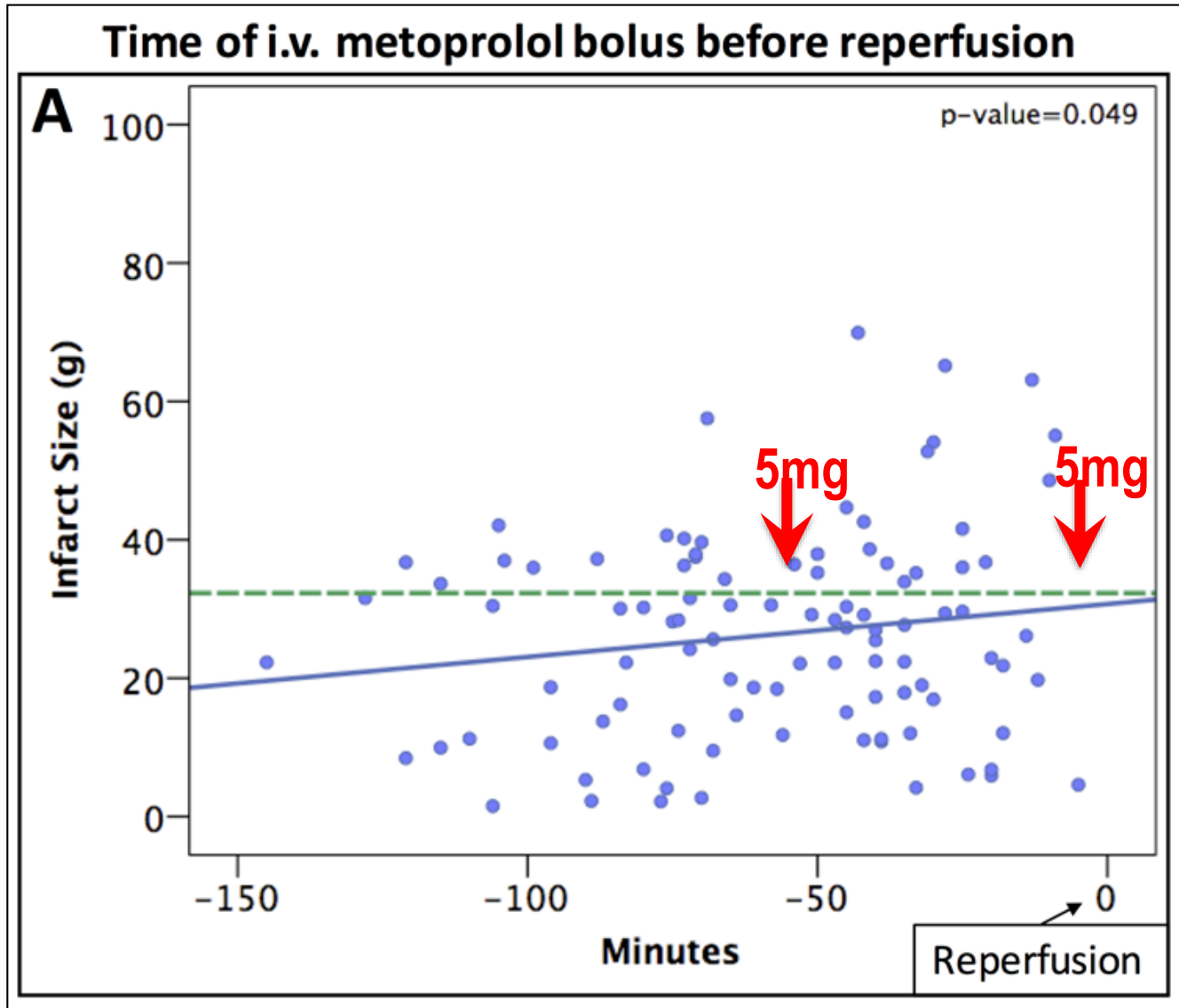


Timing of metoprolol admin





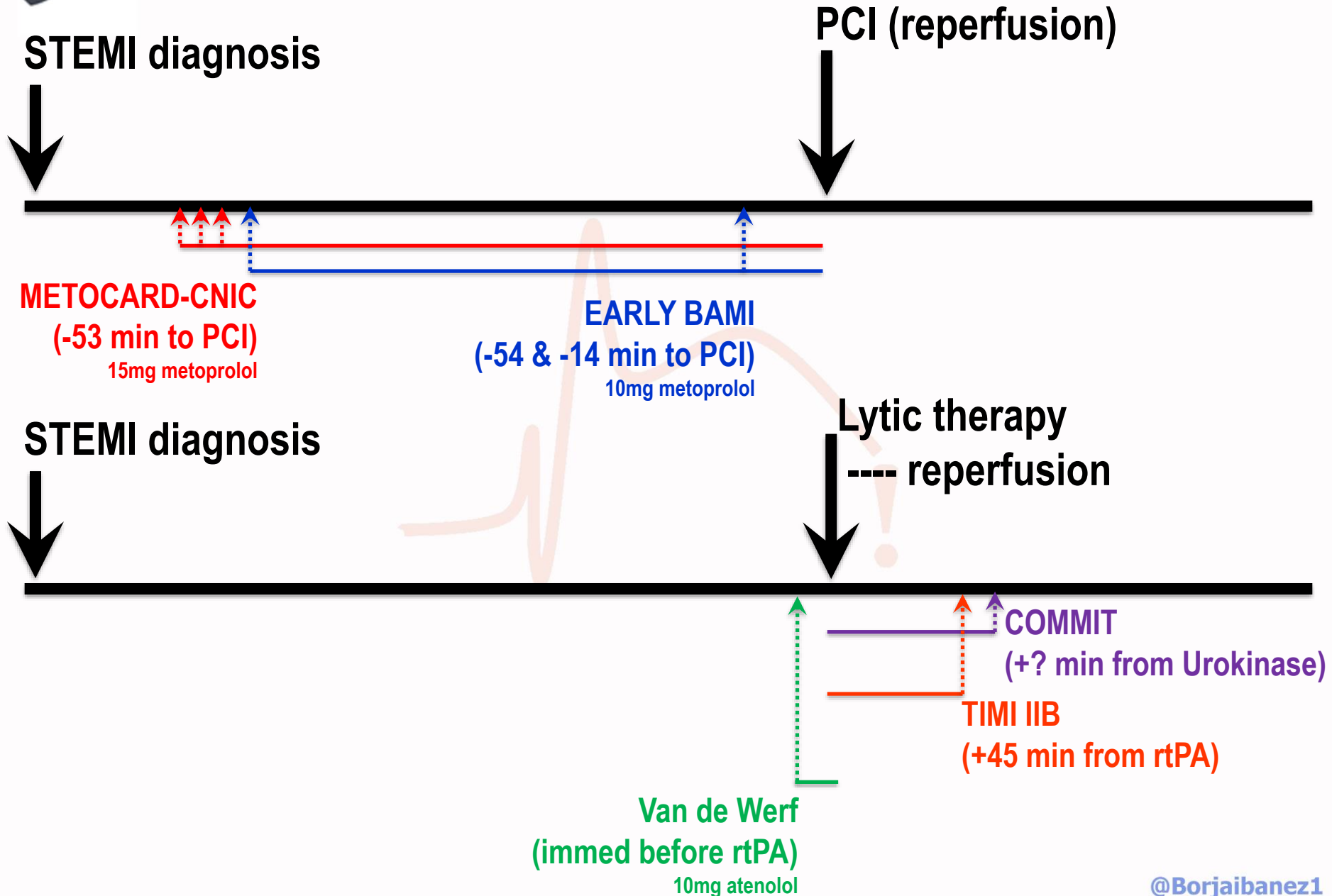
Window β -blk admin in trials



In EARLY BAM1 5mg metoprolol did not have any effect on BP or HR

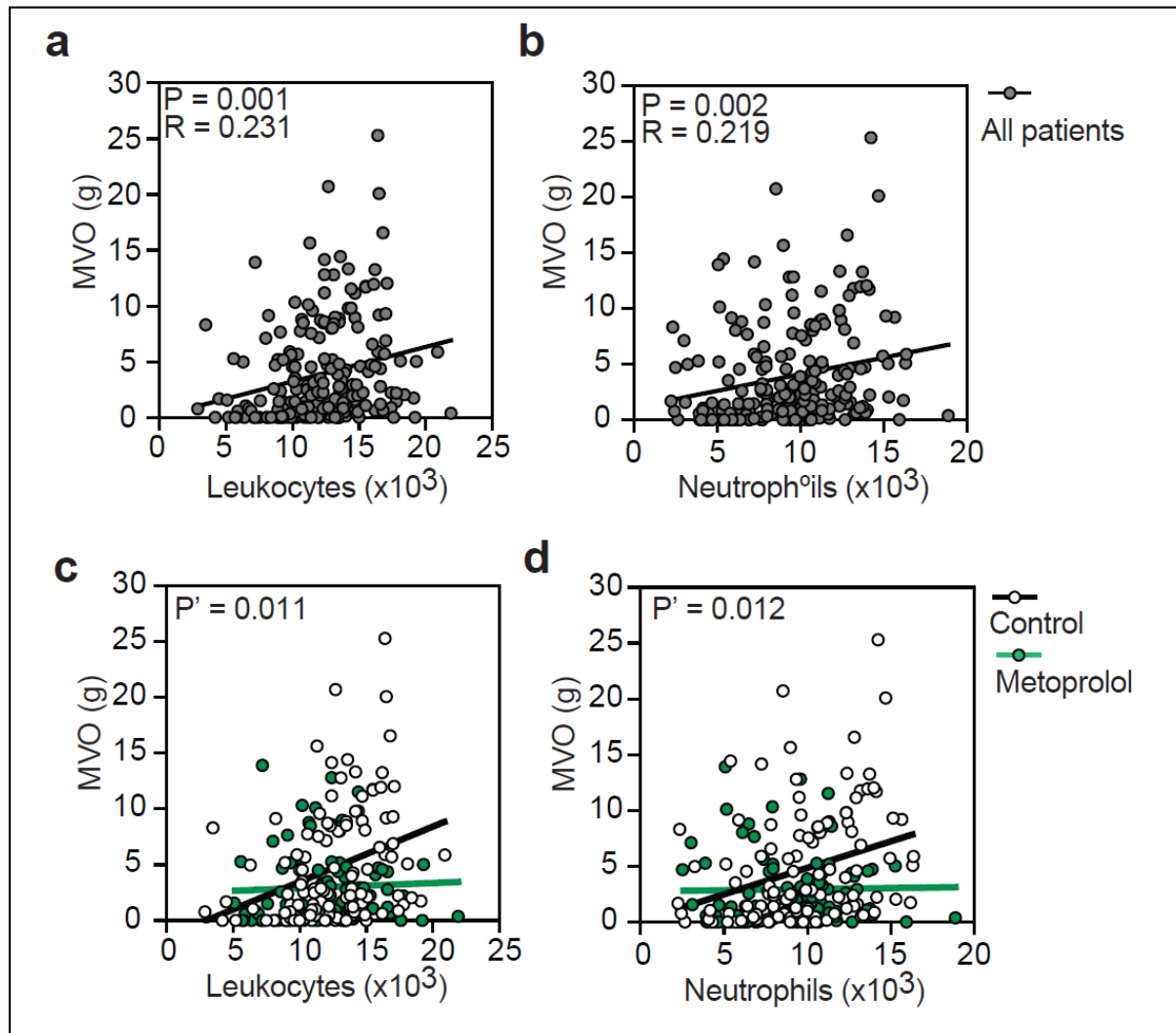


Window β -blk admin in trials *enic*





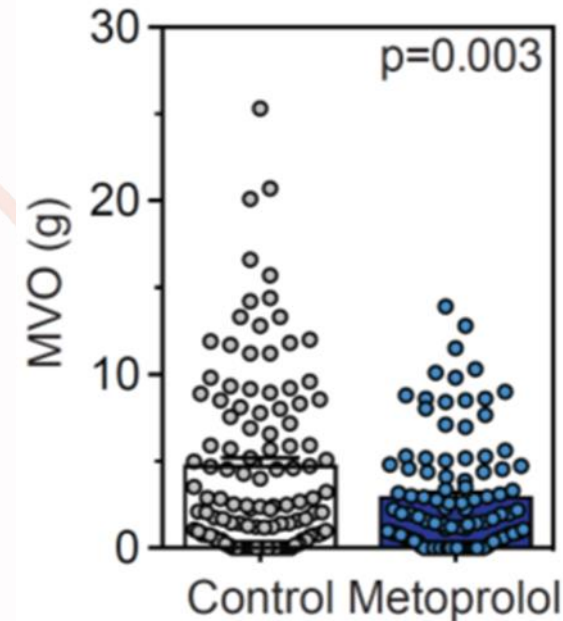
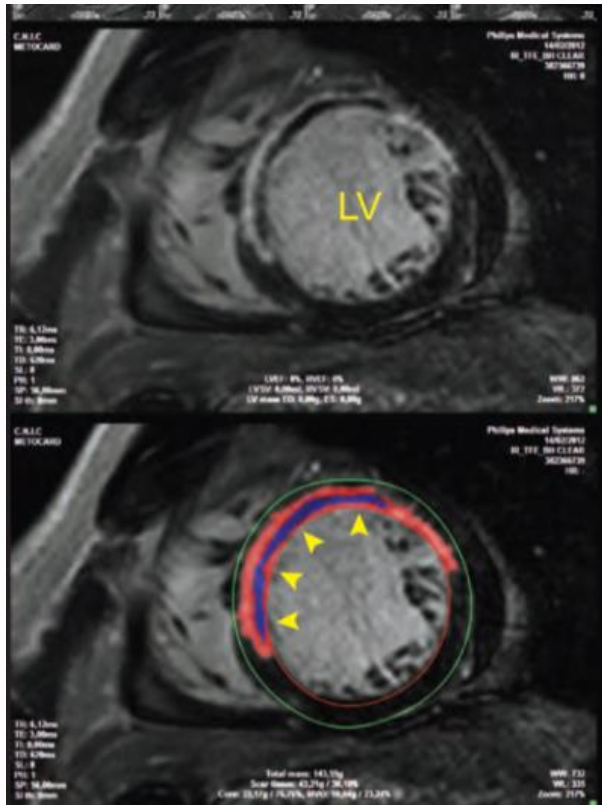
Neutrophils and MVO



-Metoprolol abrogates the impact of neutrophilia on MVO



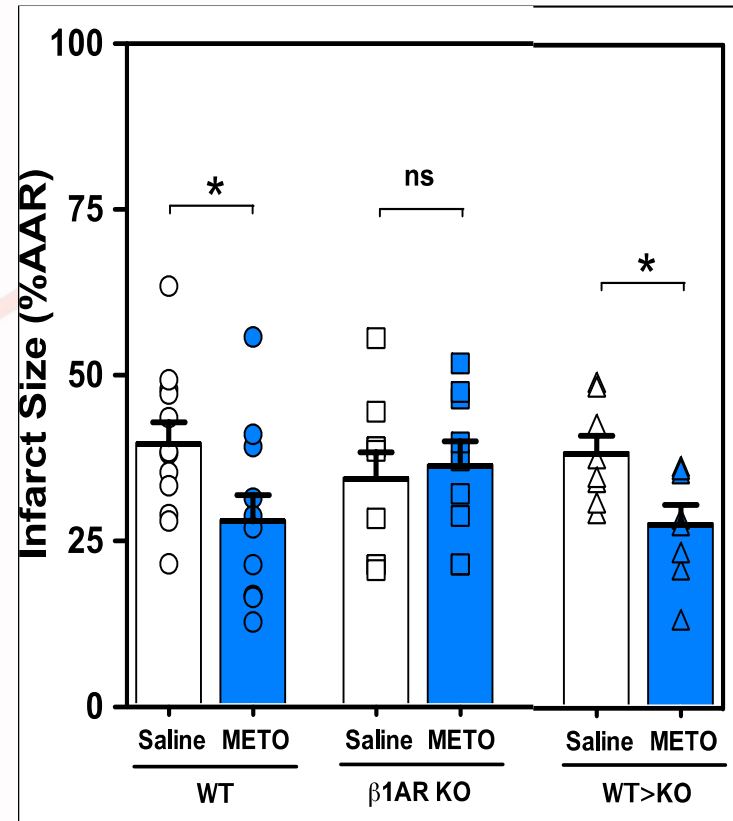
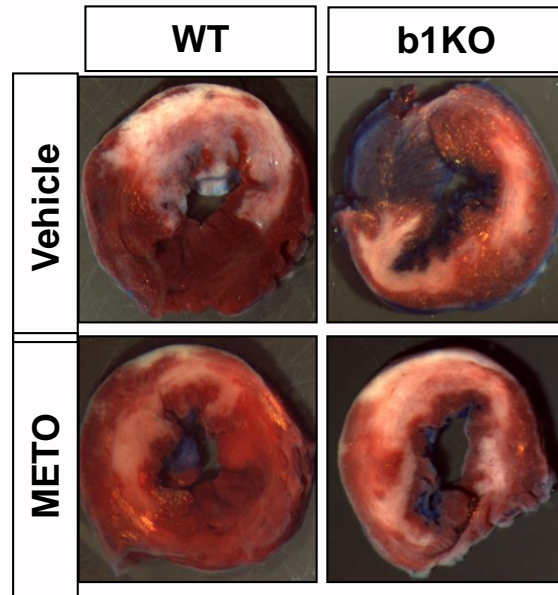
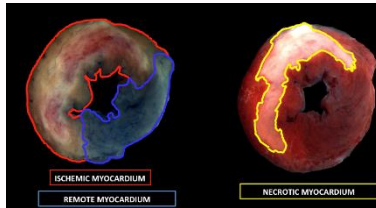
EARLY METOPROLOL



Metoprolol reduces Microvascular Obstruction in STEMI patients.

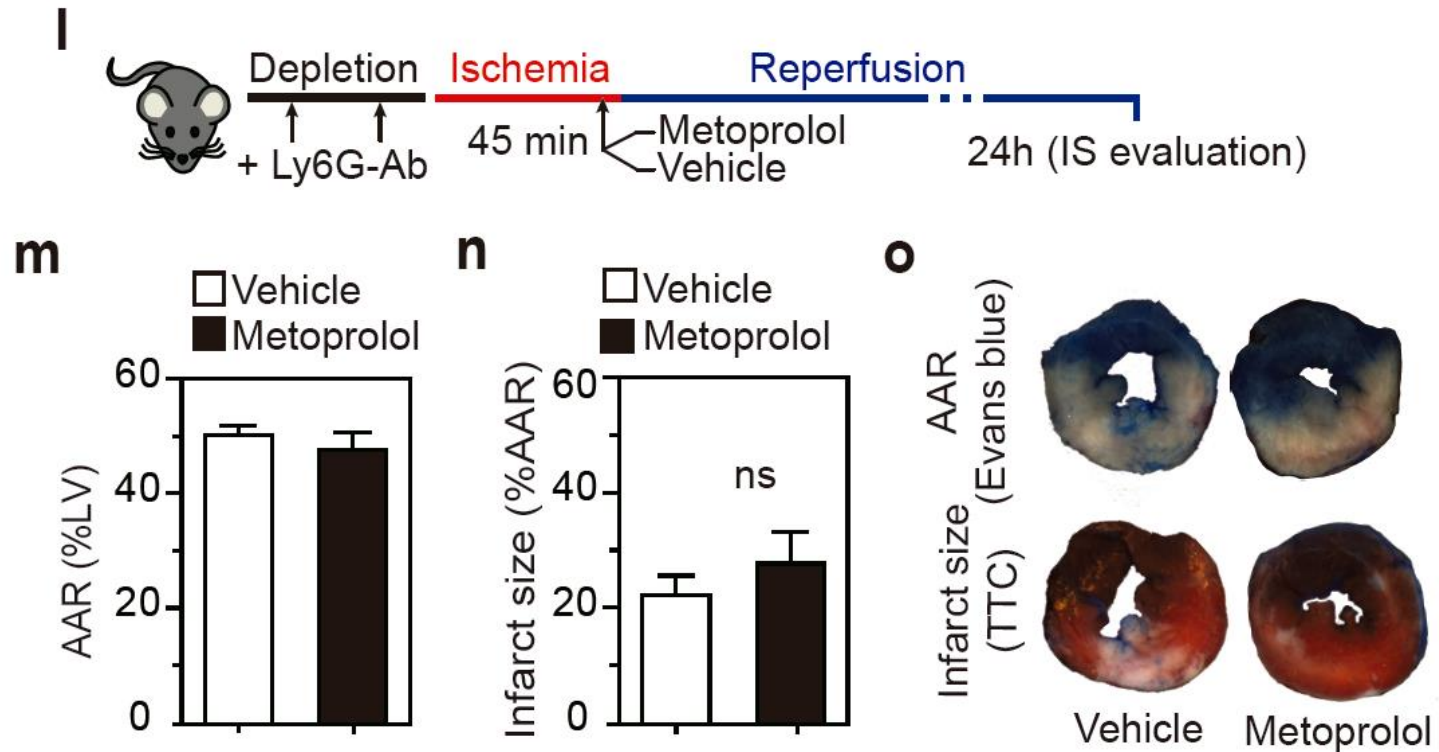


IS reduction. Role of circulating cells





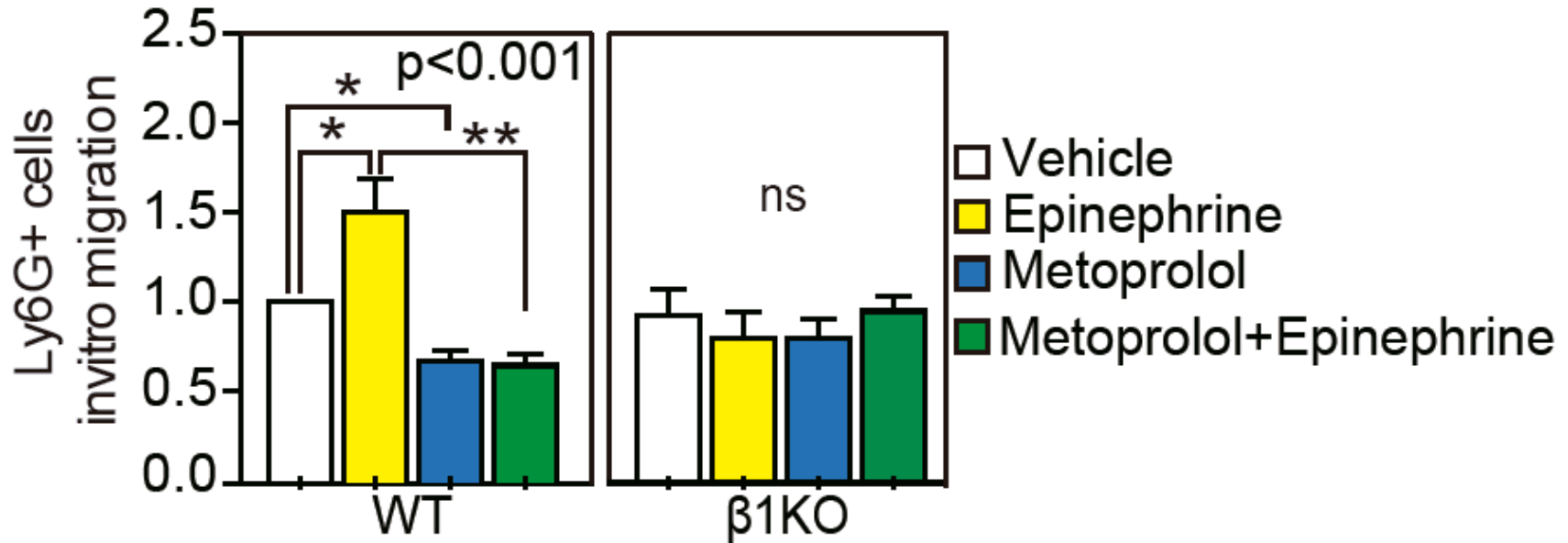
Metoprolol, MI size & neutrophils *cnic*



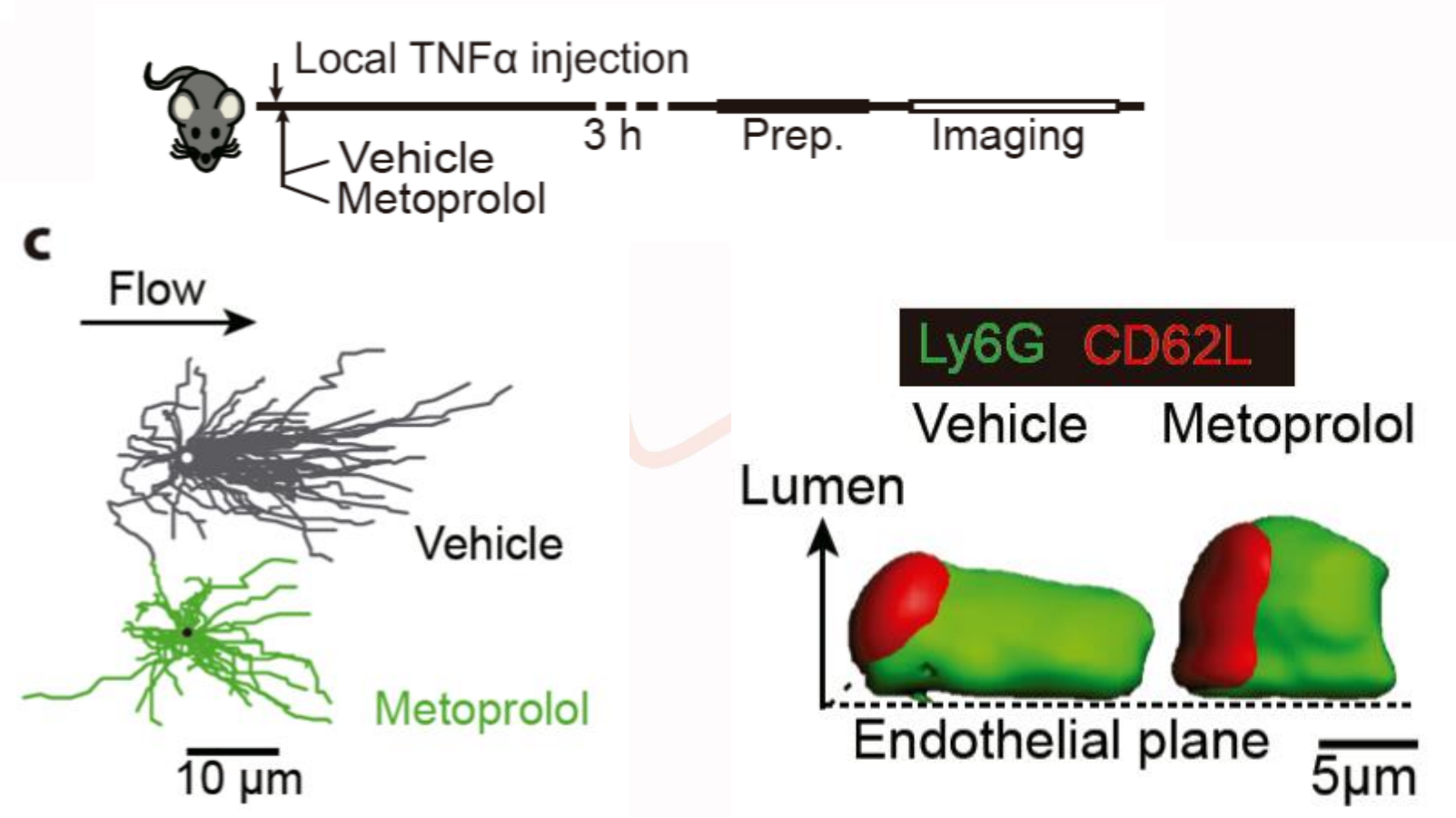
Metoprolol does not protect the heart during I/R in the absence of neutrophils



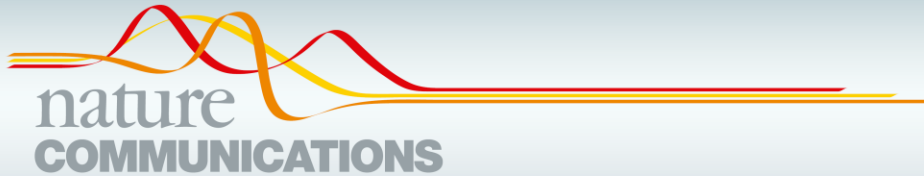
a



Metoprolol inhibits migration of neutrophils in a beta1-mediated manner



Metoprolol stuns neutrophils to protect the heart



ARTICLE

Received 22 Mar 2016 | Accepted 30 Jan 2017 | Published 18 Apr 2017

DOI: [10.1038/ncomms14780](https://doi.org/10.1038/ncomms14780)

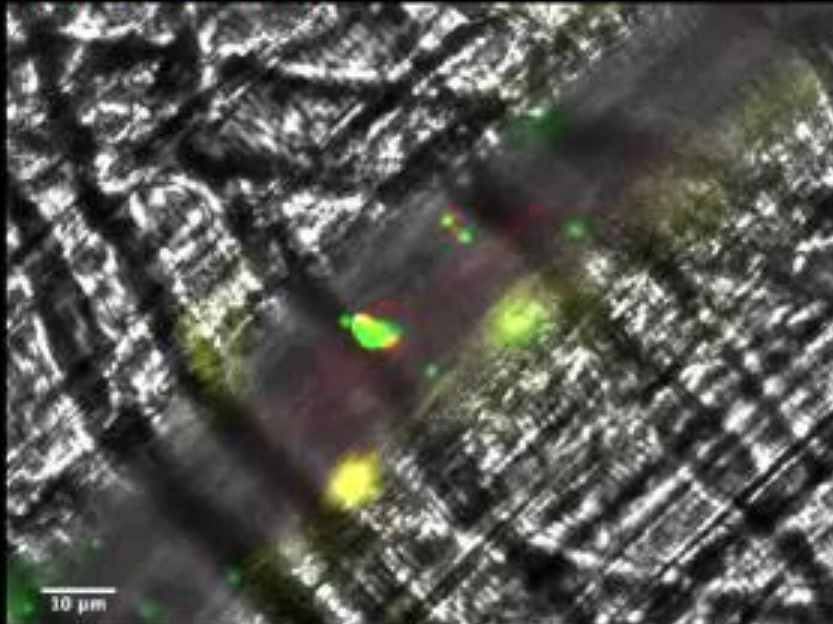
OPEN

Neutrophil stunning by metoprolol reduces infarct size

Jaime García-Prieto^{1,2}, Rocío Villena-Gutiérrez¹, Mónica Gómez¹, Esther Bernardo³, Andrés Pun-García¹, Inés García-Lunar^{1,2,4,5}, Georgiana Crainiciuc¹, Rodrigo Fernández-Jiménez^{1,2,3}, Vinatha Sreeramkumar^{1,4}, Rafael Bourio-Martínez^{1,6}, José M. García-Ruiz^{1,2,7}, Alfonso Serrano del Valle¹, David Sanz-Rosa^{1,2,4}, Gonzalo Pizarro^{1,2,4,8}, Antonio Fernández-Ortiz^{1,2,3}, Andrés Hidalgo^{1,9}, Valentín Fuster^{1,10} & Borja Ibanez^{1,2,11}



Ly6G CD62L CD41 Brightfield



SALINE



METOPROLOL



- Early i.v. admin to reduce MI size
- Chronic oral treatment



Evidence about the benefits of maintenance β blocker after MI is based on trials:

- Without reperfusion in STEMI
- Without revasc in NSTEMI
- No DAPT

Two trials in reperfusion era:

CAPRICORN

(post-MI + LVEF \leq 40%)

COMMIT

(acute phase i.v. β blocker+oral vs. placebo. very short follow-up: 30 days)



Articles

Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial

Lancet 2001; 357: 1385–90

*The CAPRICORN Investigators**

AMI (45% reperfused by fibrinolysis)

3-21 days post-MI

All on ACEi

Original design underpowered for all cause death (633 deaths expected, 267 occurred).

Change in primary endpoint to composite: 633 events

Final sample size: 1959 patients

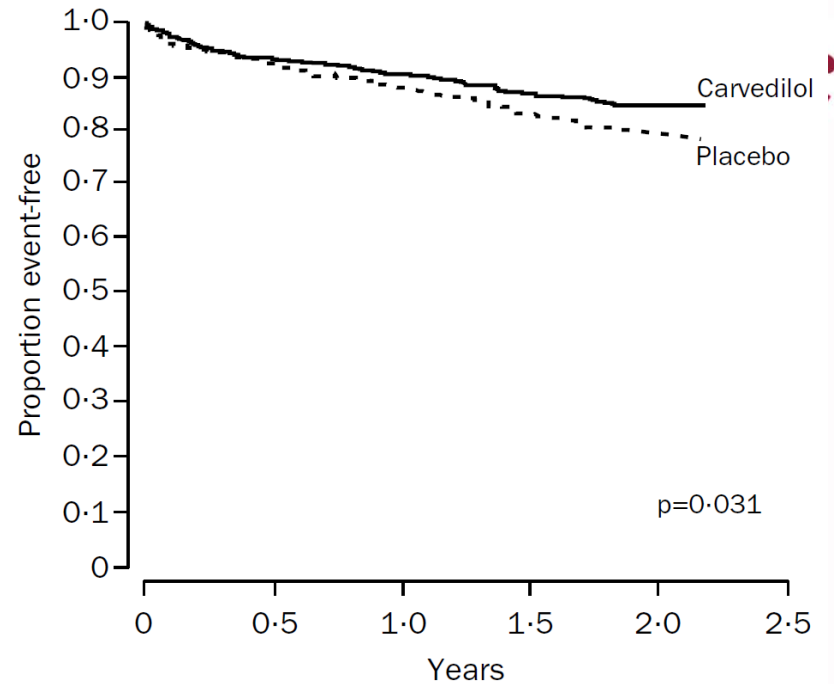
Median follow-up 1.3 years



Background

CAPRICORN TRIAL

Lancet 2001; 357: 1385–90



Numbers at risk

Carvedilol	975	856	648	364	117	16
Placebo	984	861	638	358	123	8

Figure 2: Kaplan-Meier estimates of all-cause mortality

	Carvedilol group (n=975)	Placebo group (n=984)	Hazard ratio (95% CI)	p
Primary endpoints				
All-cause mortality	116 (12%)	151 (15%)	0.77 (0.60–0.98)	0.031
All-cause mortality or cardiovascular-cause hospital admission	340 (35%)	367 (37%)	0.92 (0.80–1.07)	0.296
Secondary endpoints				
Sudden death	51 (5%)	69 (7%)	0.74 (0.51–1.06)	0.098
Hospital admission for heart failure	118 (12%)	138 (14%)	0.86 (0.67–1.09)	0.215
Other endpoints				
Cardiovascular-cause mortality	104 (11%)	139 (14%)	0.75 (0.58–0.96)	0.024
Death due to heart failure	18 (2%)	30 (3%)	0.60 (0.33–1.07)	0.083
Non-fatal myocardial infarction	34 (3%)	57 (6%)	0.59 (0.39–0.90)	0.014
All-cause mortality or non-fatal myocardial infarction	139 (14%)	192 (20%)	0.71 (0.57–0.89)	0.002

Table 2: Primary, secondary, and other endpoints

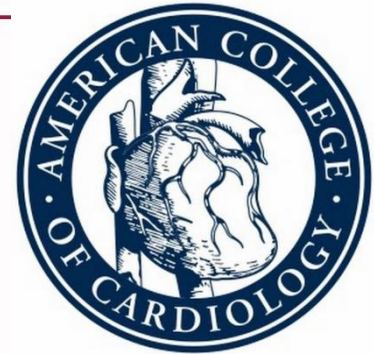


Guidelines

Recommendation for post-MI chronic β blocker



EUROPEAN SOCIETY OF CARDIOLOGY®



cnic

STEMI + LVEF \leq 40%

IA

IA

NSTEMI + LVEF \leq 40%

IA

IA

STEMI + LVEF $>$ 40%

IaB

IB*

NSTEMI + LVEF $>$ 40%

-

IaC

All based on pre-reperfusion trials, observational data, and registries

*3 years, thereafter IaB



Effect of Beta-Blocker Dose on Survival After Acute Myocardial Infarction

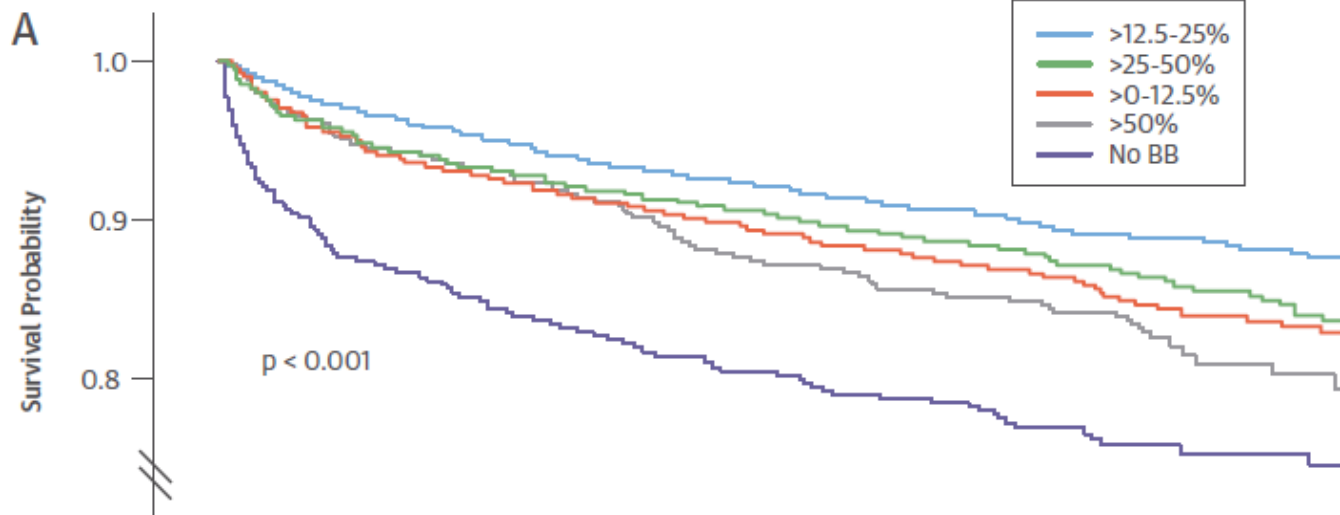
Jeffrey J. Goldberger, MD, MBA,* Robert O. Bonow, MD,* Michael Cuffe, MD,† Lei Liu, PhD,‡
Yves Rosenberg, MD, MPH,§ Prediman K. Shah, MD,|| Sidney C. Smith, Jr, MD,¶ Haris Subacius, MA,*
on behalf of the OBTAIN Investigators

J Am Coll Cardiol 2015;66:1431-41

Discharge Beta-Blocker

No,	Yes,
n = 567	n = 6,115
(8.5%)	(91.5%)

40% STEMI





β -Blockers and Mortality After Acute Myocardial Infarction in Patients Without Heart Failure or Ventricular Dysfunction



Tatendashe B. Dondo, MSc,^a Marlous Hall, PhD,^a Robert M. West, DPHIL,^b Tomas Jernberg, MD, PhD,^c
Bertil Lindahl, MD, PhD,^d Hector Bueno, MD, PhD,^{e,f,g} Nicolas Danchin, MD,^{h,i,j} John E. Deanfield, BA, MB BCHIR,^k
Harry Hemingway, BA, MB BCHIR, MSc,^l Keith A.A. Fox, MD, MBChB,^m Adam D. Timmis, MD, MA,ⁿ
Chris P. Gale, MBBS, PhD, MEd, MSc^{a,o}

J Am Coll Cardiol 2017;69:2710-20

179000 (50% STEMI), 95% on bblk

Unadjusted 1-year mortality
(4.9% vs. 11.2%; $p < 0.001$)

Pt not prescribed with bblk were older and sicker

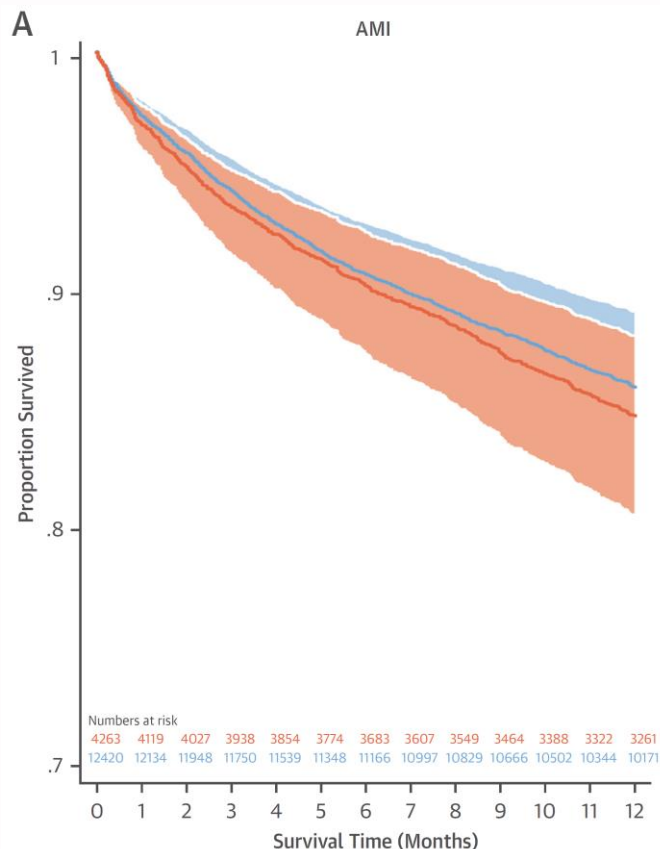


β -Blockers and Mortality After Acute Myocardial Infarction in Patients Without Heart Failure or Ventricular Dysfunction



Tatendashe B. Dondo, MSc,^a Marlous Hall, PhD,^a Robert M. West, DPHIL,^b Tomas Jernberg, MD, PhD,^c Bertil Lindahl, MD, PhD,^d Hector Bueno, MD, PhD,^{e,f,g} Nicolas Danchin, MD,^{h,i,j} John E. Deanfield, BA, MB BCHIR,^k Harry Hemingway, BA, MB BCHIR, MSc,^l Keith A.A. Fox, MD, MBChB,^m Adam D. Timmis, MD, MA,ⁿ Chris P. Gale, MBBS, PhD, MEd, MSc^{a,o}

J Am Coll Cardiol 2017;69:2710-20



Adjusted (propensity)
16000 / 179000 (**9% !**)

Trimmed Propensity Score Analyses
(n = 16,683)

β -blocker
Survival Time
4.7 (3.4-5.9) Months

No β -blocker
Survival Time
4.6 (4.0-5.2) Months



LIMITATIONS TO ALL THESE OBSERVATIONAL STUDIES

- Confounded by indication (>80% of patients receive β blockers and those not receiving are older and sicker)
- Problems with propensity scores (unadjusted event rate much lower in β blockers, residual confounders, trimmed populations)

EDITORIAL COMMENT

JACC 2017;69:2721-24

The Swing of β -Blockers

Time for a System Reboot*

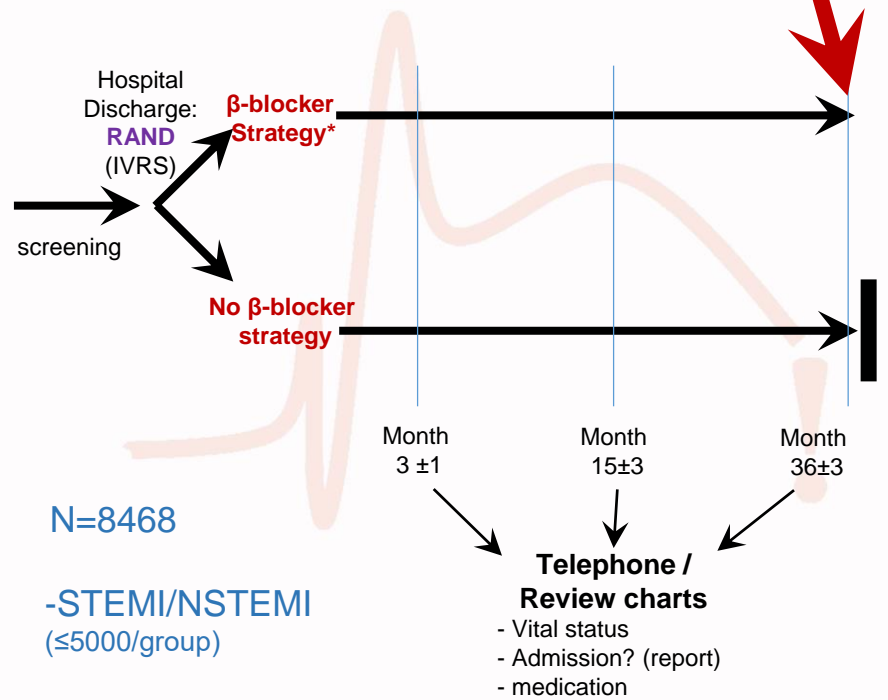
Borja Ibáñez, MD, PhD,^{a,b,c} Sergio Raposeiras-Roubin, MD, PhD,^d José M. García-Ruiz, MD^{a,c,e}



RE β OOT

TREatment With β -Blockers After MyOcardial Infarction WithOut Reduced Ejection FracTtion

PRIMARY ENDPOINT
(death / re-MI / HF admission)



N=8468

-STEMI/NSTEMI
(\leq 5000/group)

-LVEF>40%

***Type and dose of β blocker at discretion of treating physician**

Acknowledgements



INSTITUTO DE INVESTIGACIÓN SANITARIA
FUNDACIÓN JIMÉNEZ DÍAZ



Fundació Fundació Princesa de Girona



Fundación **BBVA**



FUNDACIÓN
MUTUAMADRILEÑA

