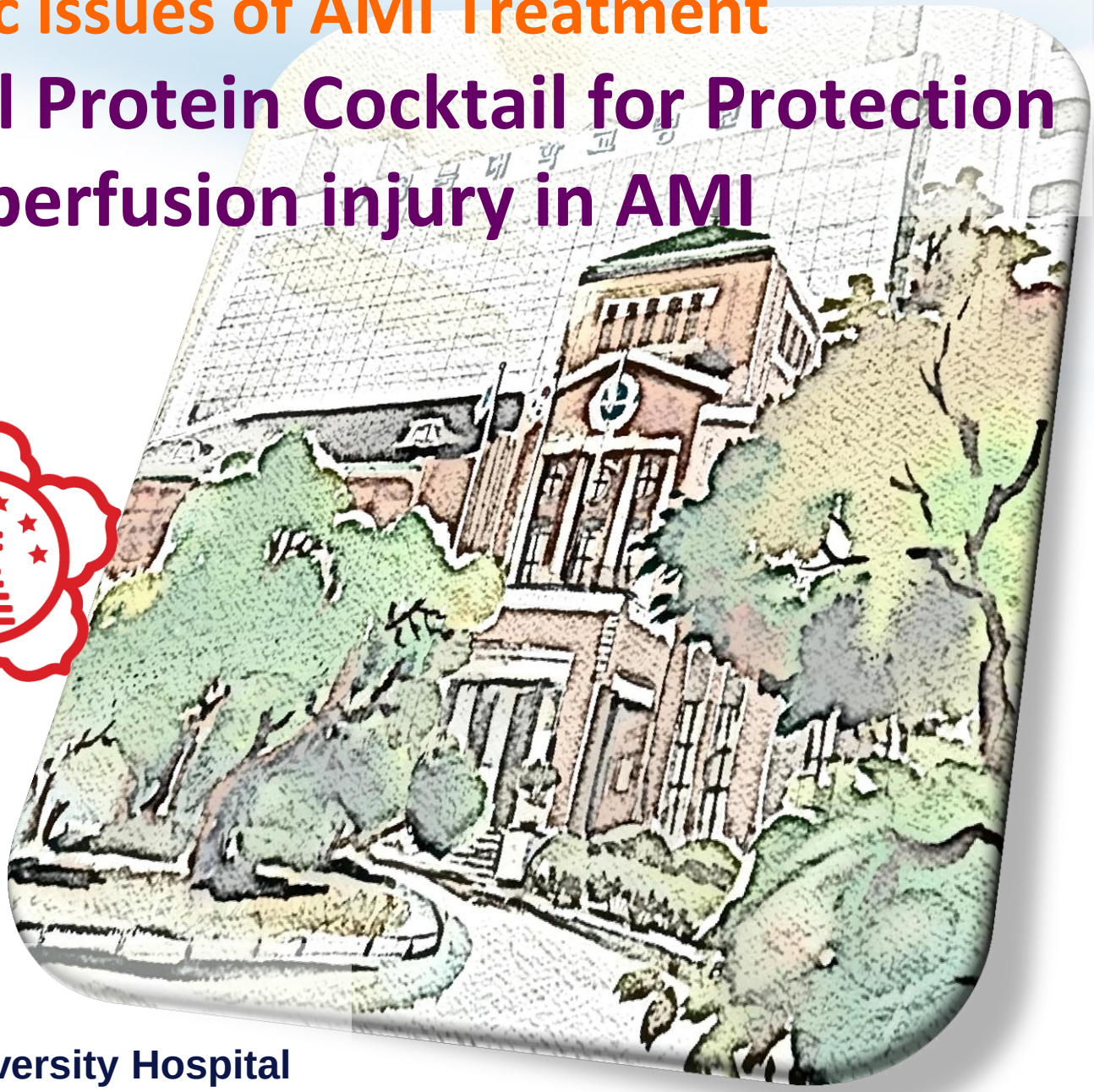
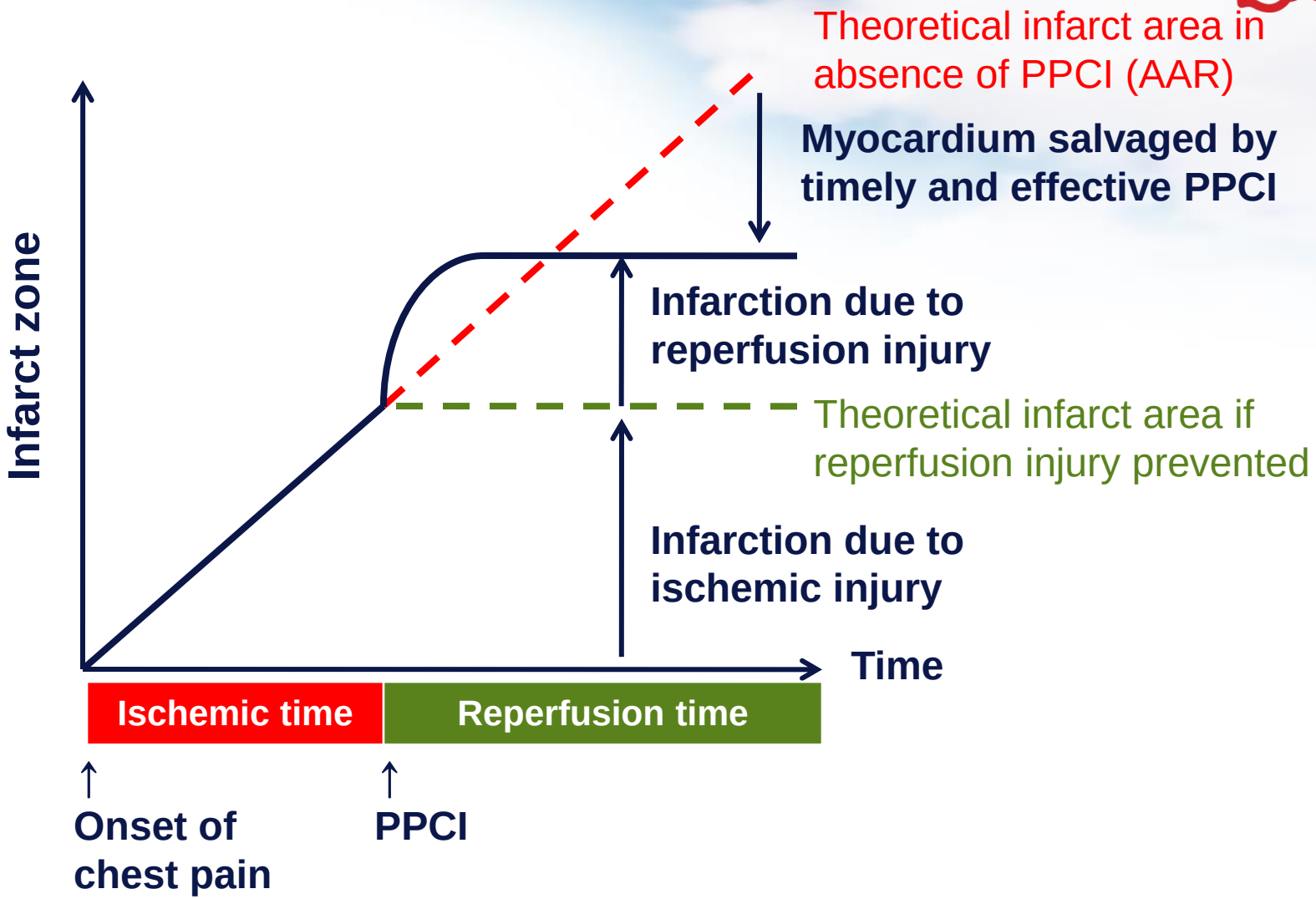
Specific issues of AMI Treatment

What's a Novel Protein Cocktail for Protection of Reperfusion injury in AMI



Jang Hoon Lee, MD
Kyungpook National University Hospital

Contributors of final MI size

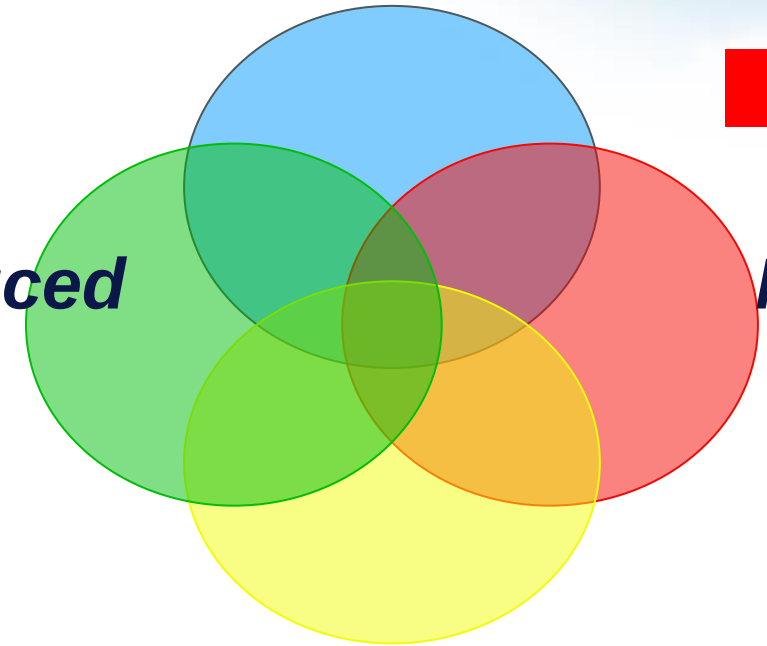


Four recognized form of myocardial RI

Lethal myocardial RI

Irreversible

Reperfusion-induced arrhythmia



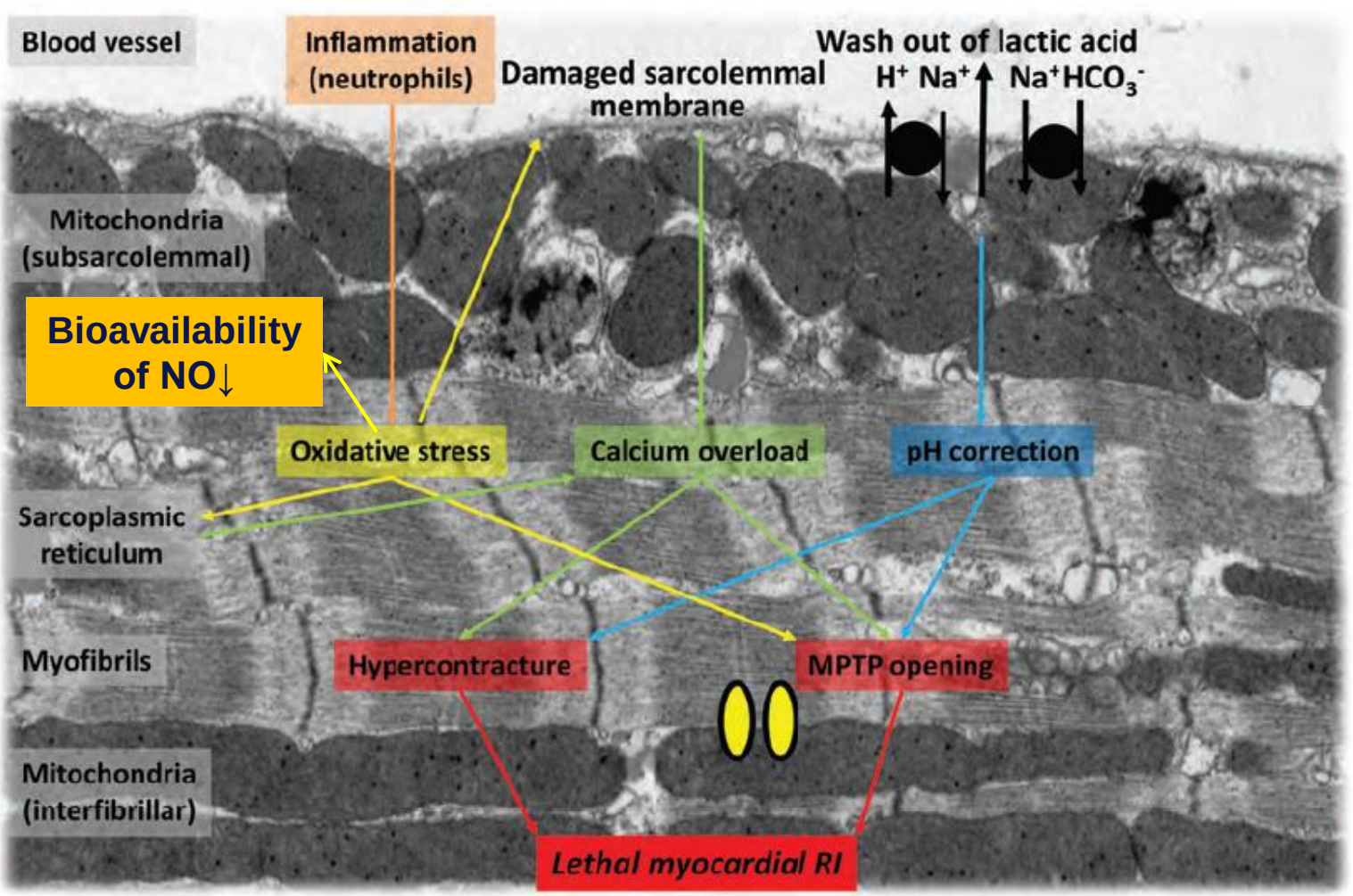
Microvascular obstruction

Reversible

Myocardial stunning

Niccoli et al, JACC 2009

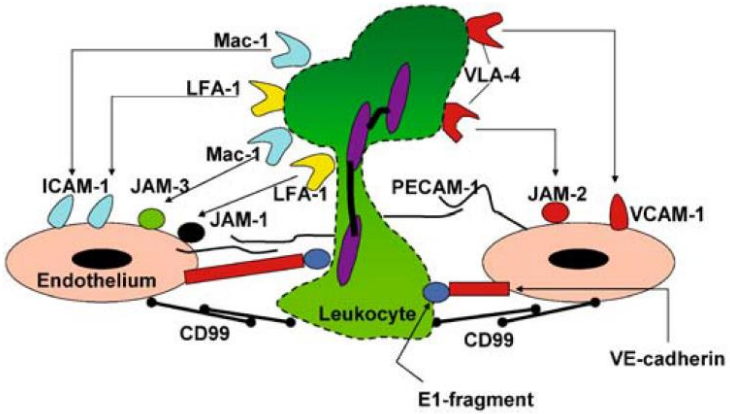
Major components of myocardial RI

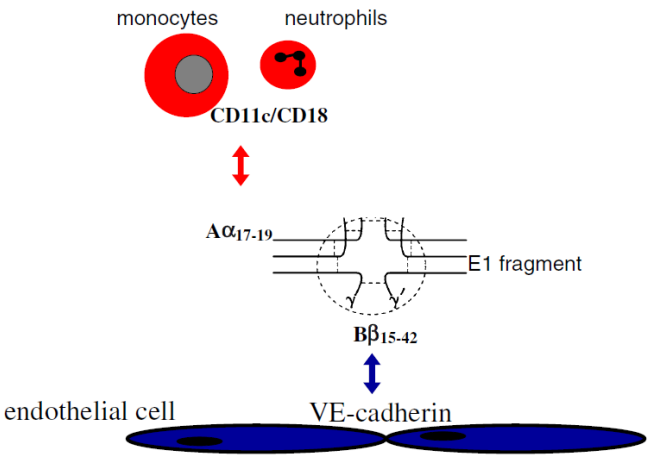


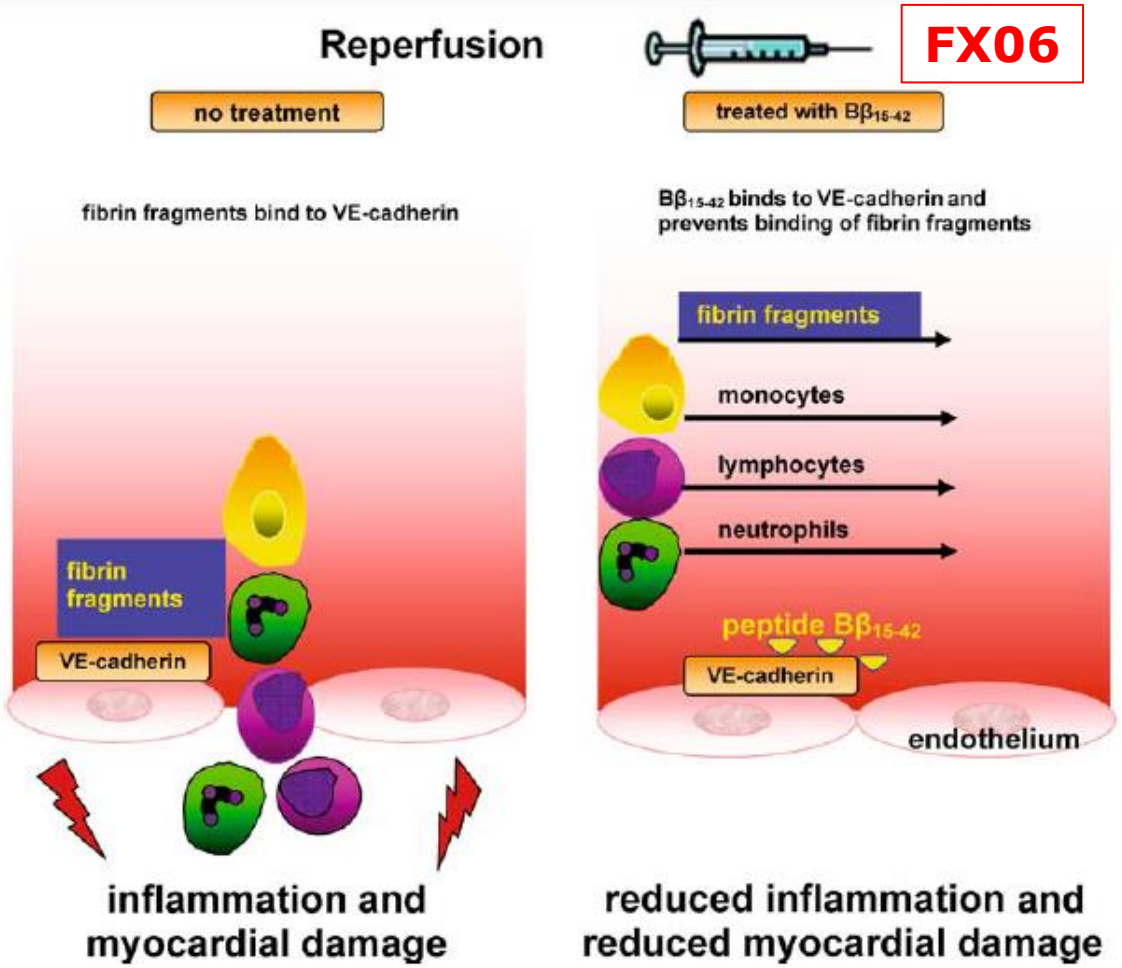
Pharmacological agents for preventing myocardial RI (I)

Drug	Mechanism of action	Study	Results
FX06	Fibrin-derived peptide; binds to vascular endothelial-cadherin and prevents leukocyte infiltration and plasma leakage	FIRE (2009)	
Exenatide	Glucagon-like peptide	Lonborg et al (2011)	
Adenosine	Multifactorial effects on endothelium including vasodilation, neutrophil inhibition, decreased free radical formation	AMISTAD-II (2005)	
NO	Vasodilation, neutrophil inhibition, decreased free radical formation	NOMI (2014)	

Fibrin(ogen) and its fragments in the pathophysiology and treatment of myocardial infarction





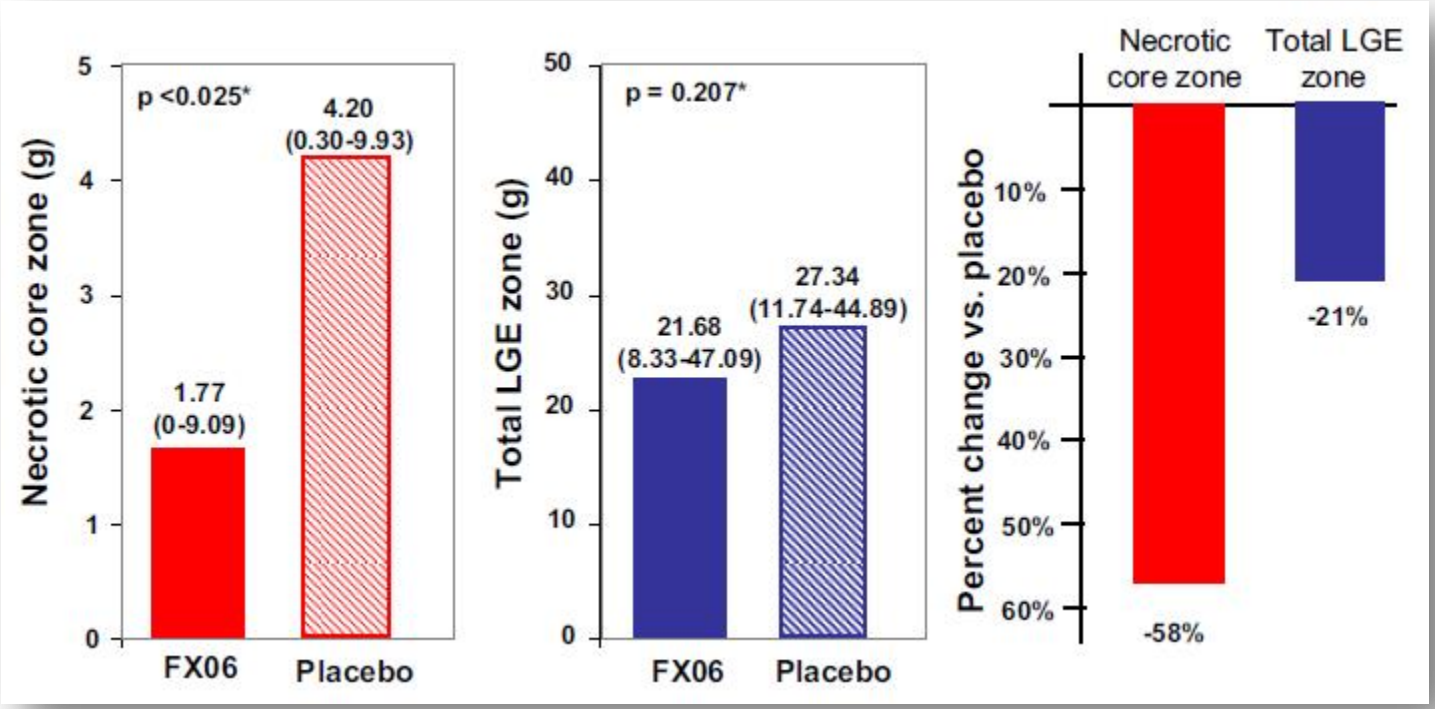


Zacharowski K et al. J Mol Med 2006;84:469-477

Effect of Intravenous FX06 as an Adjunct to Primary Percutaneous Coronary Intervention for Acute ST-Segment Elevation Myocardial Infarction

Results of the F.I.R.E. (Efficacy of FX06 in the Prevention of Myocardial Reperfusion Injury) Trial

Patients with STEMI (n=234)
Bolus of FX06 (200mg iv) twice versus placebo during PPCI
Primary endpoint: infarct size defined as total LGE mass after 5 days

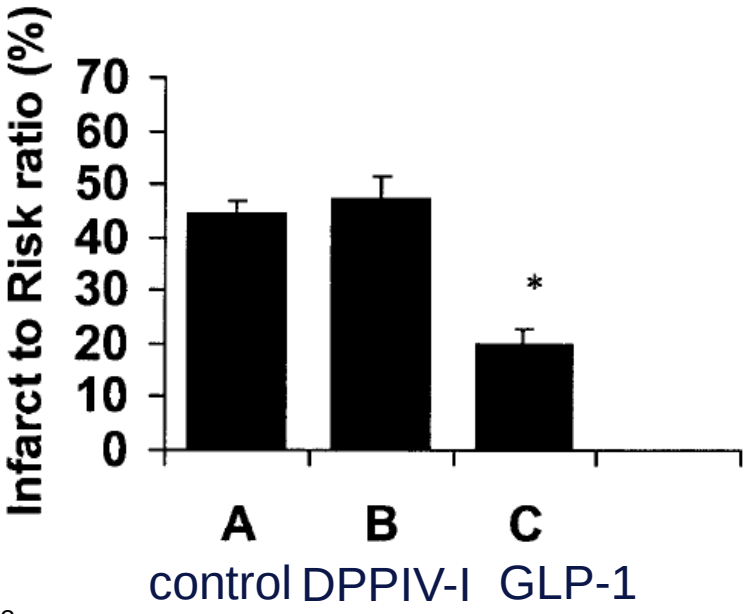


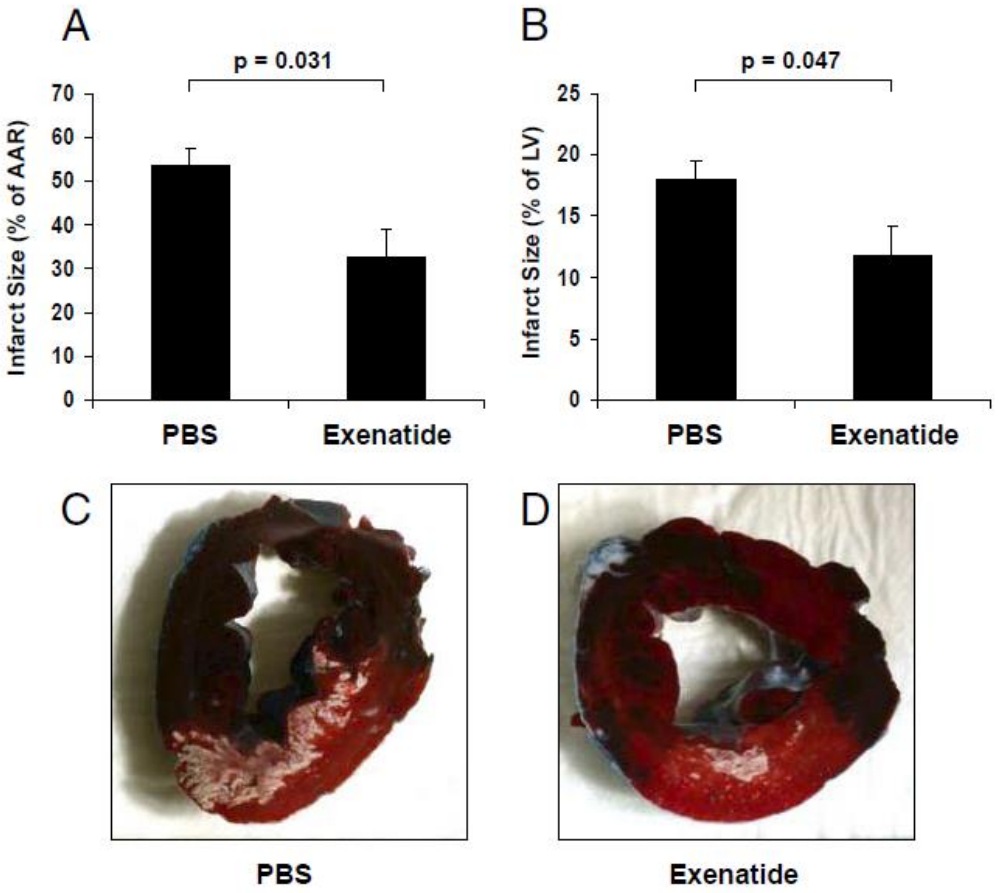
Atar D et al. JACC 2009;53:720-9

Glucagon-like Peptide 1 Can Directly Protect the Heart Against Ischemia/Reperfusion Injury

Exenatide Reduces Infarct Size and Improves Cardiac Function in a Porcine Model of Ischemia and Reperfusion Injury

GLP-1 receptor is widely expresse
Function by causing intracellular C

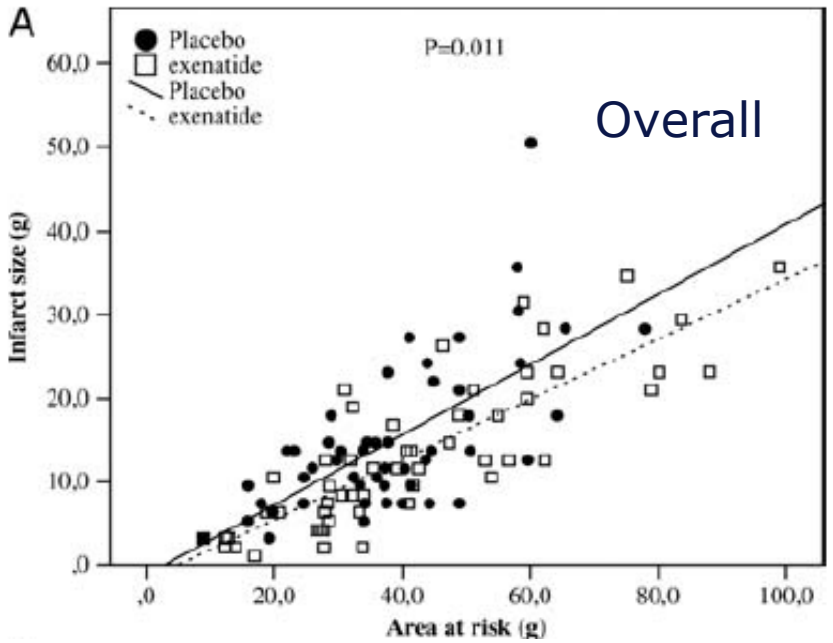


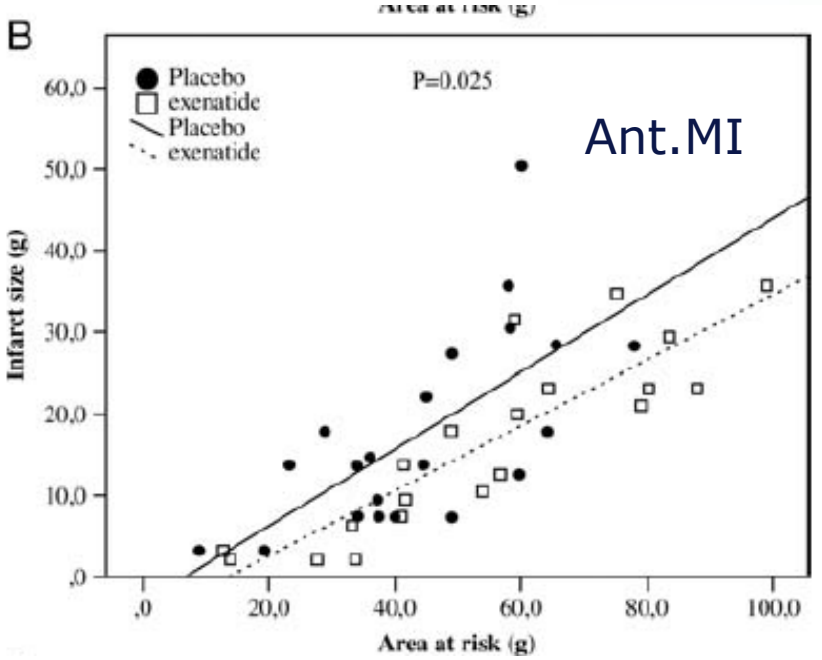


European Heart Journal (2012) **33**, 1491–1499
doi:10.1093/eurheartj/ehr309

Exenatide reduces reperfusion injury in patients with ST-segment elevation myocardial infarction

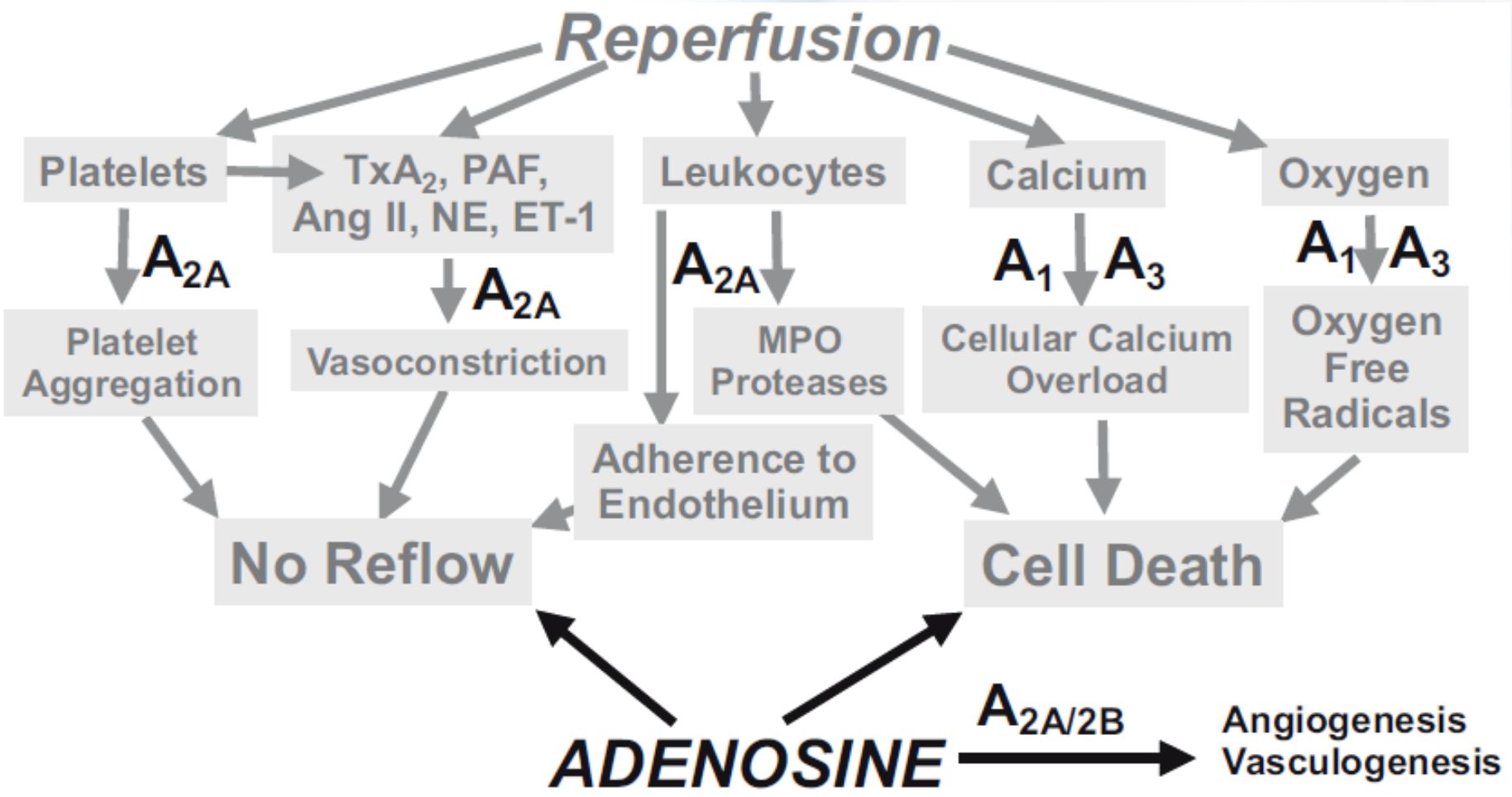
Patients with STEMI (n=172)
Exenatide (25mg; 15min prior to PPCI and infused over 6hr) vs. placebo
Primary endpoint: salvage index calculated from myocardial area at risk





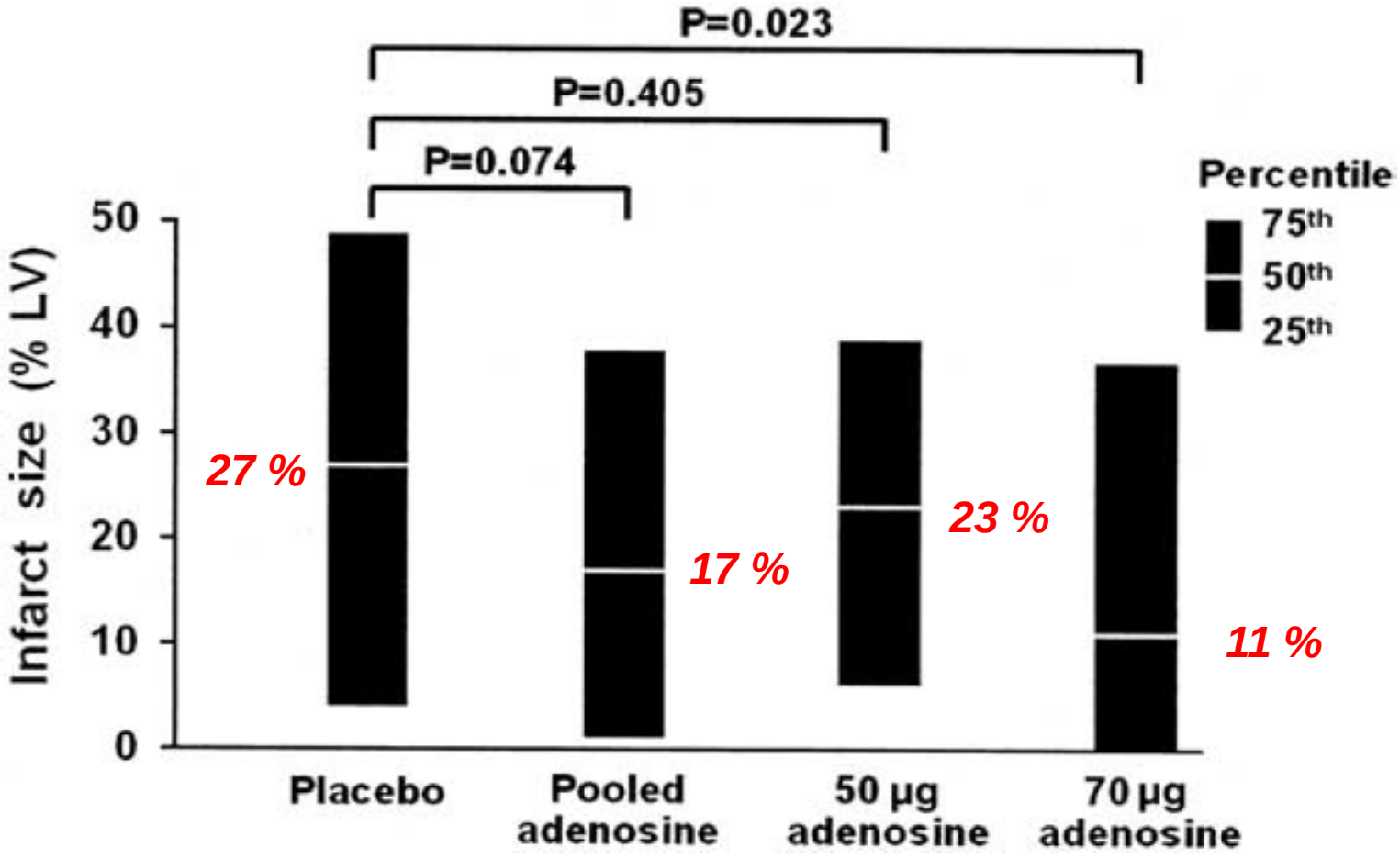
Lonborg J et al. EHJ 2012;33:1491-9

Adenosine Inhibits Mechanisms Involved in Reperfusion Injury

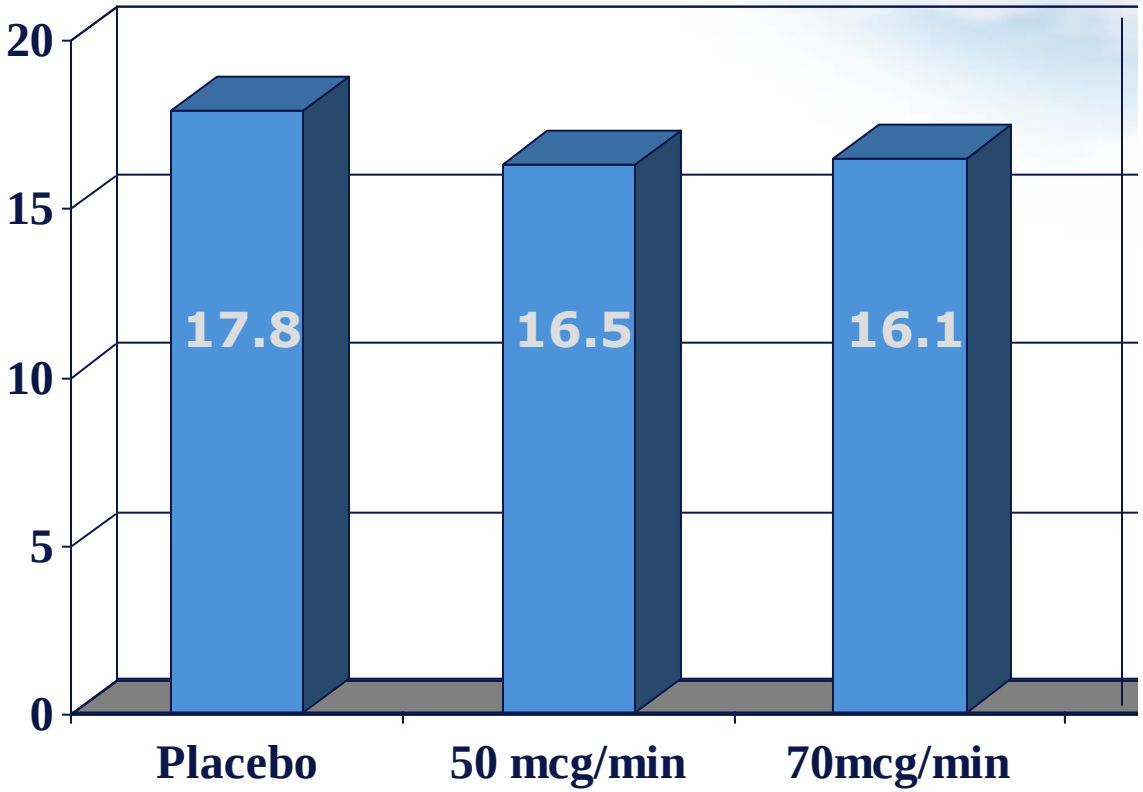


AMISTAD-II

Randomized,placebo-controlled, double blind
2118 anterior STEMI



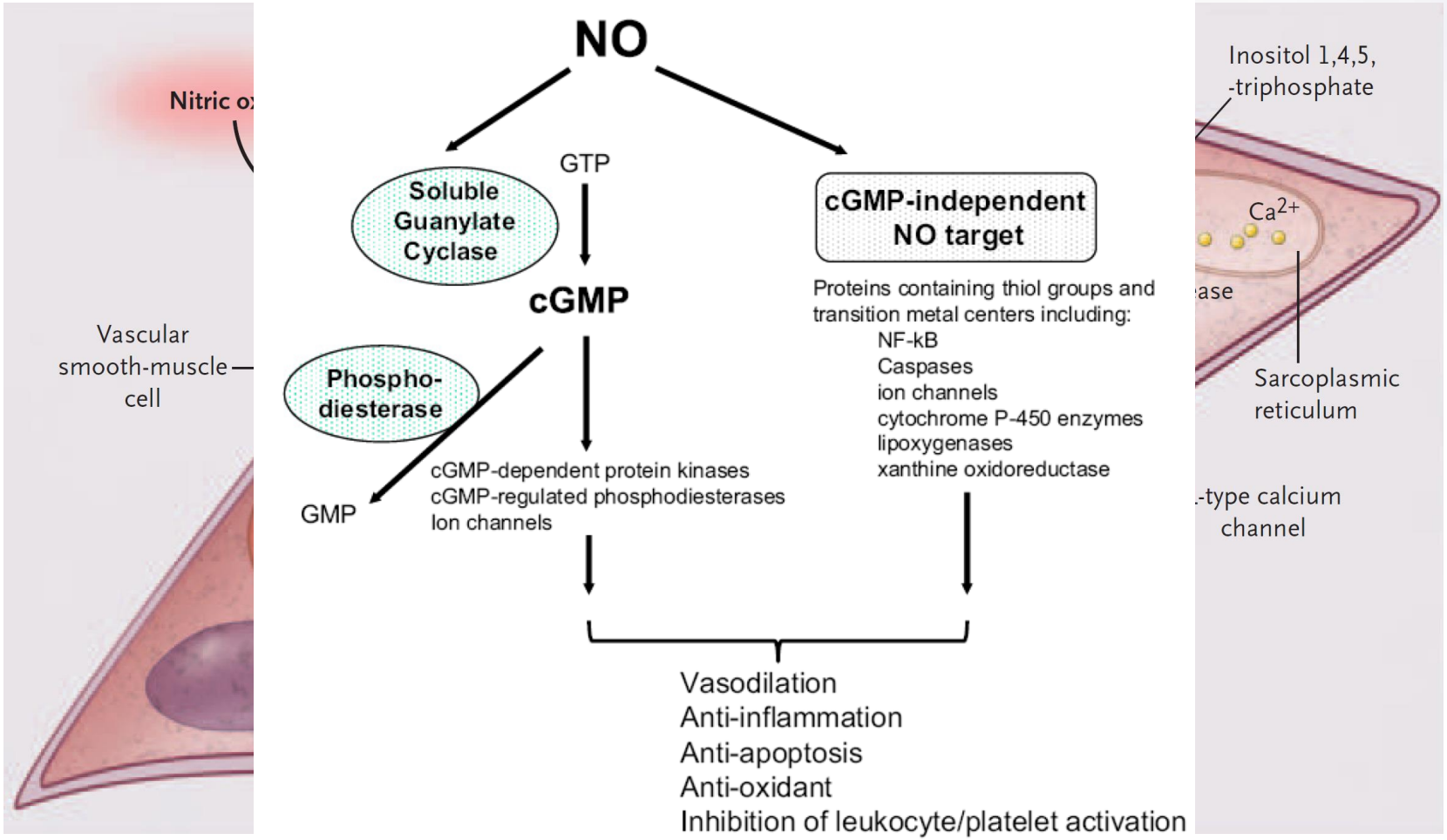
AMISTAD 2: Primary Endpoints (death, CHF at 6 months)



p=ns

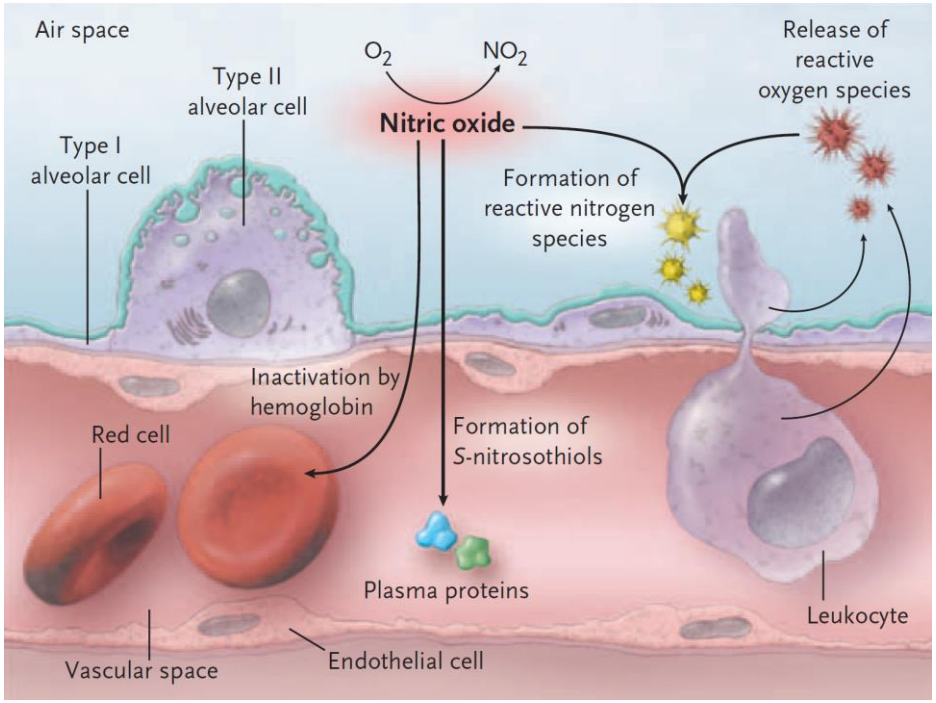
Per-protocol, time to RX, apparent reperfusion success, etc.

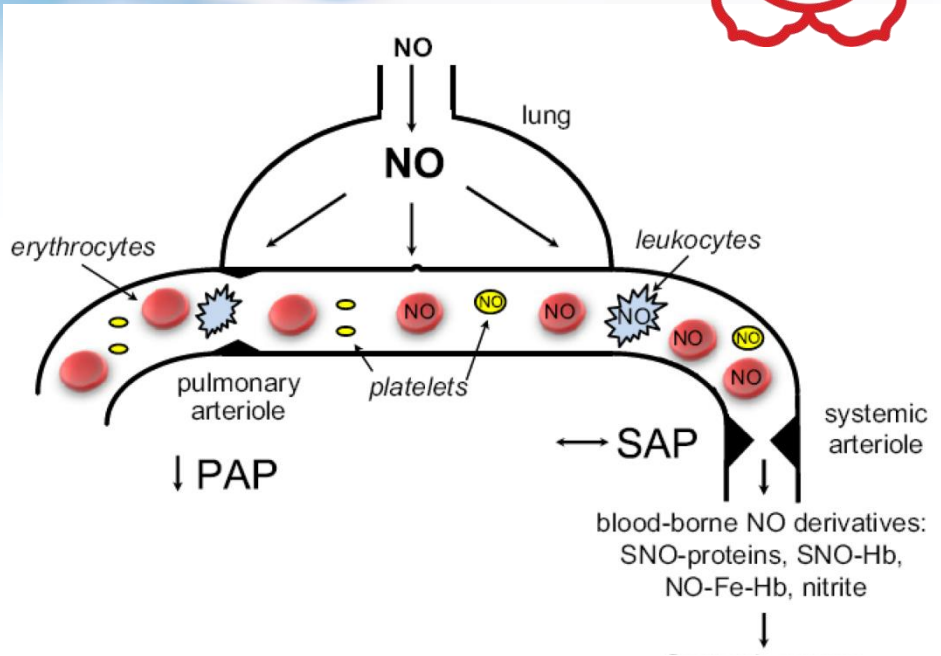
Nitric Oxide signaling pathway



Griffiths MJD et al. N Engl J Med 2005;353:2683-95
Hataishi R et al. A J P Heart Circ Physiol 2006

Inhaled NO for Cardioprotection during Ischemia





- Inhalation of 40 and 80 ppm NO for 24h reduced IS/AAR in mice
  (Hataishi R et al. AJ P Heart Circ Physiol. 2006; Nagasaka Y et al. Anesthesiology. 2008)

- Inhalation of 80 ppm NO for 4h reduced IS/AAR and improved functional recovery in pigs, while 2 ug/kg/min IV NTG failed to do so.
  (X. Liu et al. JACC 2007)

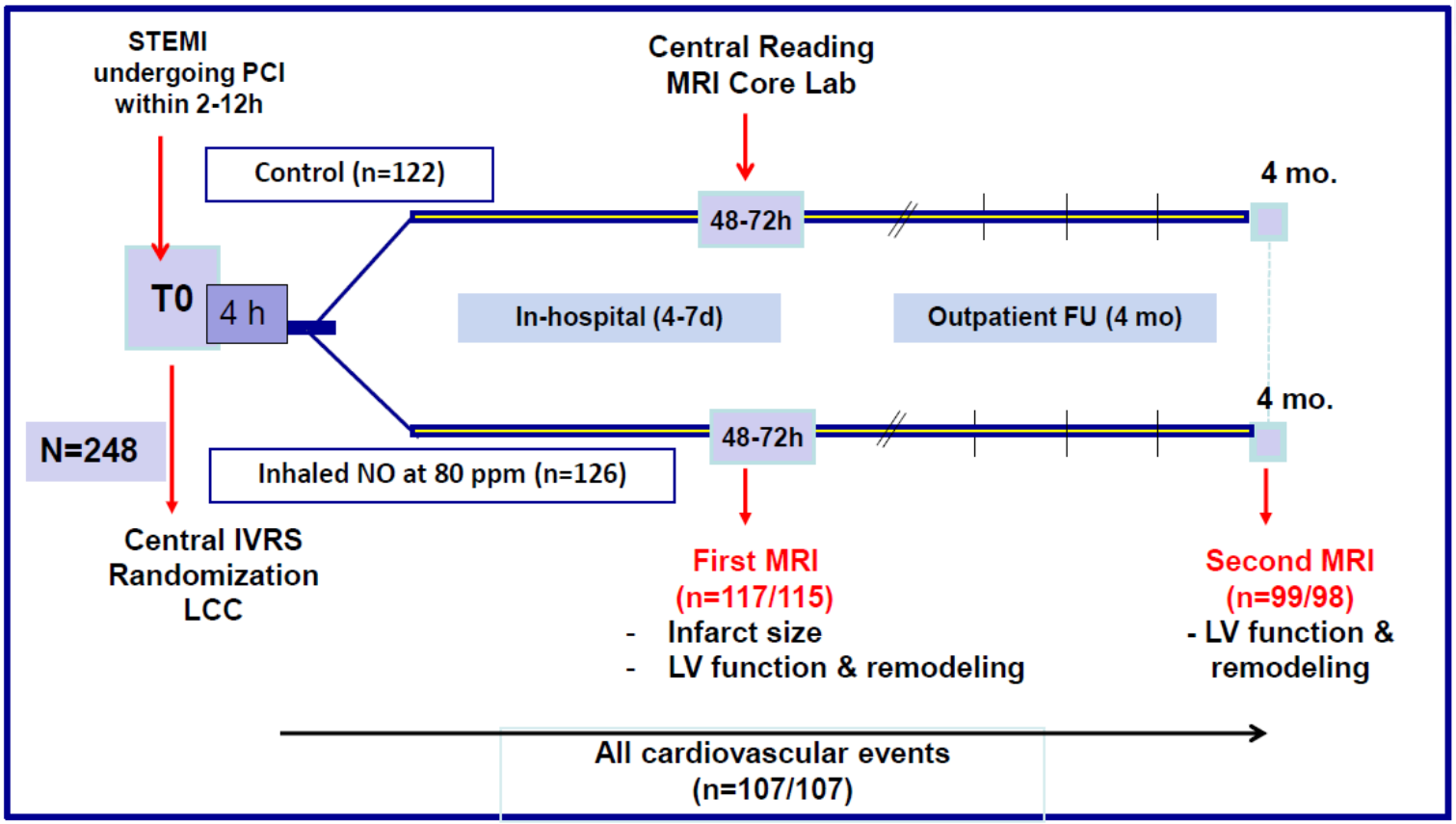
Griffiths MJD et al. N Engl J Med 2005;353:2683-95
Hataishi R et al. A J P Heart Circ Physiol 2006

Nitric Oxide for Inhalation to Reduce Reperfusion Injury in STEMI - NOMI

*Stefan P. Janssens, MD, PhD on behalf of the **NOMI investigators**:*

K.D. Bloch, MD, J. Bogaert, MD, PhD, B. Merkely, MD, PhD,

F. Van de Werf, MD, PhD, P. Vranckx, MD, PhD, J. Zalewski, MD, PhD



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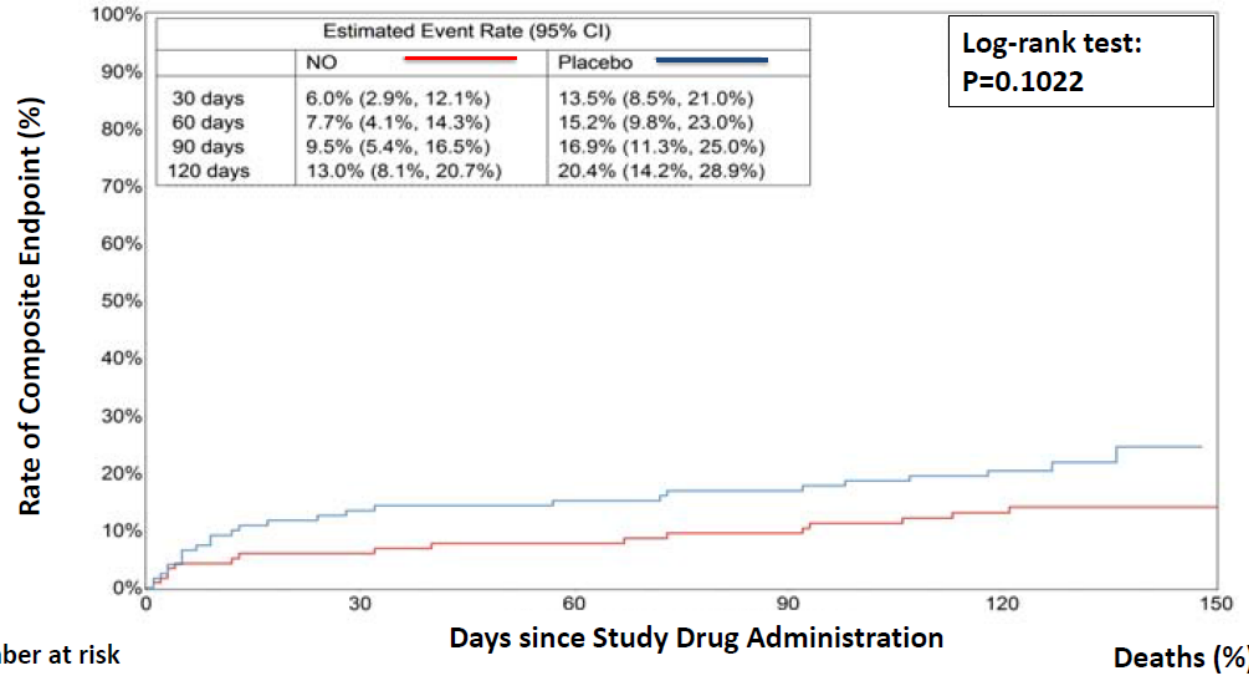
NOMI: Kaplan-Meier for Composite Endpoint

(death, recurrent ischemia, stroke or rehospitalization)



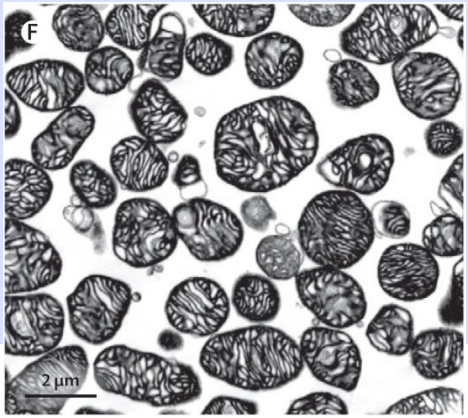
Number at risk						Deaths (%)
NO	119	109	106	104	97	5 (4.1)
CON	125	101	99	97	91	8 (6.3)

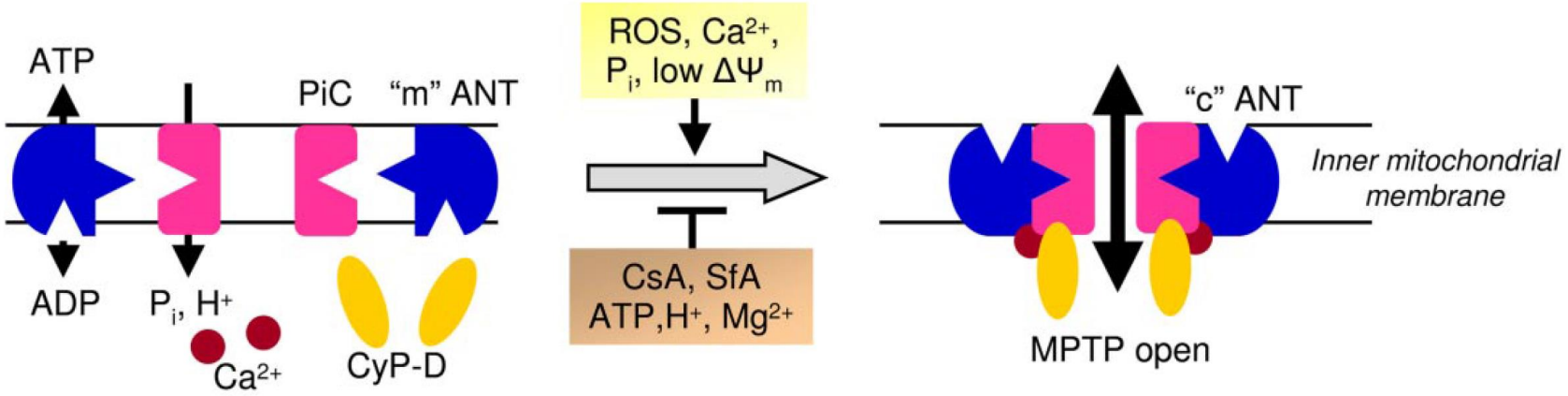
Pharmacological agents for preventing myocardial RI (II)

Drug	Compound	Study	Results
Cyclosporine	Inhibitor of the mitochondrial permeability transition pore	CIRCUS (2012)	In progress
TRO40303	Reduces opening of the mitochondrial permeability transition pore	MitoCare (2014)	
Atrial Natriuretic Peptide	Activates reperfusion injury salvage kinase pathway	J-WIND (2007)	

MPTP (Mitochondrial permeability transition pore) : important target for cardioprotection

A nonselective channel of inner mitochondrial membrane
Opening of MPTP
→ Mitochondrial membrane depolarization
& Uncoupling of oxidative phosphorylation
→ Matrix swelling & OMM rupture
→ APT depletion
→ Cell death

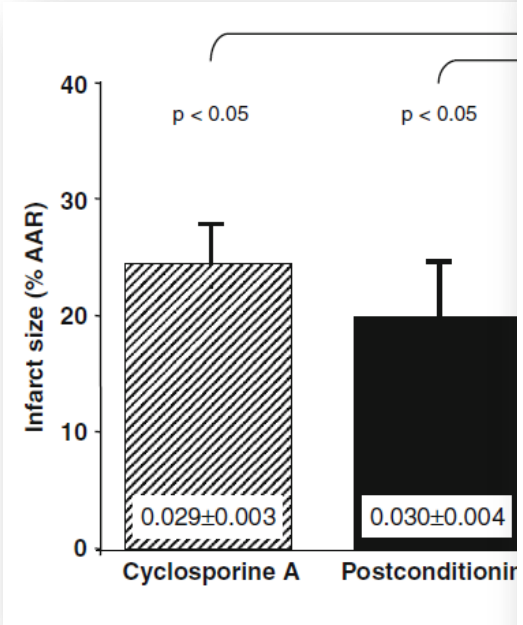


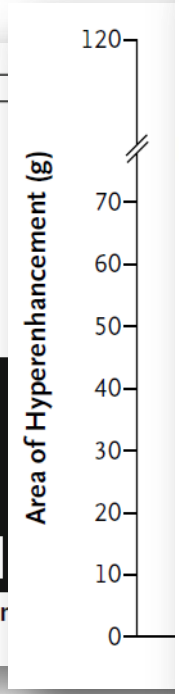


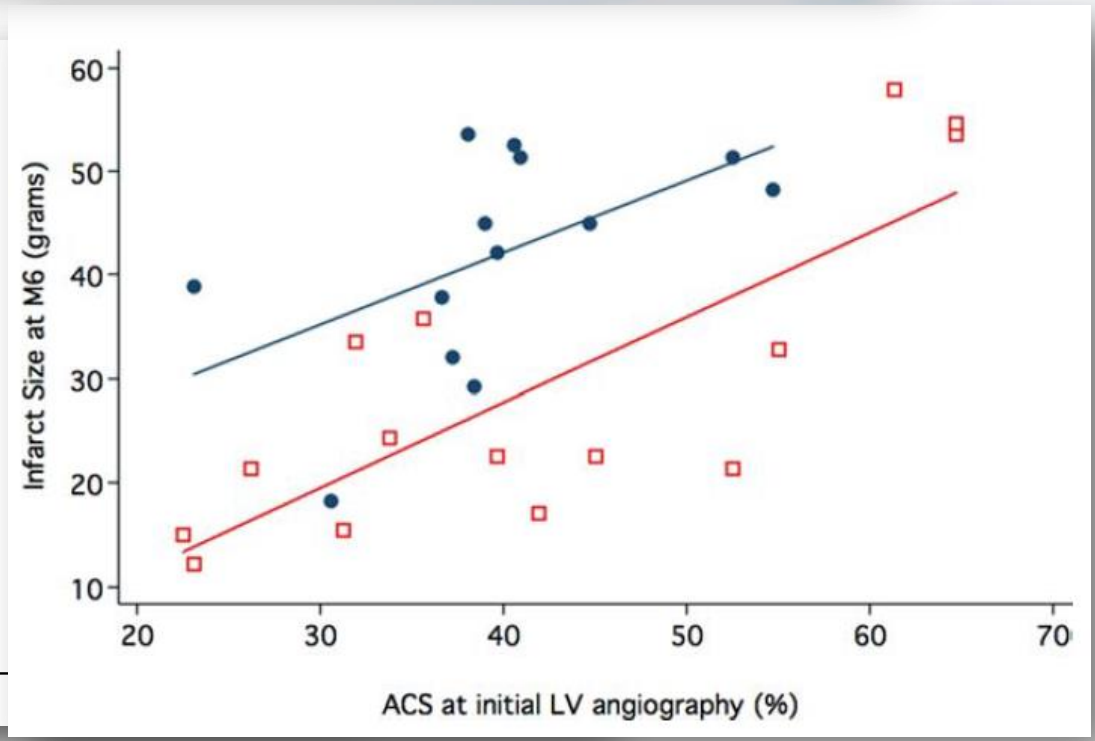
Cyclosporine A at Reperfusion Reduces Infarct Size in Pigs

Effect of Cyclosporine on Reperfusion Injury in Acute Myocardial Infarction

Effect of Cyclosporine on Left Ventricular Remodeling After Reperfused Myocardial Infarction

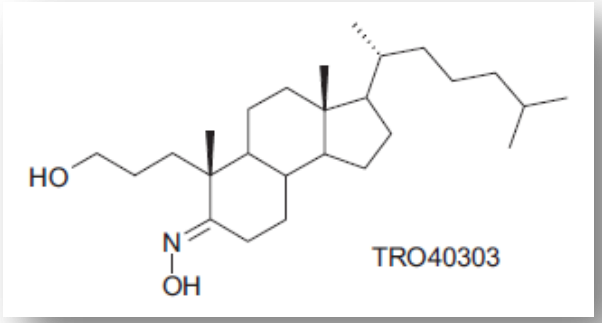


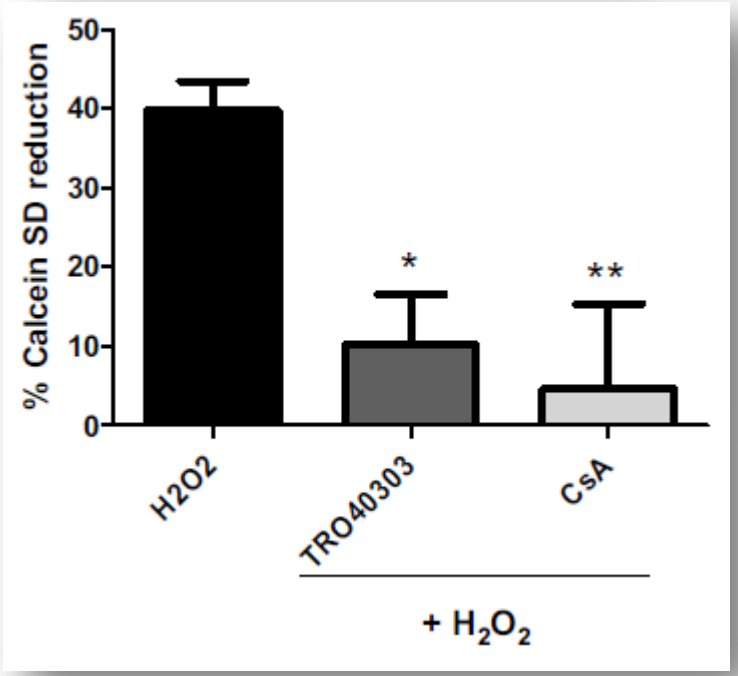


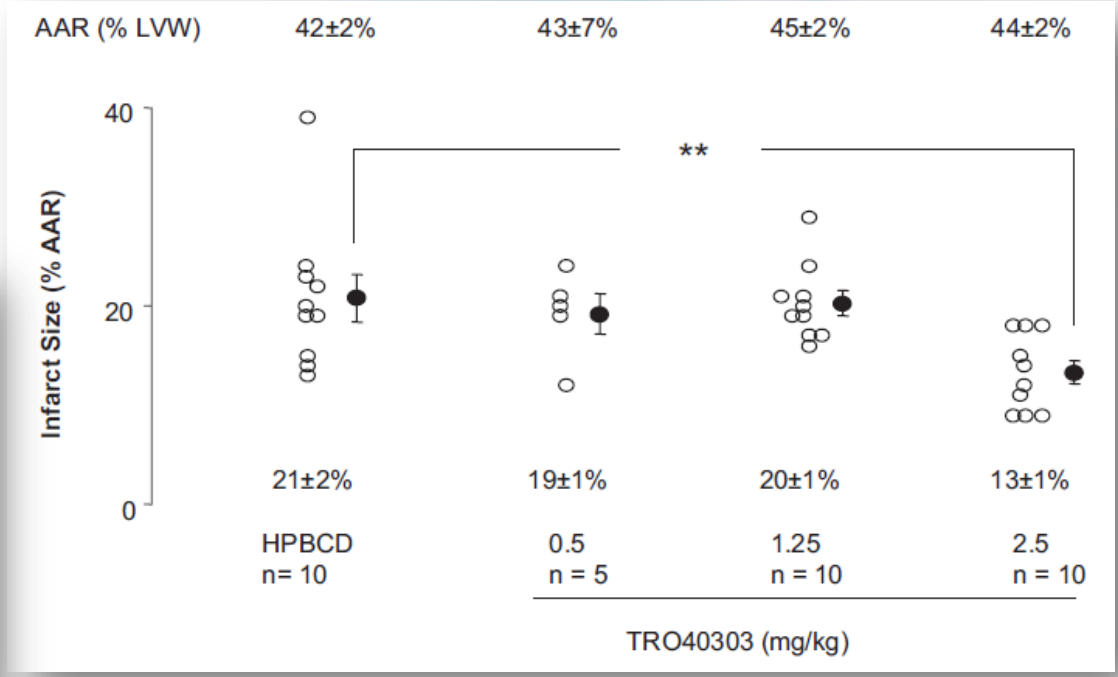


Skyschally A et al. Cardiovasc Drugs Ther 2010;24:85-87
Piot C et al. NEJM 2008;359:473-481
Mewton N et al. JACC 2010;55:1200-1205

TRO40303, a New Cardioprotective Compound, Inhibits Mitochondrial Permeability Transition





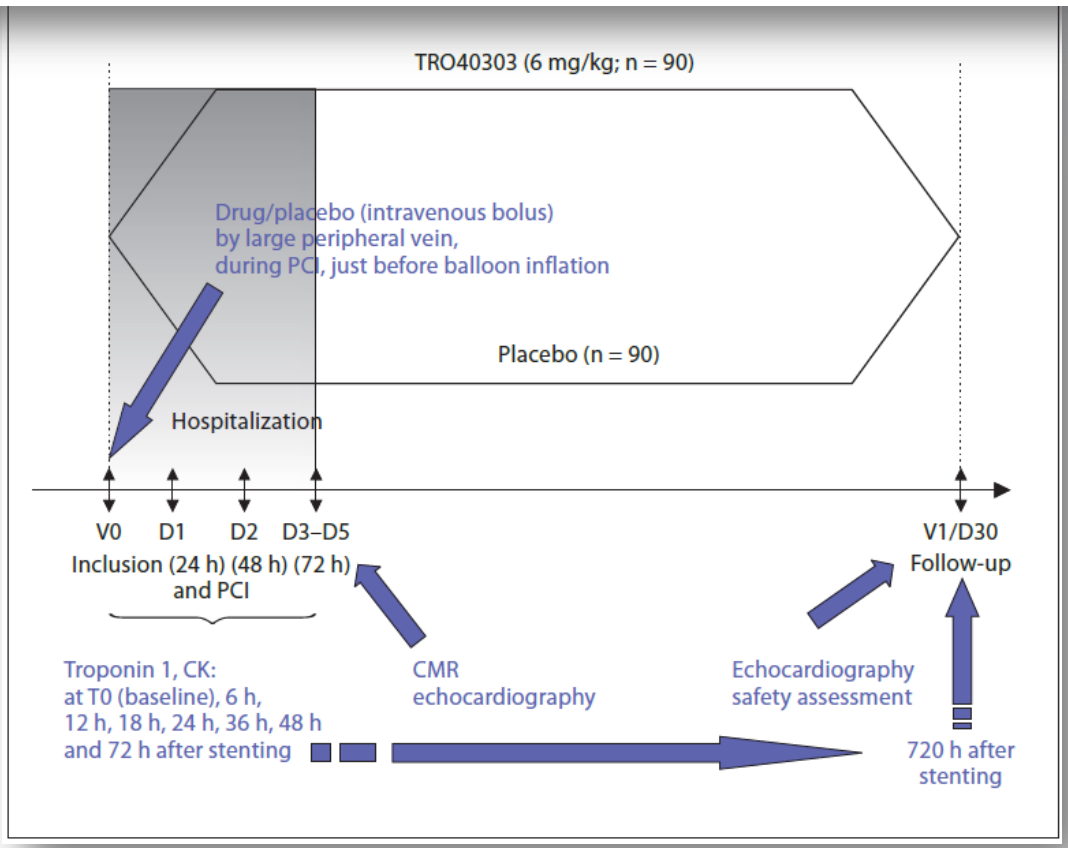


Infarct size reduction 38%

Schaller S et al. J Pharmacol Exp Ther 2010;333:696-706

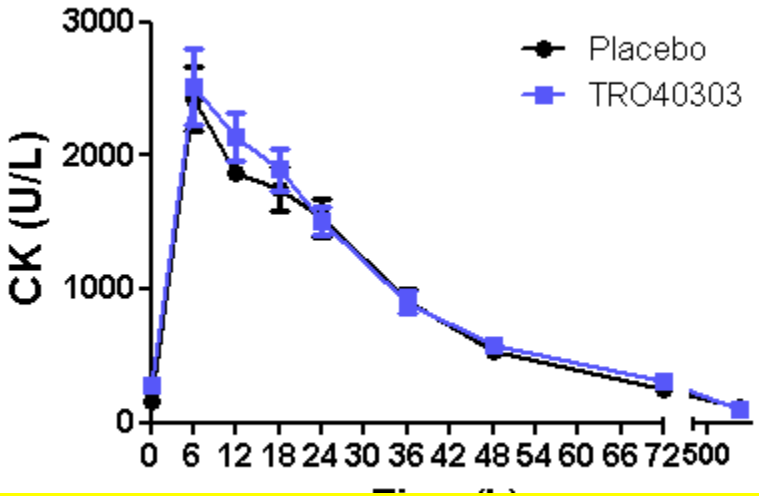
European Heart Journal
doi:10.1093/eurheartj/ehu331

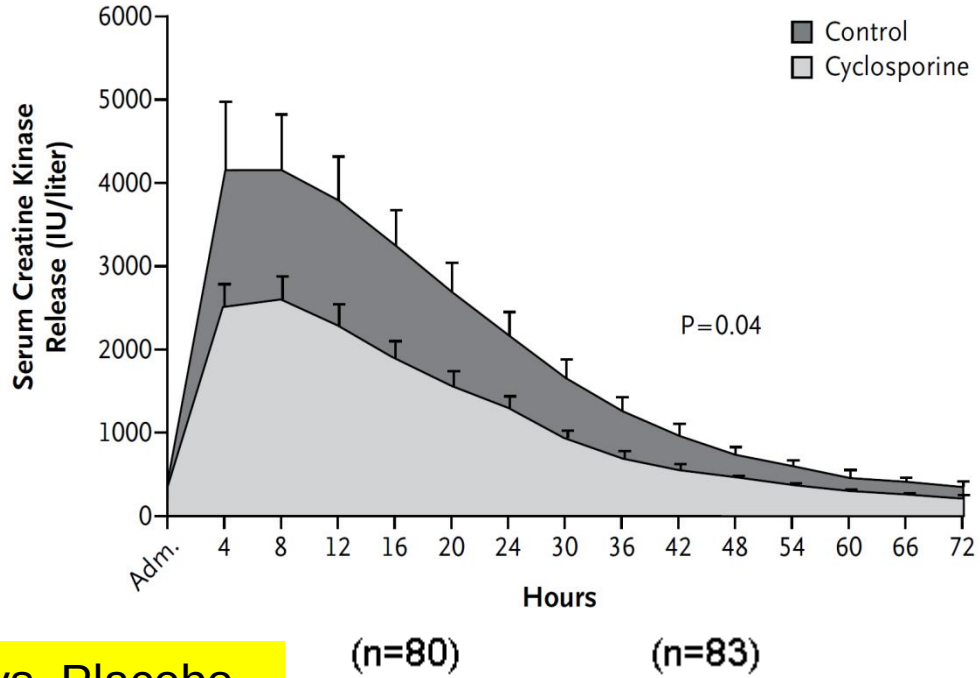
Effect of intravenous TRO40303 as an adjunct to primary percutaneous coronary intervention for acute ST-elevation myocardial infarction: MITOCARE study results



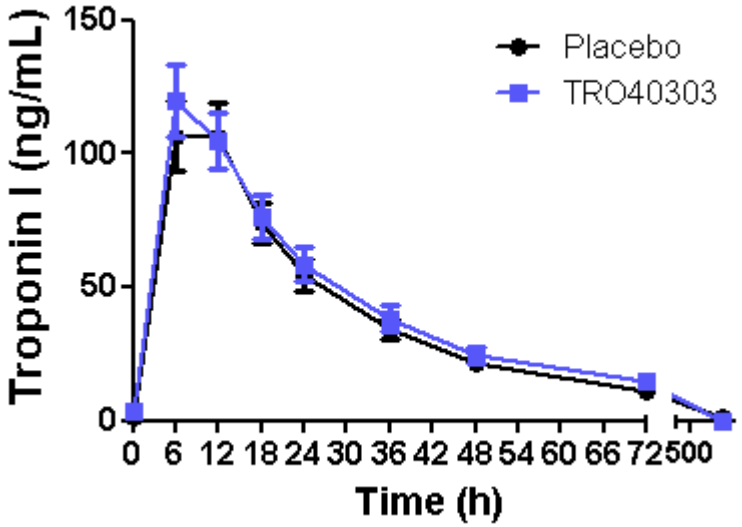
MITOCARE Study Group. EHJ 2014

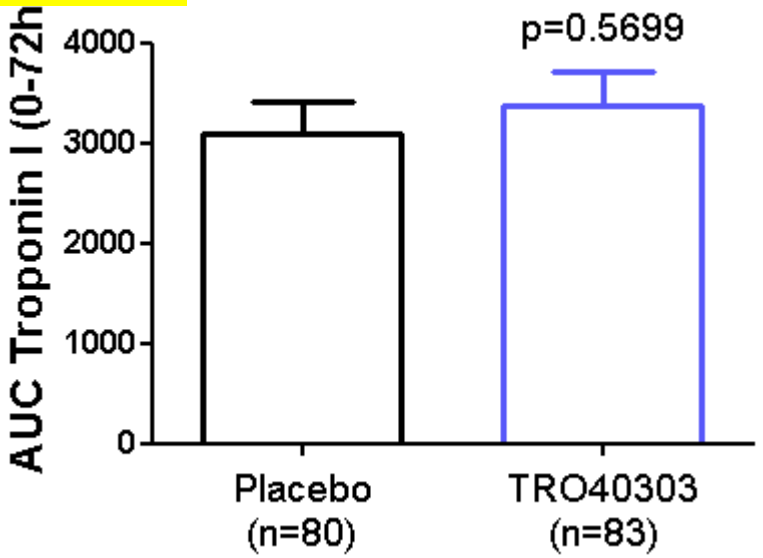
Study Results:





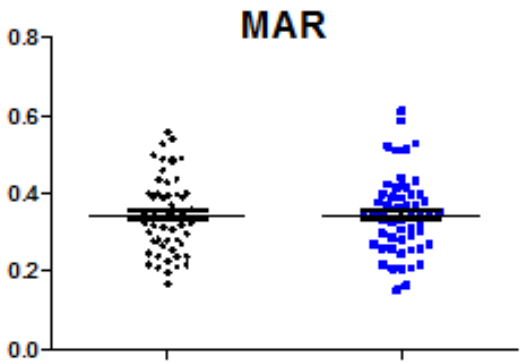
Admission CK (U/L) between TRO40303 vs. Placebo
273.36±410.80 vs. 161.18± 144.29 (p = 0.065)

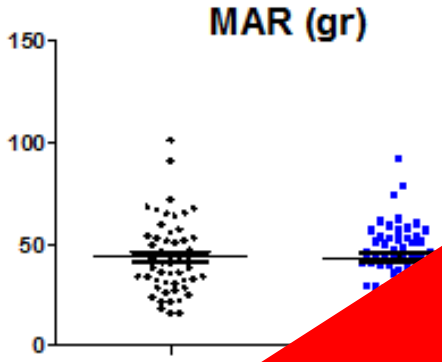


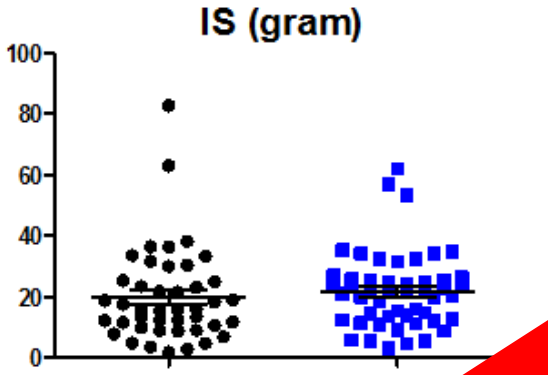


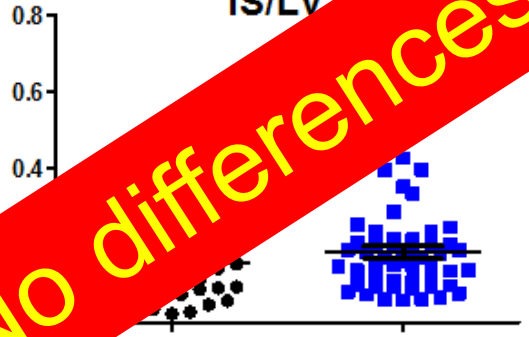
Mean +/- SEM. Analysis of AUC by ANCOVA. N = 163

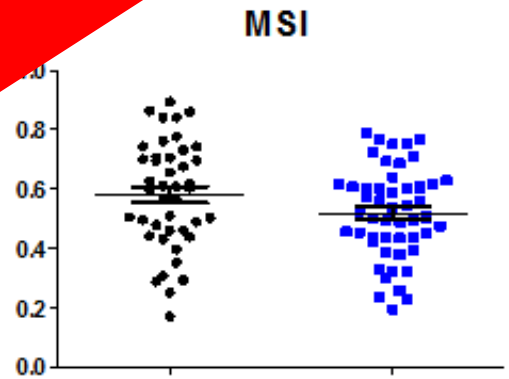
MRI Endpoints



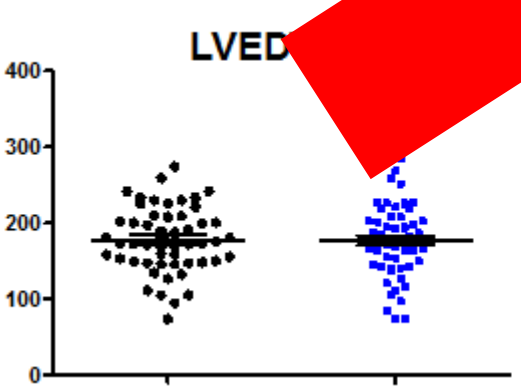


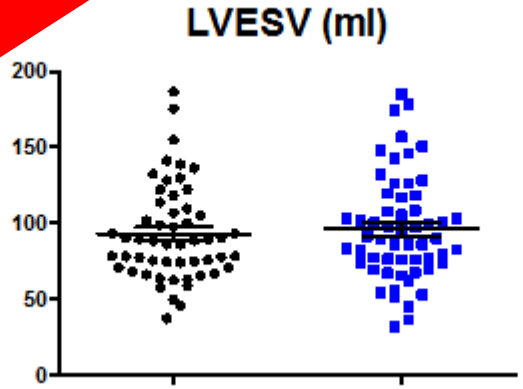


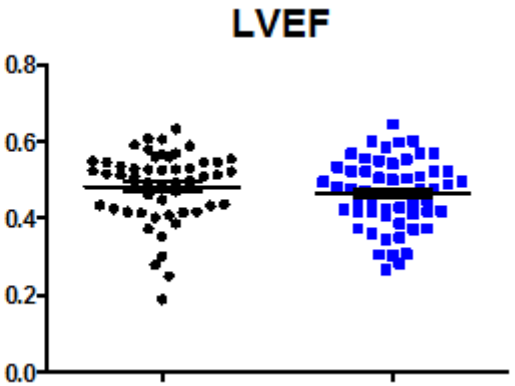




No differences







Procedural Characteristics

(Median (min-max), N patients or % per group)

Before PCI	Placebo		TRO40303	
TIMI-flow: at least one single index occlusion			83	
Culprit Arte			72	
Culprit Artery TIMI-flow 1	4		11	
TIMI-flow of culprit artery after PCI	**Placebo**		**TRO40303**	
Grade 0	**5**	**6.25 %**	**6**	**12.05 %**
Grade 1	**0**		**4**	
Grade 2	4		4	
Grade 3	71		69	

Deleterious or pro-thrombotic effect of TRO40303??

Procedural characteristics were well-balanced between the two groups except for unsuccessful reperfusion

Safety

No difference in AE's in both study arms

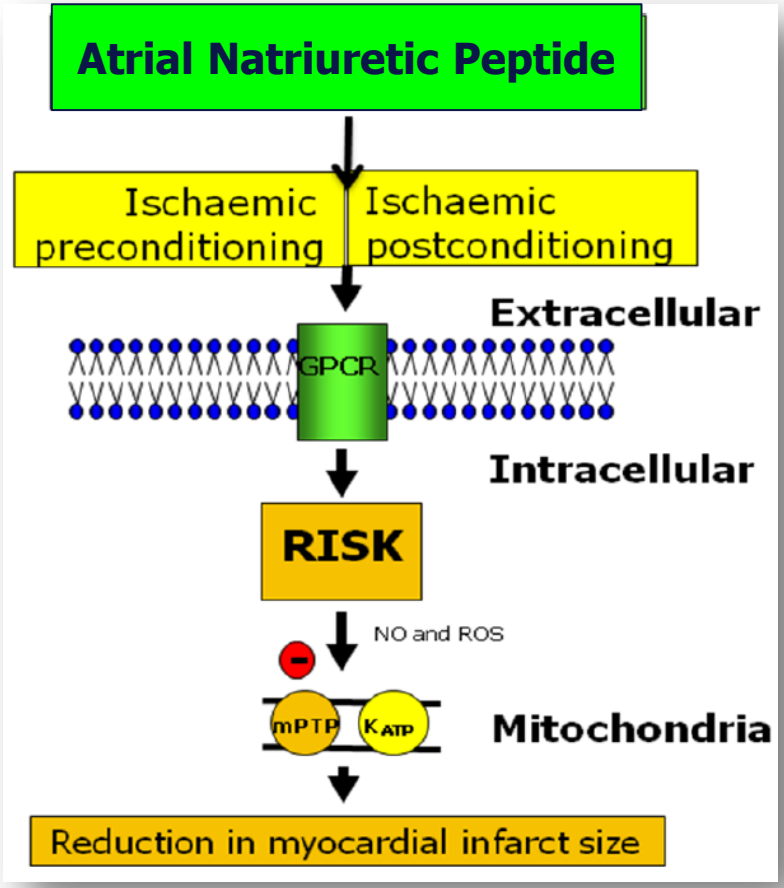
CEC adjudicated SAE's:

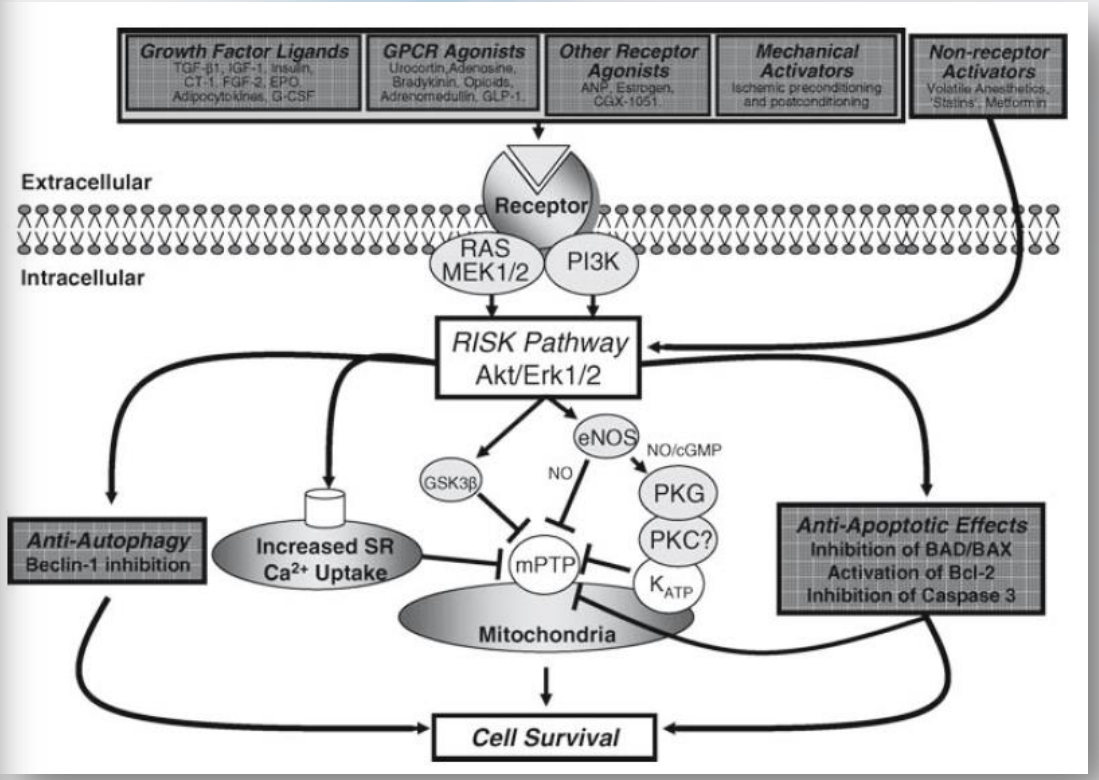
Number of events	Placebo	TRO40303
Total number of events	11	26
Cardiogenic shock	2	4
Death	1	3
Heart Failure	1	3
Myocardial Infarction	0	1
Revascularization	**2**	**9**
Ventricular Arrhythmia	5	6

	Placebo	TRO40303
Number of patients with at least one event	8 (10%)	21 (24.7%)

Fischer exact Test: P=0.013

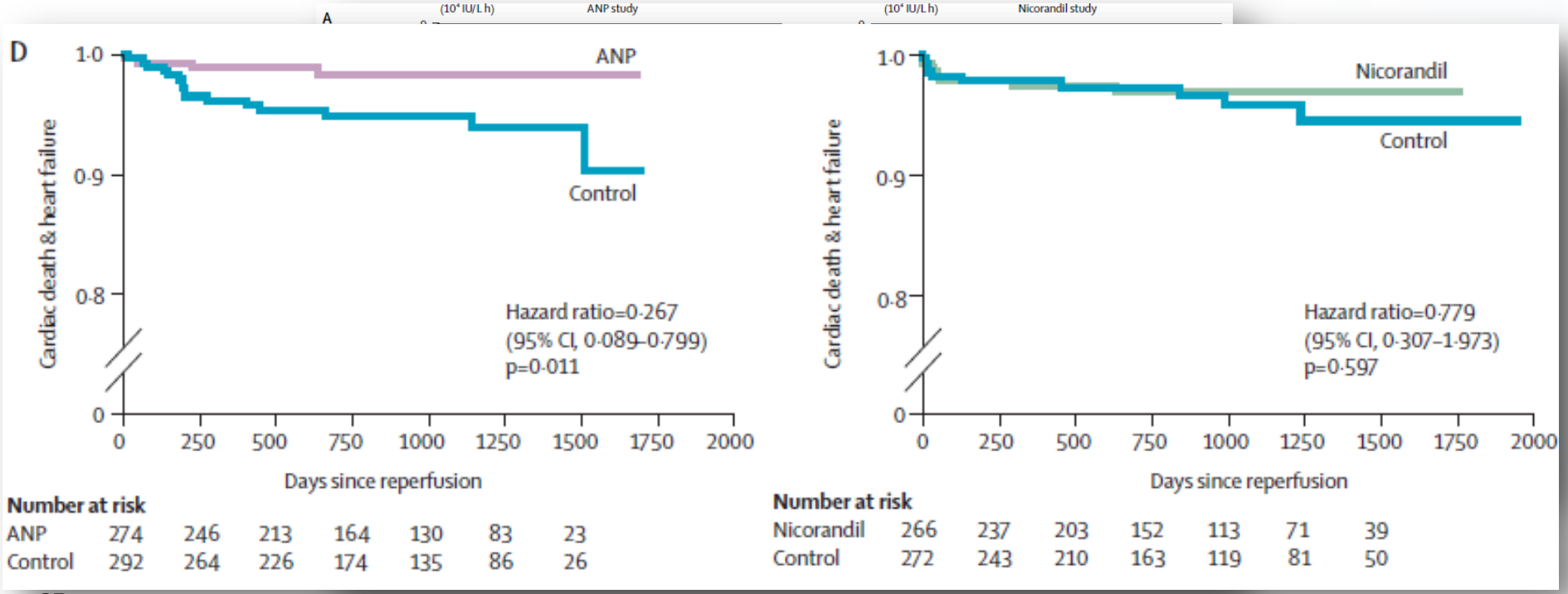
Reperfusion injury salvage kinase signalling: taking a RISK for cardioprotection





Human atrial natriuretic peptide and nicorandil as adjuncts to reperfusion treatment for acute myocardial infarction (J-WIND): two randomised trials

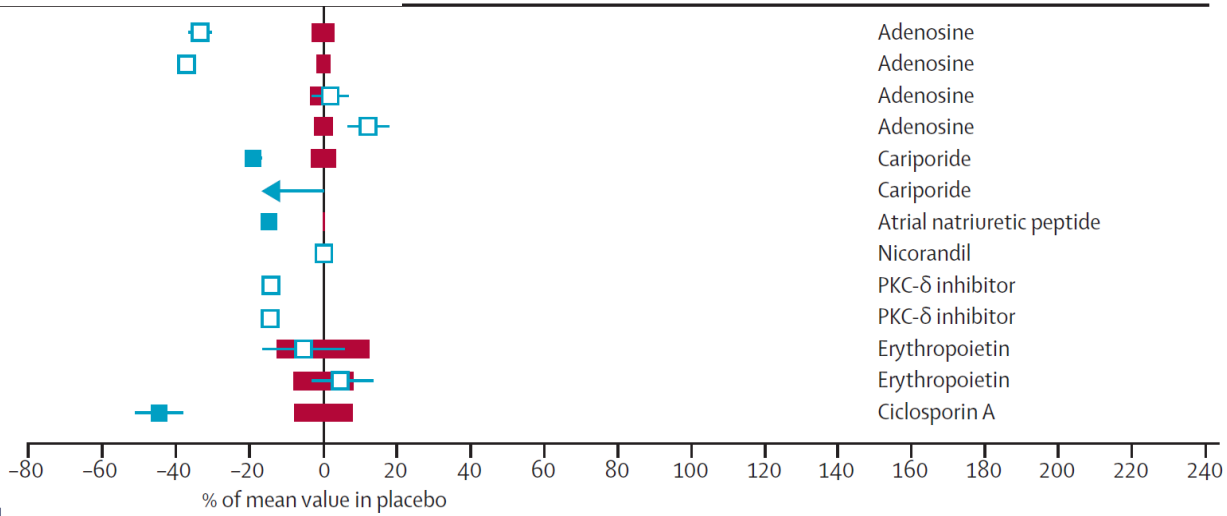
Patients with AMI undergoing reperfusion treatment (n=1216)
ANP iv (0.025ug/kg/min for 3 days) vs. placebo
Nicorandil iv (0.067mg/kg then 1.67ug/kg/min for 24-h) vs. placebo
Primary endpoint: infarct size and LVEF



Kitakaze M et al. Lancet 2007;370:1483-1493

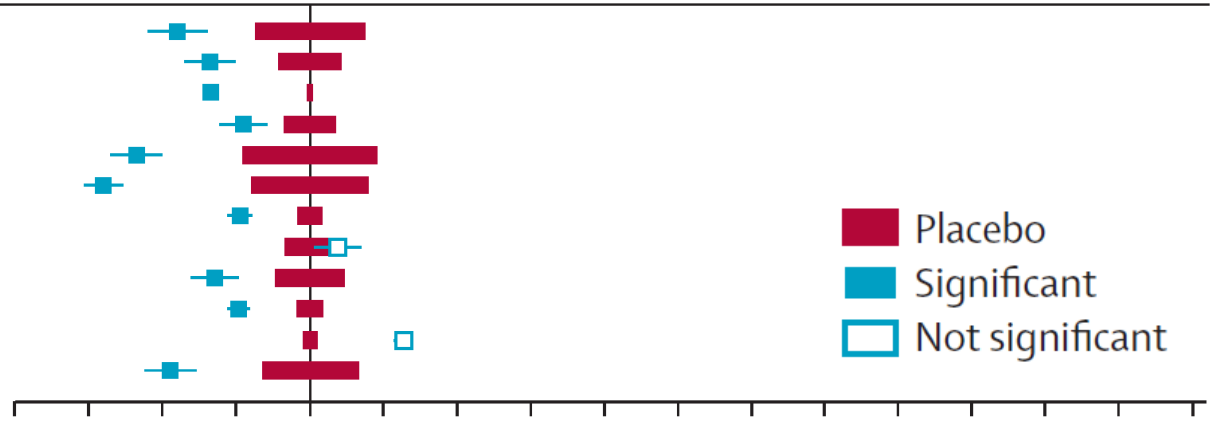
Pharmacological intervention of cardioprotective signaling

Study	Clinical scenario	Endpoint	Intervention	Placebo (n)	
Mahaffey et al[85]	STEMI AMI	SPECT	101	96	Adenosine
Ross et al[86]	STEMI AMI	SPECT	702	703	Adenosine
Fokkema et al[87]	STEMI AMI	CK	226	222	Adenosine
Desmet et al[88]	STEMI AMI	MRI	51	49	Adenosine
Theroux et al[89]	NSTEMI AMI	CK-MB	2909	2910	Cariporide
Mentzer et al[90]	CABG	CK-MB	2870	2891	Cariporide
Kitakaze et al[91]	STEMI AMI	CK	255	280	Atrial natriuretic peptide
Kitakaze et al[91]	STEMI AMI	CK	269	260	Nicorandil
Bates et al[92]	STEMI AMI	CK-MB	102	52	PKC-δ inhibitor
Mochly-Rosen et al[93]	STEMI AMI	CK	227	227	PKC-δ inhibitor
Ott et al[94]	STEMI AMI	MRI	45	47	Erythropoietin
Najjar et al[95]	STEMI AMI	MRI	68	68	Erythropoietin
Piot et al[96]	STEMI AMI	CK	30	28	Ciclosporin A



Ischemic postconditioning

Staat et al[49]	STEMI AMI	CK	28	27	
Ma et al[50]	STEMI AMI	CK	47	47	
Yang et al[51]	STEMI AMI	CK	23	18	
Laskey et al[52]	STEMI AMI	CK	13	12	
Thibault et al[53]	STEMI AMI	TnI	17	21	
Zhao et al[54]	STEMI AMI	TnI	25	26	
Lonborg et al[55]	STEMI AMI	MRI	59	59	
Sorensson et al[56]	STEMI AMI	CK	28	38	
Xue et al[57]	STEMI AMI	CK-MB	23	20	
Garcia et al[58]	STEMI AMI	CK-MB	22	21	
Freixa et al[59]	STEMI AMI	CK	40	39	
Thuny et al[60]	STEMI AMI	MRI	25	25	



Additional Issue

- Whether reperfusion injury occurs at all in man?

- Whether this type of injury really does account for a significant part of the remaining infarct?

Take Home Message

- **No-Reflow and Reperfusion Injury**
  - Exenatide, adenosine?
- **Ischemic Pre- and Postconditioning**
  - CsA, ANP
- **Other Areas of Investigation**
  - NO, TRO40303


Thank you for your attention!!
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