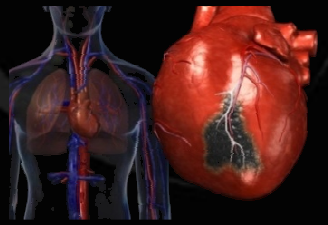
BASIC SCIENCE SUMMER SCHOOL

MONDAY 18 - THURSDAY 22 JUNE 2017

Opportunities and challenges in translating cardioprotection to the clinic

Dr. Gemma Vilahur

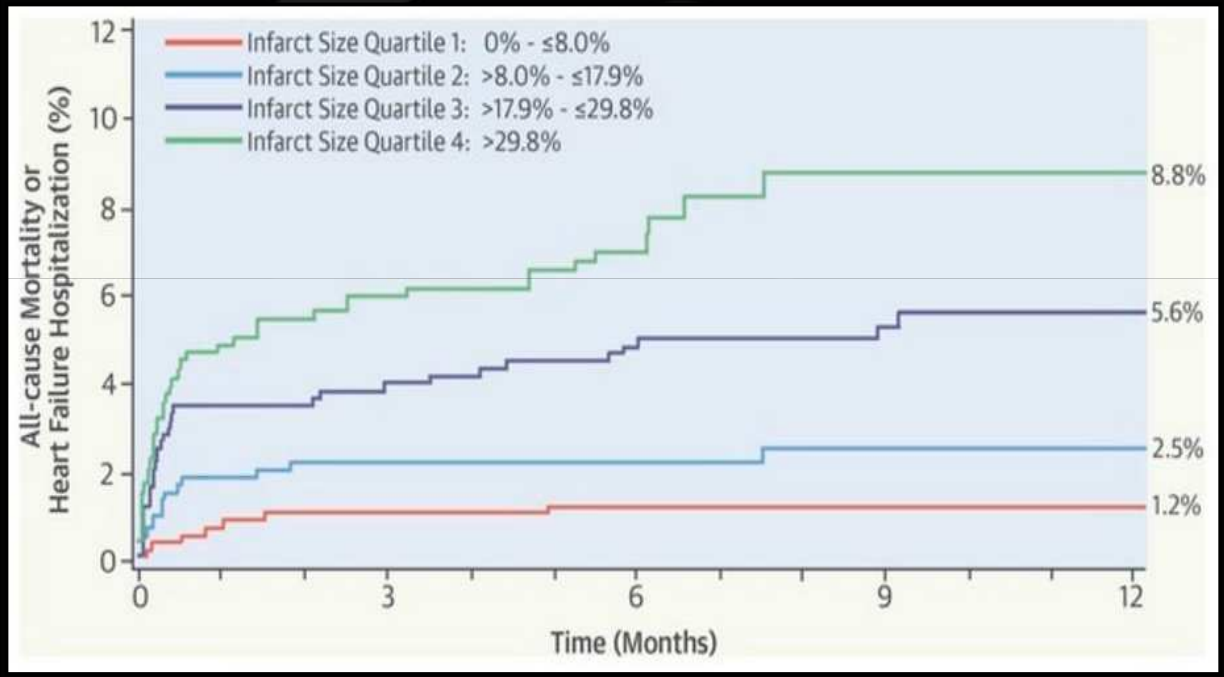


Cardiovascular Research Center
CSIC-ICCC, IIB Sant Pau, Hospital de la Santa Creu i Sant Pau
Barcelona

Why cardioprotection?

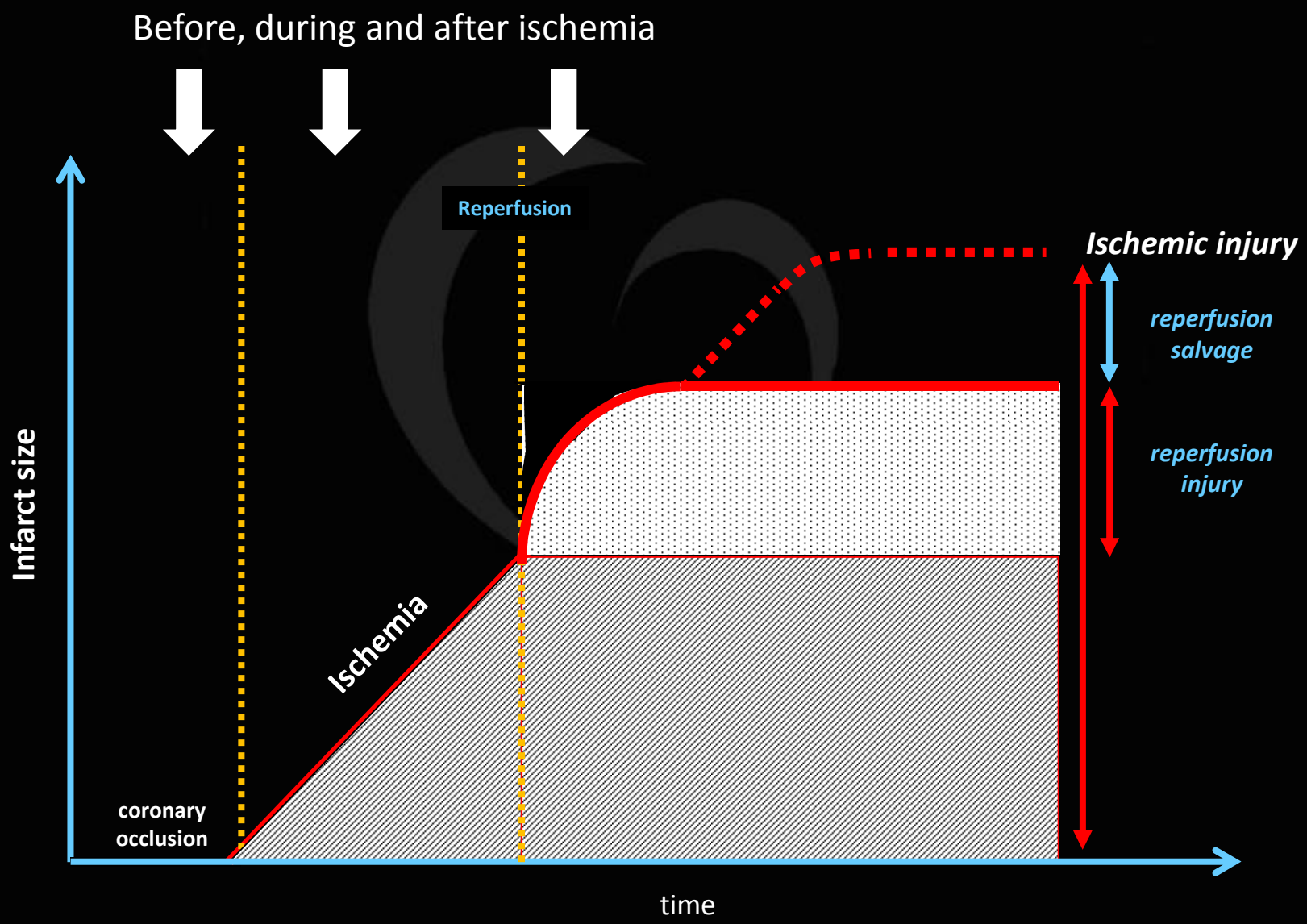
Stone et al *J Am Coll Cardiol 2016*

Infarct size and prognosis in primary PCI



OPPORTUNITIES

Treatment opportunities



Adjunct cardioprotective interventions in STEMI patients

Mechanical cardioprotection (ischemic conditioning)

Ischemic post-conditioning

Remote ischemic conditioning

Pharmacological cardioprotection

Mitochondrial -targeted

β-blockers

ANP

Exenatide

Adjunct cardioprotective interventions in STEMI patients…

Mechanical cardioprotection (ischemic conditioning)

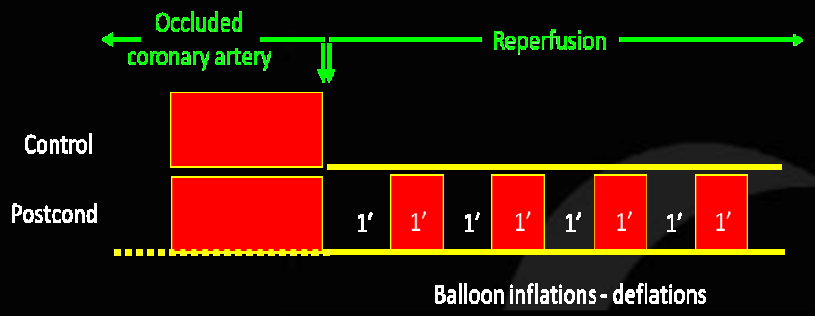
- Ischemic post-conditioning
- Remote ischemic conditioning

Pharmacological cardioprotection

- Mitochondrial -targeted
- Beta-blockers
- Adenosine
- Antiplatelet agents
- ANP
- Exenatide

Ischemic Post-Conditioning: experimental data

Zhao et al, *Am J Physiol 2003*

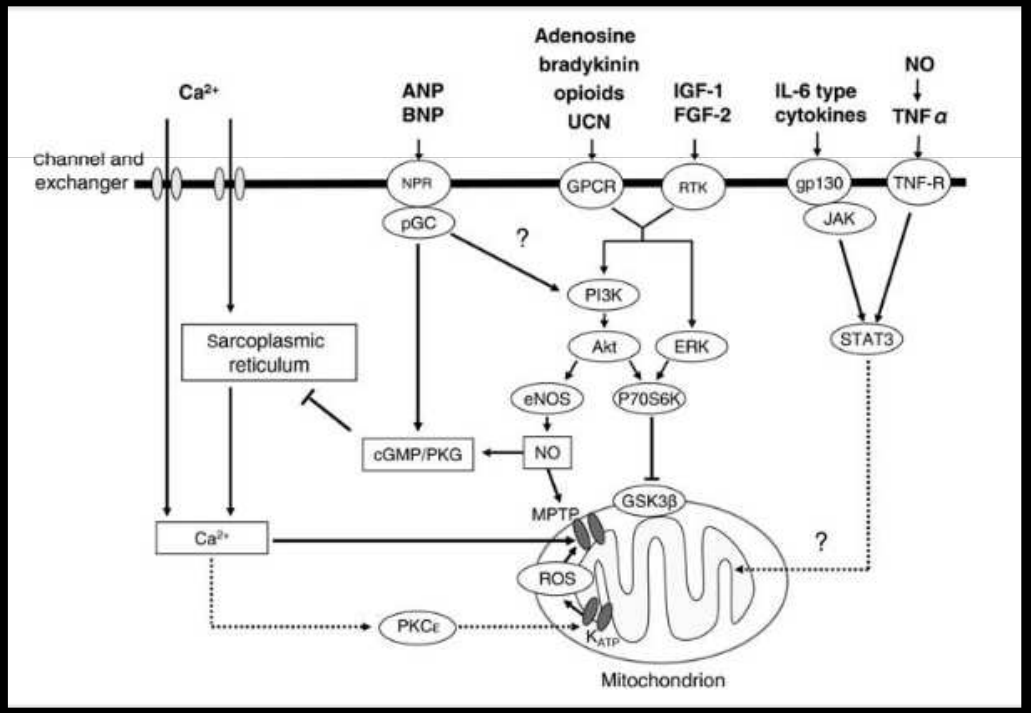


Experimentally has robustly shown to limit infarct size

Vilahur et al *Eur Heart J 2012*

Heusch et al *Circ Res 2011*

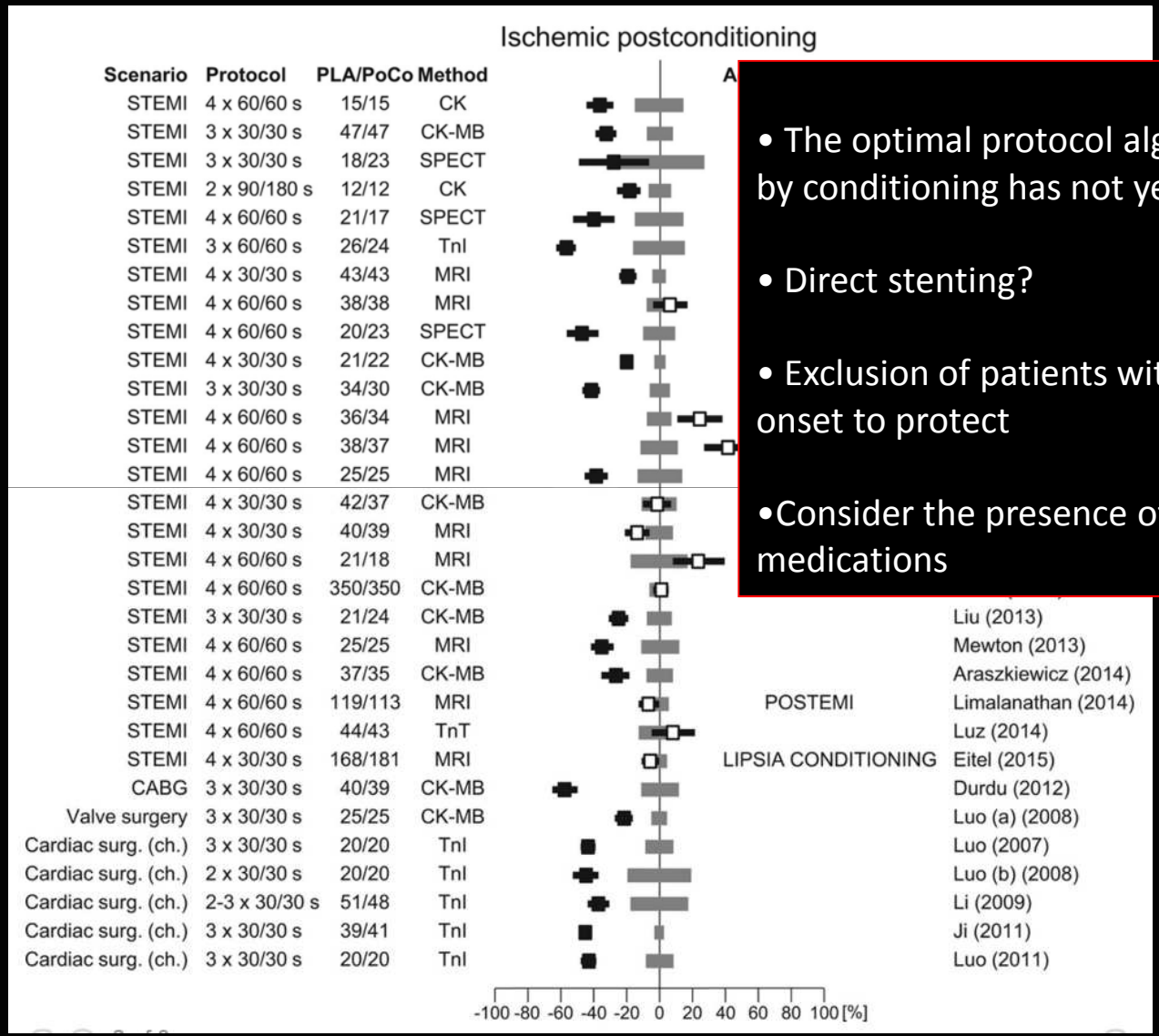
Bodi et al *I nt J Cardiol 2014*



Ovize et al Cardiovasc Res 2010

Hausenloy D. Thrombosis Haemost 2009

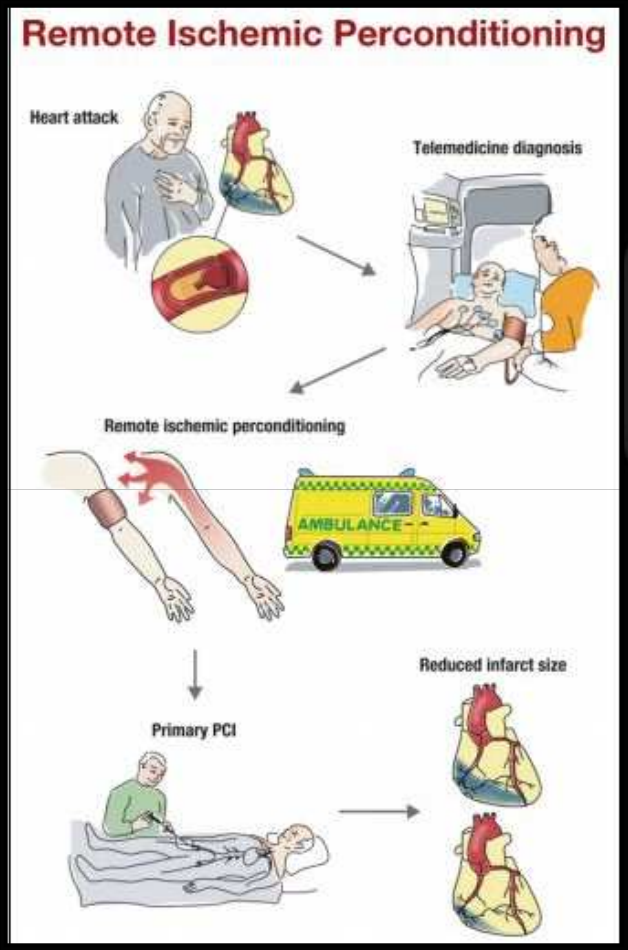
Ischemic Post-Conditioning: in the clinical arena



- The optimal protocol algorithm for cardioprotection by conditioning has not yet been defined
- Direct stenting?
- Exclusion of patients with >6 hours of symptom onset to protect
- Consider the presence of co-morbidities or co-medications

Heusch et al . Circulation Res 2016
Ferdinandy et al . Pharmacol Rev 2014

Remote ischemic post-conditioning: basic concepts



Rahbek et al J Cardiovasc Pharmacol Therap 2017

Circulating humoral factors

- Adenosine
- NO
- miRNA
- NO
- Hormones
- Neuropeptides
- Cytokines/chemokines
- RNAs

Activation of efferent neural pathways

- Brainstem is involved?
- Which levels of the spinal cord are mandatory?

RECEPTOR ACTIVATION
G-protein coupled receptors

↓

SIGNALING
RISK, SAFE pathways

↓

MITOCHONDRIA
(mPTP)

↓

CARDIOPROTECTION

Remote ischemic post-conditioning: Clinical arena

Remote ischemic conditioning

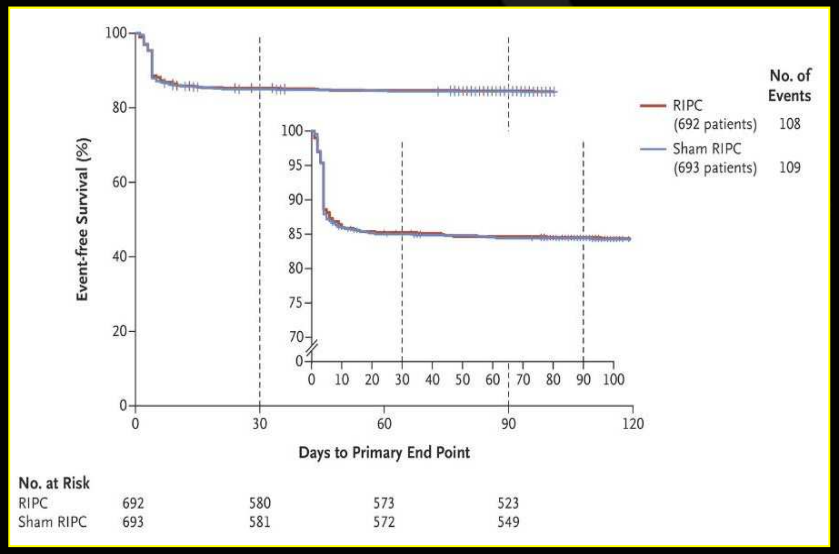
Scenario	Protocol	PLA/RIC	Method	Acronym	Authors
STEMI	per 4 x 5/5 min A	69/73	SPECT	CONDI	Bøtker (2010)
STEMI	per 4 x 5/5 min A	110/108	SPECT		Munk et al. (2010)
STEMI	per 4 x 5/5 min A	30/33	TnI		Rentoukas (2010)
STEMI	post 3 x 5/5 min L	48/48	CK-MB		Crimi (2013)
STEMI	per 3 x 5/5 min A	17/18	CK-MB	RIPOST-MI	Prunier (2014)
STEMI	per 3 x 5/5 min A#	160/158	MRI	LIPSIA CONDITIONING	Eitel (2015)
STEMI	per 4 x 5/5 min A	43/40	MRI		White (2015)
STEMI	per 4 x 5/5 min A	258/261	CK-MB	ERIC-LYSIS	Yellon (2015)

ABROGATES RIPC CARDIOPROTECTIVE EFFECTS

PROPOFOL anaesthesia

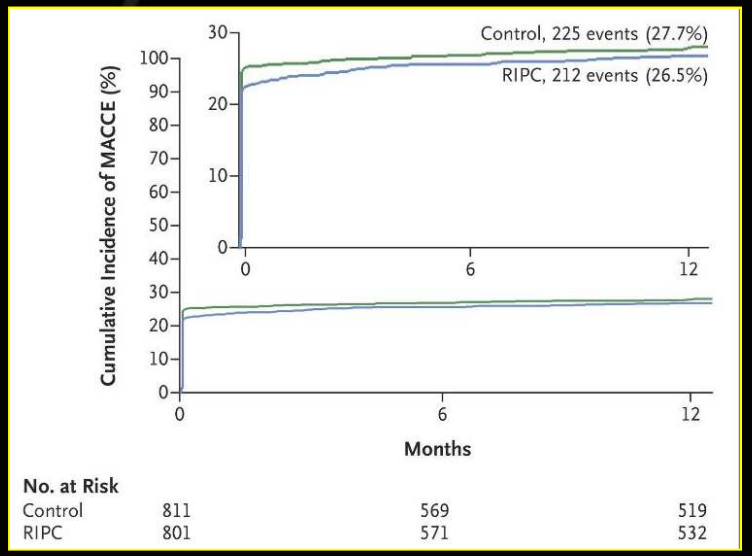
But in cardiac surgery..

Phase III trial



Meybohm et al N Eng J Med 2015

Phase III trial

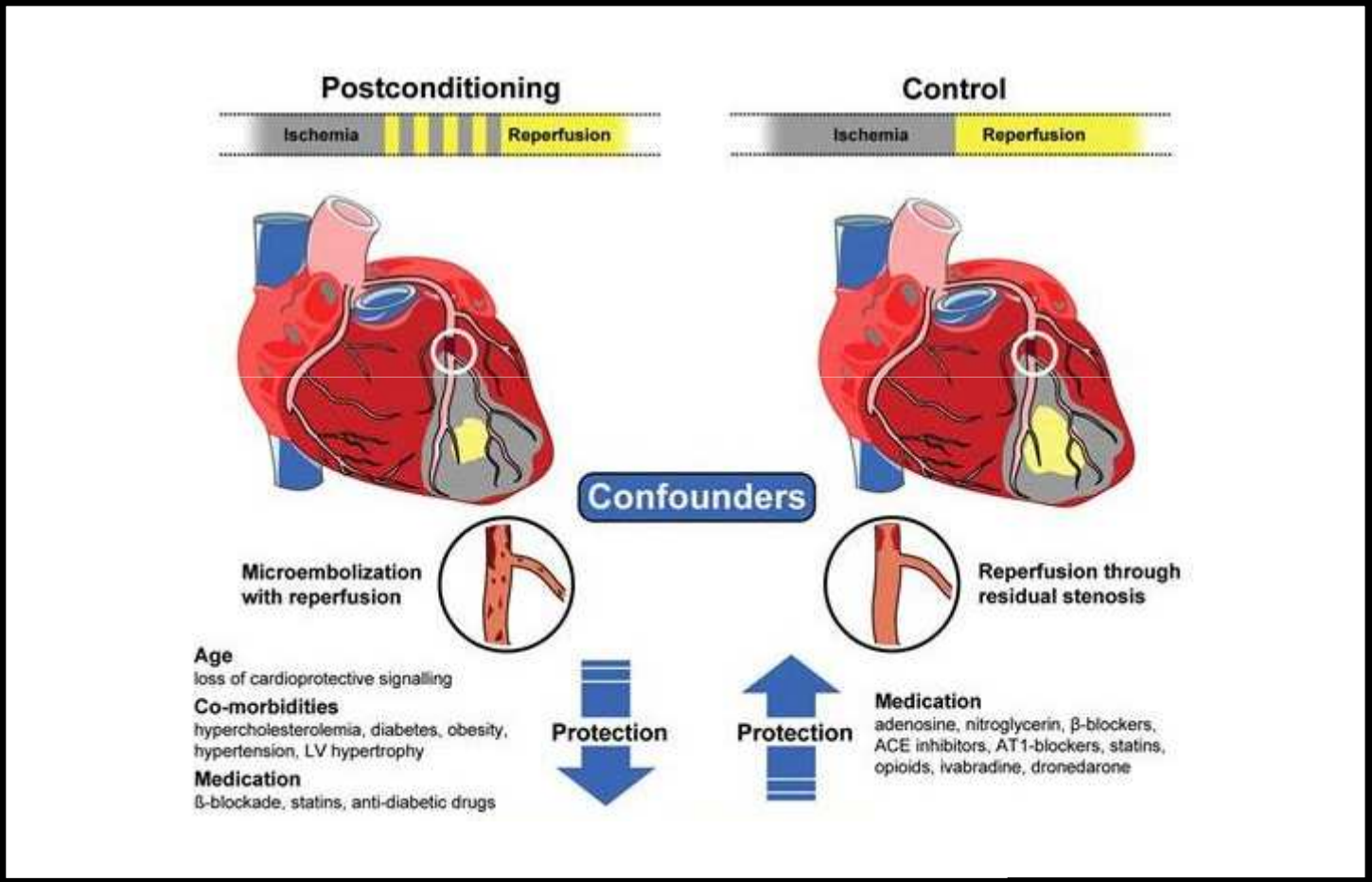


Hausenloy et al N Eng J Med 2015

Co-morbidities / Co-medications

STEMI patients are under medication known to exert cardioprotection

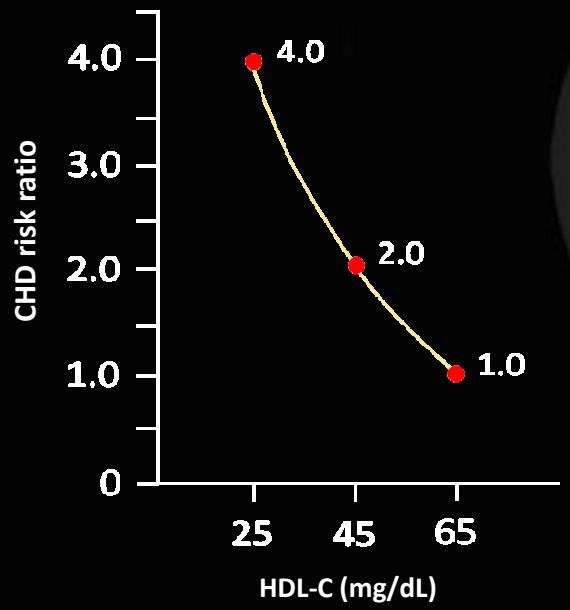
STEMI is linked to CV risk factors and co-morbidities which reduces IPost-C cardioprotection

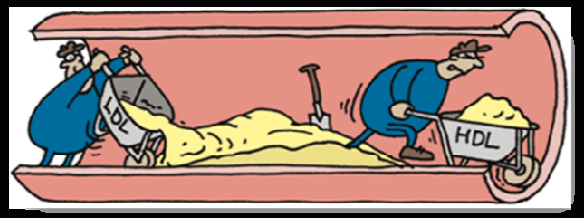


Ferdinandy et al . *Pharmacol Rev 2014*

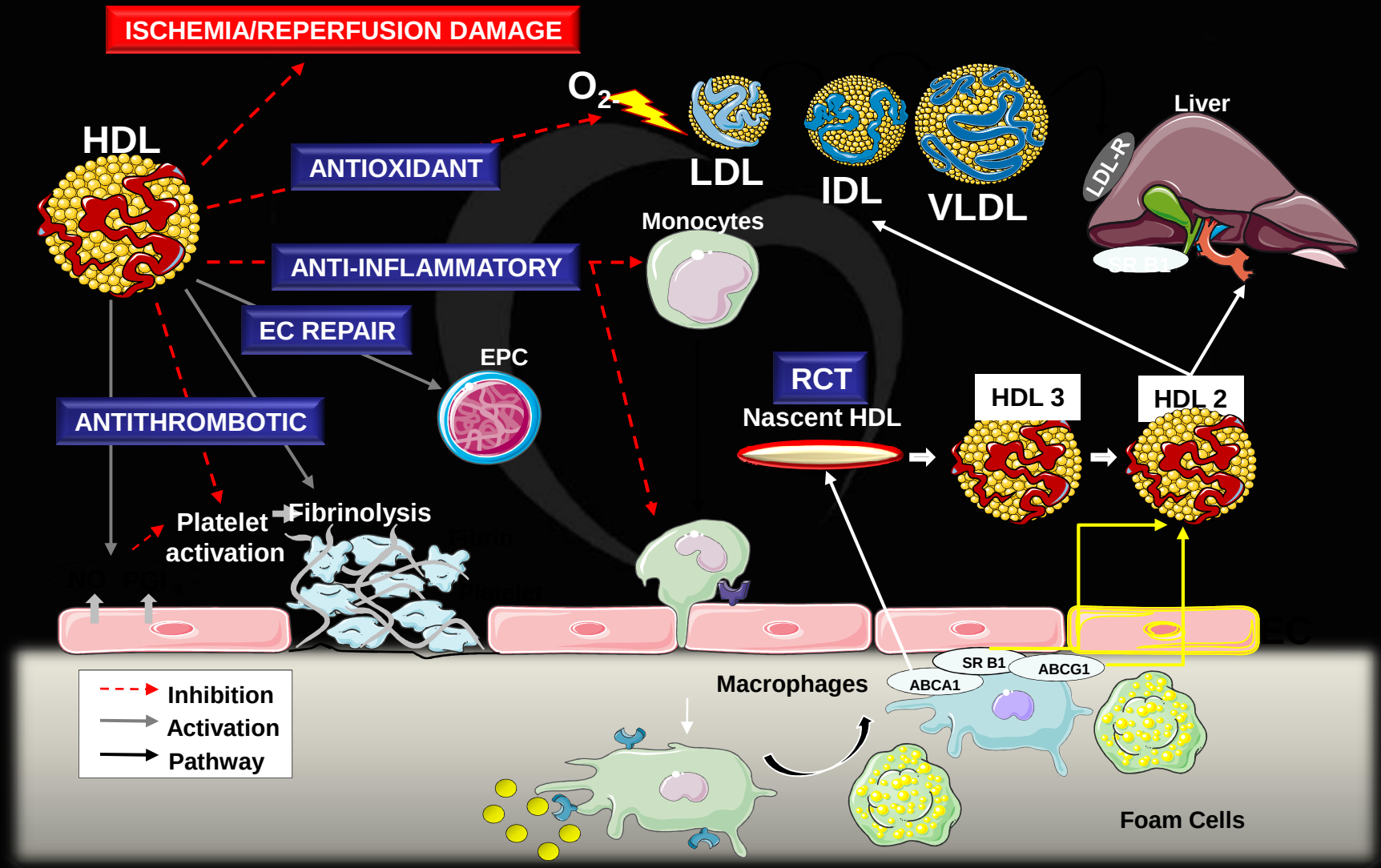
Heusch et al. *Eur Heart J 2012*

HDL and cardioprotection: impact of CV risk factors



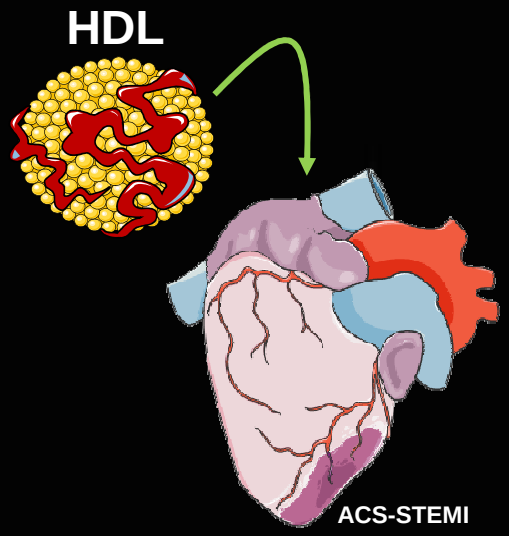


Cardio-vascular protective effects of HDL



Badimon L & Vilahur G . *N Y Acad Sciences 2012*

HDL and cardioprotection: HDL reduce infarct size

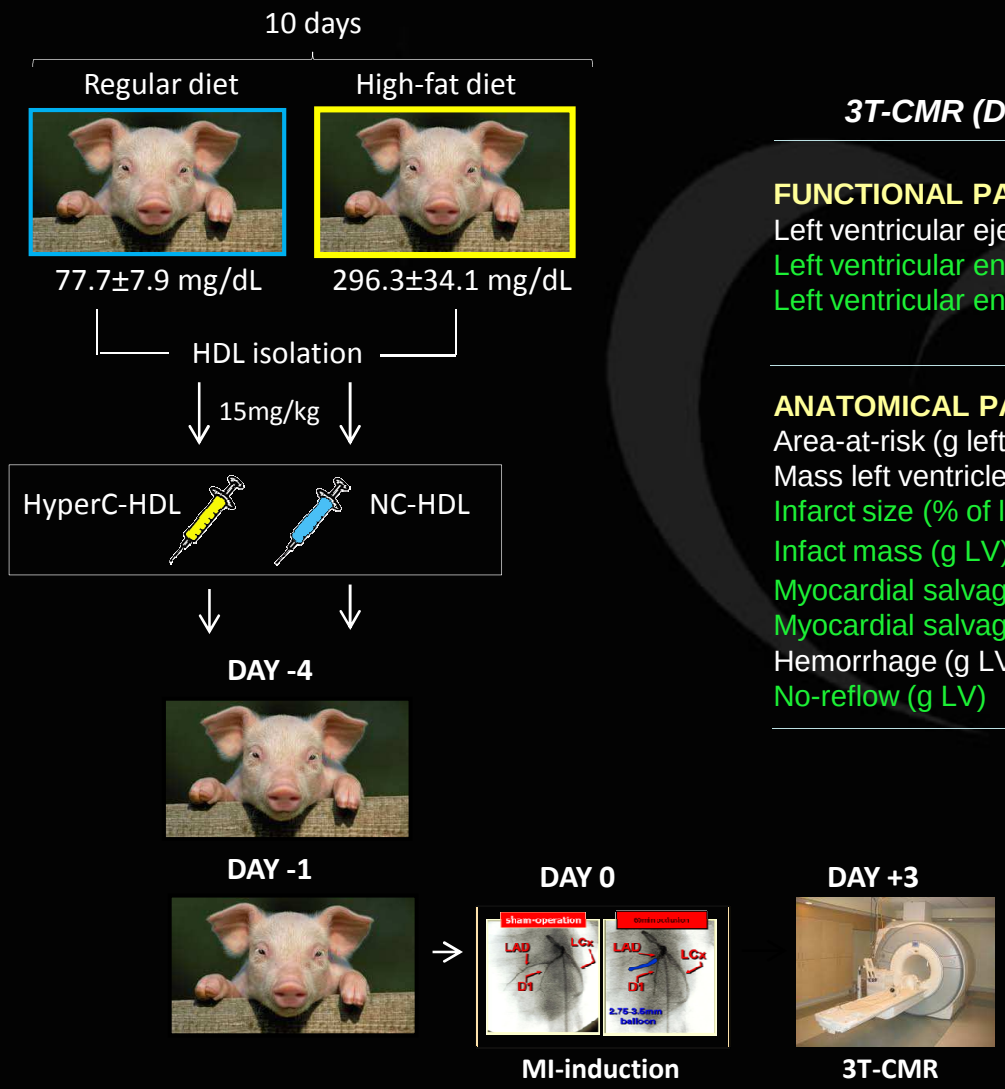


Theilmeier et al *Circulation 2006*

Vilahur et al *J Am Col Cardiol 2015*

Ability of HDL to protect the heart in the setting of ischemia/reperfusion is altered by CV risk factors (hypercholesterolemia)?

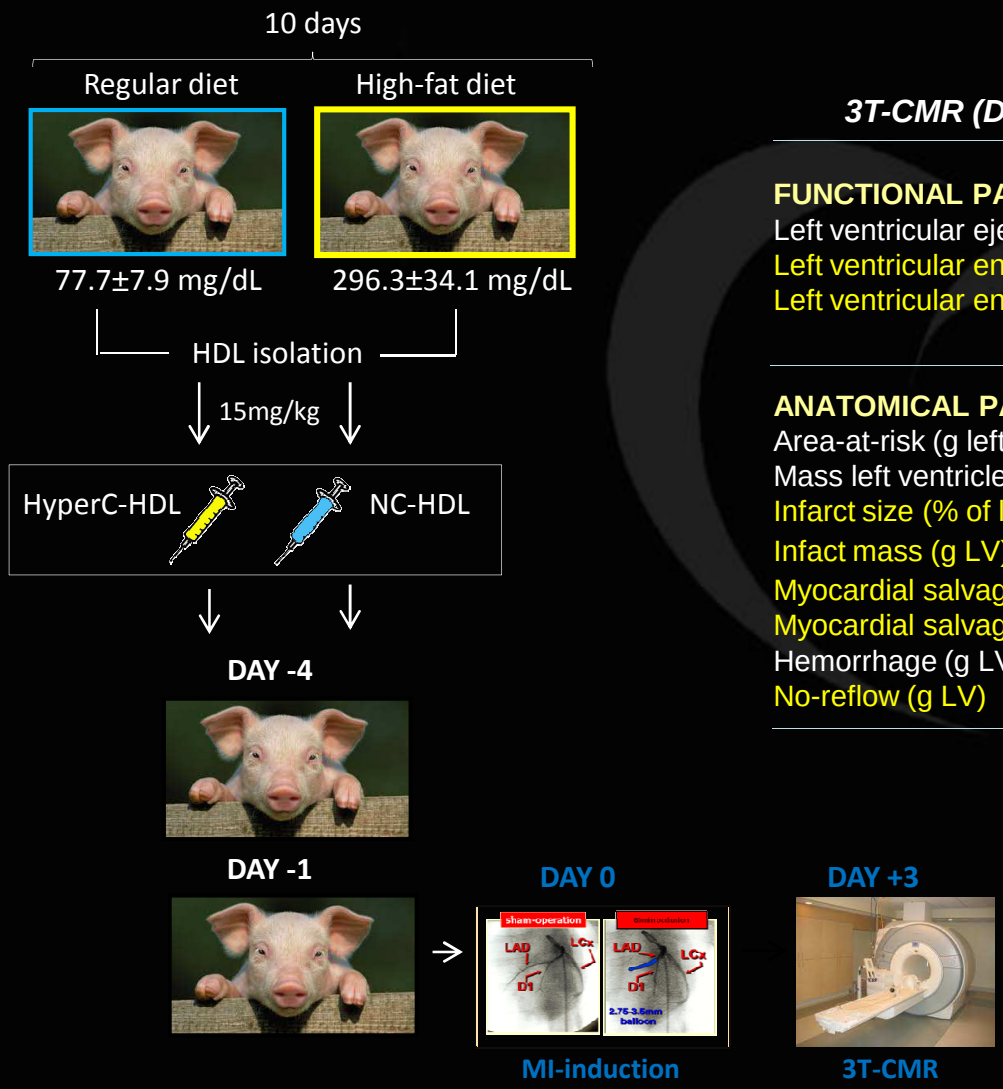
HDL ability to protect against Ischemia/reperfusion is found to be impaired under dislipidemic conditions



3T-CMR (Day 3 post-MI)	*Vehicle*	*NC_{HDL}*
FUNCTIONAL PARAMETERS		
Left ventricular ejection fraction	43.7±2.2	48.0±2.7
Left ventricular end dyastolic volume	100.1±5.5	85.4±1.2*
Left ventricular end systolic volume	56.8±4.6	44.3±2.3*
ANATOMICAL PARAMETERS		
Area-at-risk (g left ventricle)	21.3±1.4	18.1±1.2
Mass left ventricle (g)	73.2±2.9	74.7±2.7
Infarct size (% of left ventricle)	23.3±1.8	13.8±1.3*
Infact mass (g LV)	17.4±1.2	10.3±1.1*
Myocardial salvage	3.9±0.5	7.8±0.9*
Myocardial salvage index	0.18±0.02	0.43±0.04*
Hemorrhage (g LV)	2.0±0.3	2.0±0.4
No-reflow (g LV)	2.5±0.2	1.9±0.1*

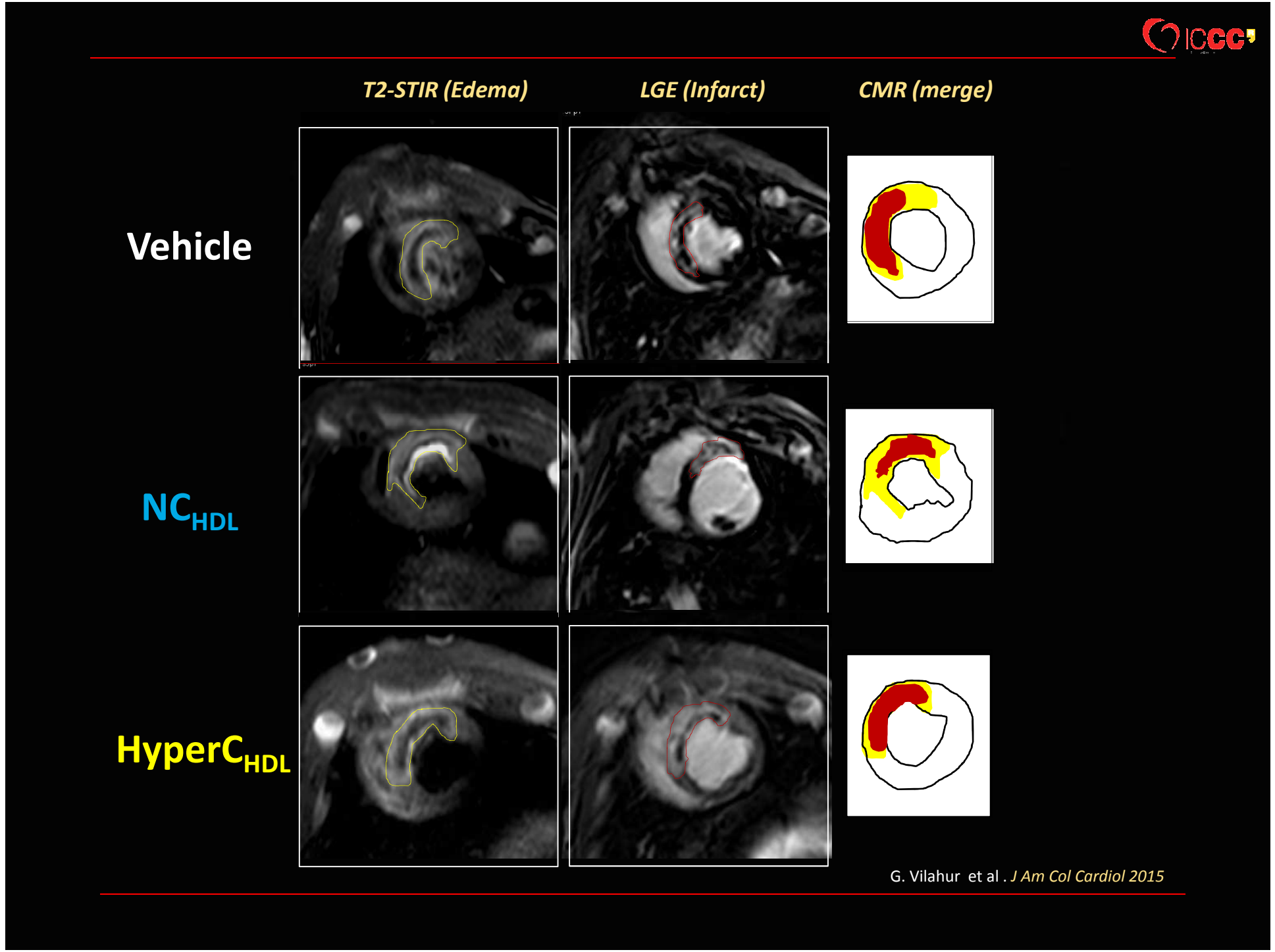
G. Vilahur et al . *J Am Col Cardiol 2015*

HDL ability to protect against Ischemia/reperfusion is found to be impaired under dislipidemic conditions



3T-CMR (Day 3 post-MI)	*Vehicle*	*NC_{HDL}*	*$HyperC_{HDL}$*
FUNCTIONAL PARAMETERS			
Left ventricular ejection fraction	43.7±2.2	48.0±2.7	43.4±1.4
Left ventricular end dyastolic volume	100.1±5.5	85.4±1.2*	104.8±3.6
Left ventricular end systolic volume	56.8±4.6	44.3±2.3*	59.1±1.3
ANATOMICAL PARAMETERS			
Area-at-risk (g left ventricle)	21.3±1.4	18.1±1.2	20.1±1.1
Mass left ventricle (g)	73.2±2.9	74.7±2.7	81.6±6.3
Infarct size (% of left ventricle)	23.3±1.8	13.8±1.3*	19.2±1.0
Infact mass (g LV)	17.4±1.2	10.3±1.1*	15.4±0.7
Myocardial salvage	3.9±0.5	7.8±0.9*	4.7±1.0
Myocardial salvage index	0.18±0.02	0.43±0.04*	0.23±0.04
Hemorrhage (g LV)	2.0±0.3	2.0±0.4	2.4±0.4
No-reflow (g LV)	2.5±0.2	1.9±0.1*	3.1±0.4

G. Vilahur et al . *J Am Col Cardiol 2015*



G. Vilahur et al . *J Am Col Cardiol 2015*

Raising HDL cholesterol in secondary prevention does not prevent CVD

In 2ª prevention higher HDL-cholesterol levels do not reduce CV events rate beyond statins

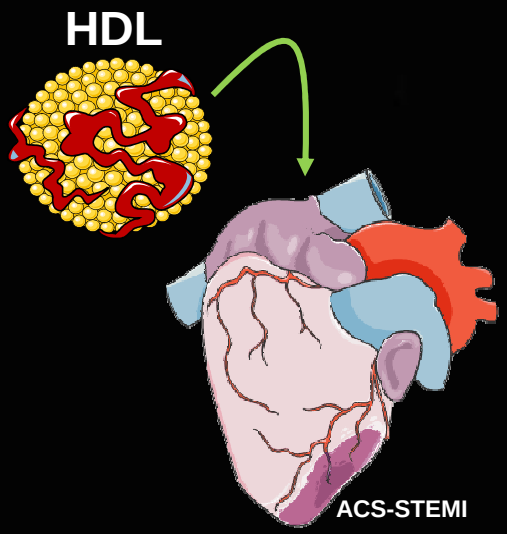
Keene D et al *BMJ 2014*

Compared to healthy subjects, HDL from patients with manifest CVD ...

↓ Cholesterol efflux capacity
↓ Anti-oxidant properties
↓ Anti-inflammatory effects

Rohatgi. New Eng J Med 2014
Sigruener et al (LURIC) PLOS one 2014
Riwanto et al JLipRes 2013
Besler C et al . J Clin Inv 2011
Kontush A & Chapman MJ. Pharmacology Rev 2006

HDL and cardioprotection



HDL loose their ability to protect the heart in the setting of ischemia/reperfusion in hypercholesterolemia

UPLC/MS

Changes on the LIPIDOME

MALDI TOF

Changes on the PROTEOME

Padro, Ben-Aicha, et al, Vilahur.
J Am Col Cardiol 2017

HDL PARTICLE functionality

↓ Antioxidant potential
↓ Cholesterol removal capacity

Chances for cardioprotection in STEMI patients…

Ischemic conditioning

- Post-conditioning
- Remote ischemic post-conditioning

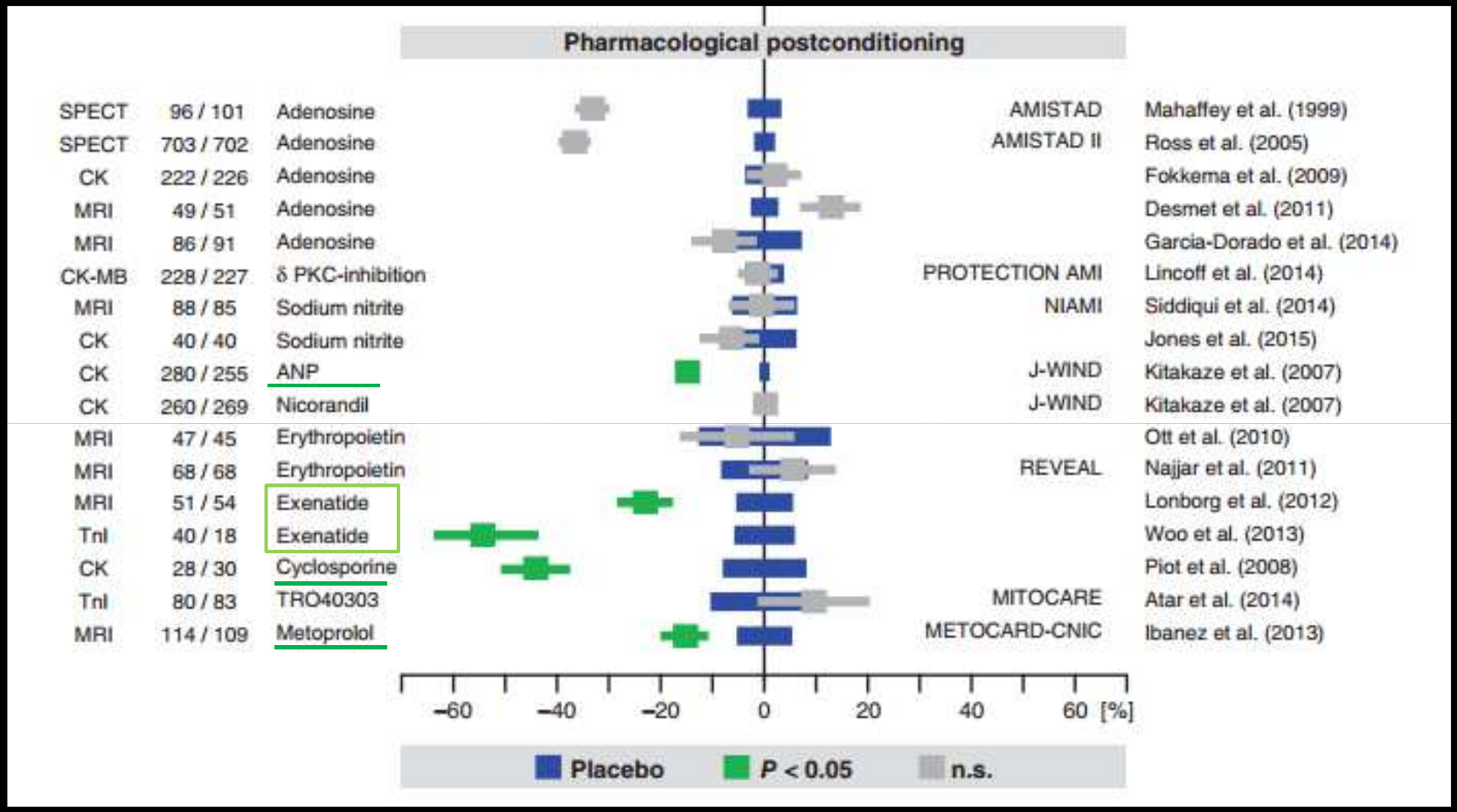
Pharmacological conditioning

- Cyclosporine
- Beta-blockers
- Statins
- Adenosine
- Antiplatelet agents
- Etc..

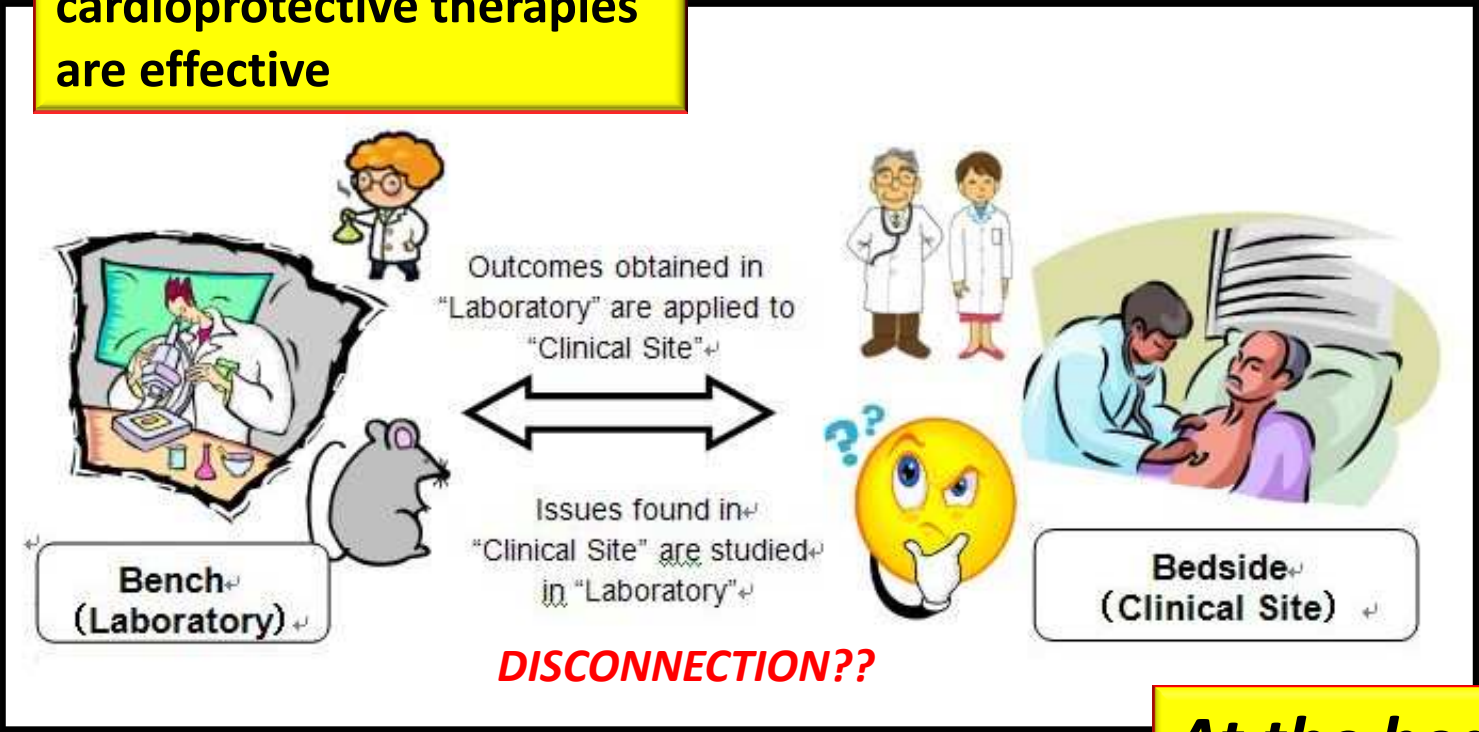
Multiple drugs have shown to reduce infarct size in experimental animal models ….

PHASE-II trials: not all have been beneficial

Gerd Heush *Comp Physiol 2015*



In the bench,
cardioprotective therapies are effective



NONE HAS DEMONSTRATED CLINICAL BENEFIT IN PHASE III TRIALS

At the bedside,
not all have demonstrated to be beneficial

The prevailing notion on the translation of cardioprotective strategies to clinical practice is disappointment.[1–7] In fact, there is (yet) no single randomized clinical trial which has unequivocally demonstrated a better clinical outcome for patients experiencing an acute myocardial infarction or undergoing cardiovascular surgery when receiving an adjunct cardioprotective agent/intervention before or at reperfusion

Gerd Heush *Circulation Research 2017*

CHALLENGES

Barriers / challenges to translating experimentally successful interventions into clinical therapies

Preclinical Level:

1.- The **MECHANISMS** of I/R injury and protection need to be **FULLY UNRAVELLED**

2.- Lack of **ROBUST PRECLINICAL DATA**

Kimmelman and Federico, Nature 2017

3.- Use of **HEALTHY** and **YOUNG** animal models that do not approximate the clinical setting

4.- Failure to disseminate **NEGATIVE RESULTS**

Barriers / challenges to translating experimentally successful interventions into clinical therapies

Clinical Level:

1.- Lact of **PHASE-II** clinical trials (dosing and timing)

Metoprolol in cardioprotection

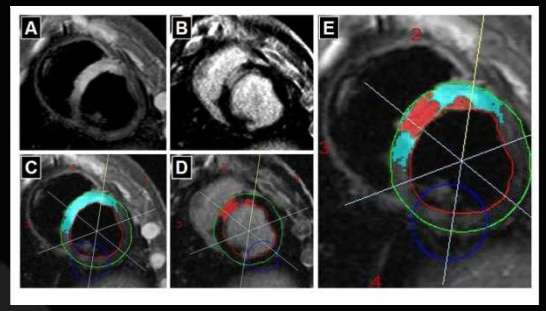
2007

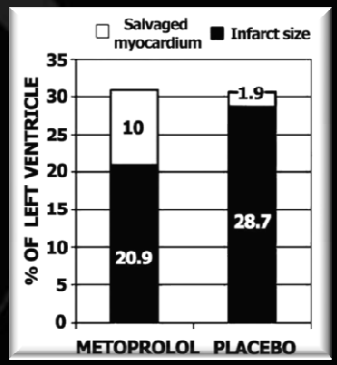
Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association

Early Metoprolol Administration Before Coronary Reperfusion Results in Increased Myocardial Salvage: Analysis of Ischemic Myocardium at Risk Using Cardiac Magnetic Resonance

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





Cardiac Function (MRI)

Placebo	Metoprolol
LVEF: 35% vs 35%	LVEF: 37% vs 43%

2011

ELSEVIER

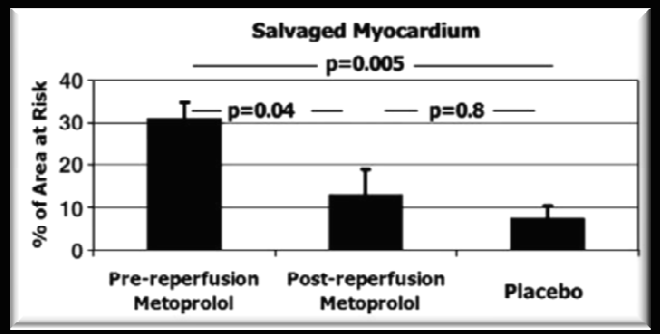
Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

The cardioprotection granted by metoprolol is restricted to its administration prior to coronary reperfusion

Borja Ibanez [a,b], Giovanni Cimmino [a], Susanna Prat-González [a], Gemma Vilahur [c], Randolph Hutter [a], Mario J. García [a], Valentin Fuster [a,b], Javier Sanz [a], Lina Badimon [c], Juan J. Badimon [a,*]



Metoprolol & cardioprotection in the clinical setting

2013

B. Ibáñez et al V.Fuster. Circulation 2013
G. Pizarro et al B. Ibáñez. J Am Col Cardiol 2014

1st STEMI

Dose: 15mgg
Timing: <6h

Metoprolol i.v pre-reperfusion

Anterior infarcts (21% IS)

No β-blockers

Dose: 10mg
Timing: <12

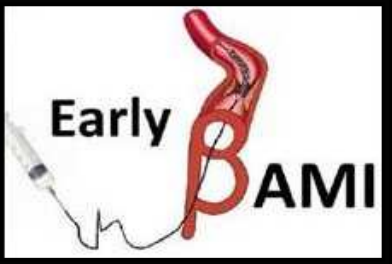
Control

All infarcts (15.3% IS)

On β-blockers 19%

PPCI

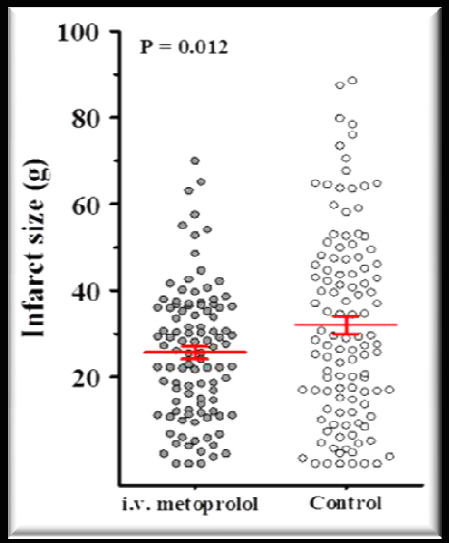
2016



Roolvink V et al. J Am Col Cardiol 2016

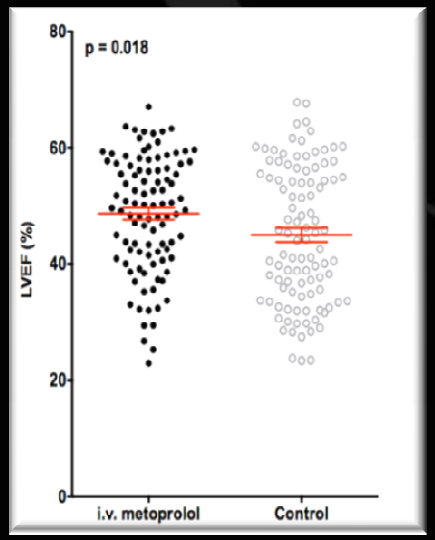
7 days after STEMI

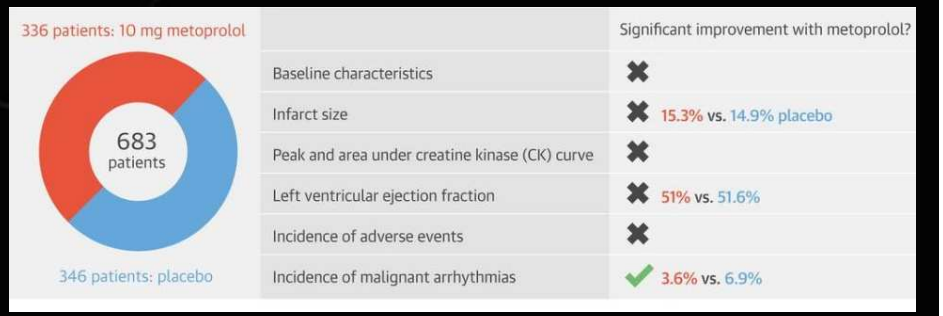
Reduced infarct size



6 months after STEMI

Improved LVEF





Barriers / challenges to translating experimentally successful interventions into clinical therapies

Clinical Level:

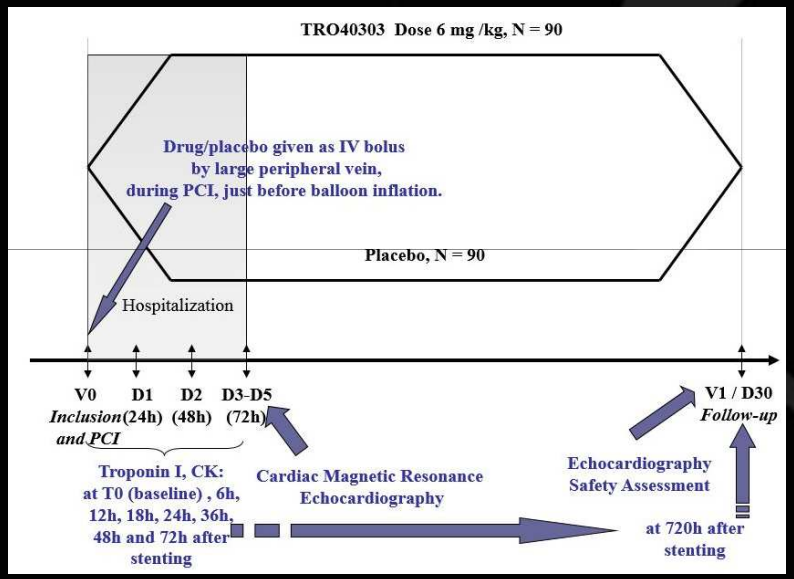
1.- Lact of **PHASE-II** clinical trials (dosing and timing)

2.- Lack of **SOLID CONSISTENT** experimental evidence

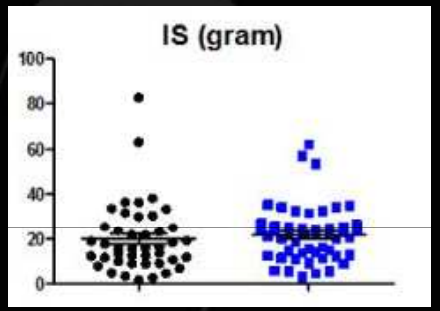
MITOCARE: TRO40304

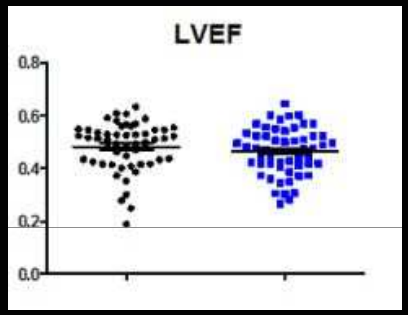
TRO40304 inhibits the opening of the mitochondrial permeability transition pore

RATIONALE: TRO40304 has been shown to reduce infarct size by 50% in rat and mouse models and to improve LVEF at 24h and 1month in these models



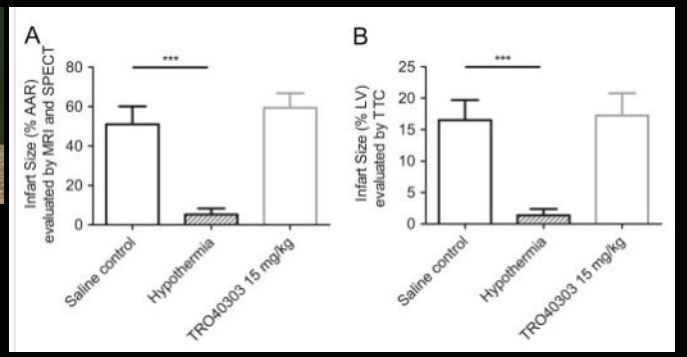
NO EFFECT





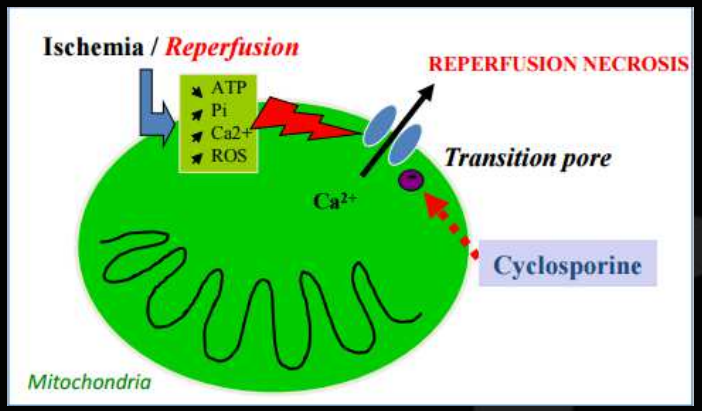
Dan Antar et al Eur Heart J 2013

NO EFFECT



Hansson et al *Eur J Pharmacol 2015*

CIRCUS: CICLOSPORINE

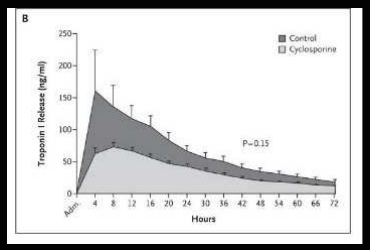


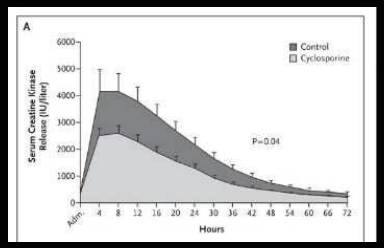
CONSISTENT DATA ON

Argaud et al J Mol Cel Cardiol 2005

Lim et al Cardiovasc Res 2007

N=58 STEMI patients





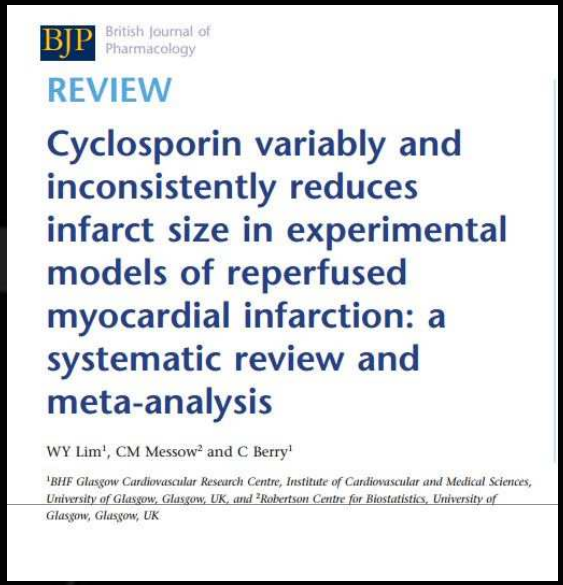
Piot et al *N Eng J Med 2008*

Sheu et al Int J Cardiol 2011

De Paulis et al Basic Res Cardiol 2013

Karlsson et al *J Cardiovasc Pharmacol Ther 2010*

INCONSISTENT DATA ON



BJP British Journal of Pharmacology

REVIEW

Cyclosporin variably and inconsistently reduces infarct size in experimental models of reperfused myocardial infarction: a systematic review and meta-analysis

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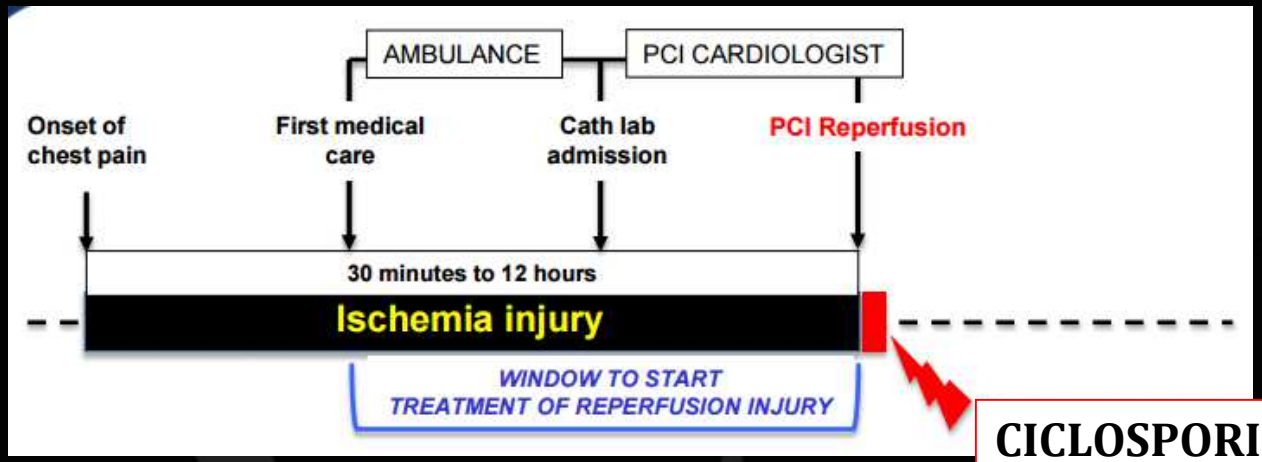
[1]BHF Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK, and [2]Robertson Centre for Biostatistics, University of Glasgow, Glasgow, UK

The only PHASE III clinial trial so far in cardioprotection…

FAILED



POTENTIAL EXPLANATIONS:

-12h symptoms CIRCUS vs 4h Phase II - (any viable tissue left at 12h?)

-Higher use of P2Y12 inhibitors CIRCUS (cardioprotective)

- Vehicle used: cremophor vs intralipid (CIRCUS) which reduces infarct size as much as CiclosporineA

Ovize et al *N Eng J Med 2015*

Barriers / challenges to translating experimentally successful interventions into clinical therapies

Clinical Level:

1.- Lack of **SOLID CONSISTENT** experimental evidence

2.- Lact of **PHASE-II** clinical trials (dosing and timing)

3.- Which **CLINICAL SCENARIO** and **OPTIMAL PATIENT** should be considered

The optimal patient and clinical scenario

NO COLLATERALS

TOTALLY OCCLUDED LAD
: LARGE INFARCTS

ADMITTED PREFERABLY
<6h AFTER SYMPTOM
ONSET

TIMI FLOW 0 PRIOR PRIOR-PPCI
TIMI FLOW >2 POST PPCI

NO PRE-INFARCTION ANGINA

FUTURE/NEW OPORTUNITIES

Identify novel targets

Test new strategies

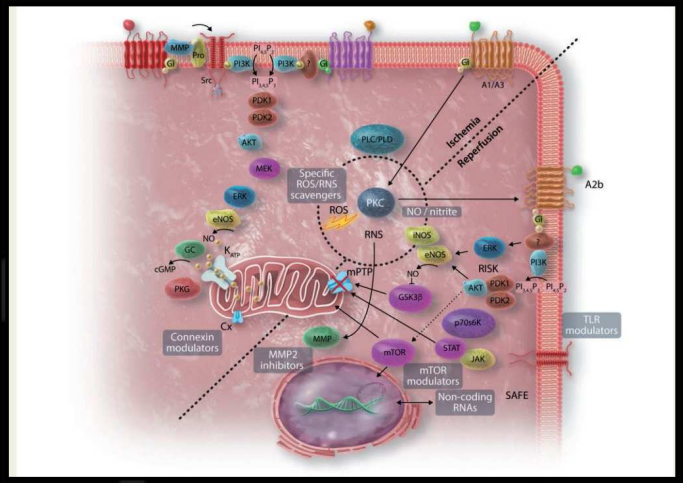
Identify novel targets

Cardiovascular Research (2017) **113**, 564–585
doi:10.1093/cvr/cvx049

Novel targets and future strategies for acute cardioprotection: Position Paper of the European Society of Cardiology Working Group on Cellular Biology of the Heart

Derek J. Hausenloy[1*†], David Garcia-Dorado[2†], Hans Erik Bøtker[3], Sean M. Davidson[4], James Downey[5], Felix B. Engel[6], Robert Jennings[7], Sandrine Lecour[8], Jonathan Leor[9], Rosalinda Madonna[10], Michel Ovize[11], Cinzia Perrino[12], Fabrice Prunier[13], Rainer Schulz[14], Joost P.G. Sluijter[15], Linda W. Van Laake[16], Jakob Vinten-Johansen[17], Derek M. Yellon[18], Kirsti Ytrehus[19], Gerd Heusch[20‡], and Péter Ferdinandy[21*‡]

Cardiovascular Research March 2017

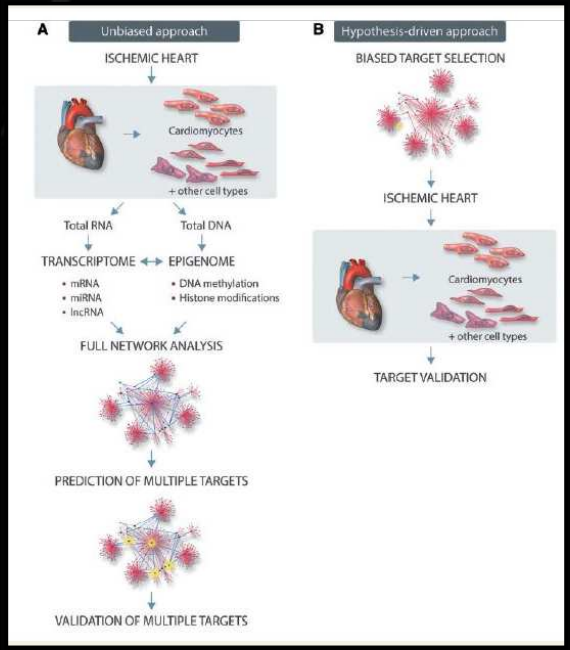


Cardiovascular Research (2017) **113**, 725–736
doi:10.1093/cvr/cvx070

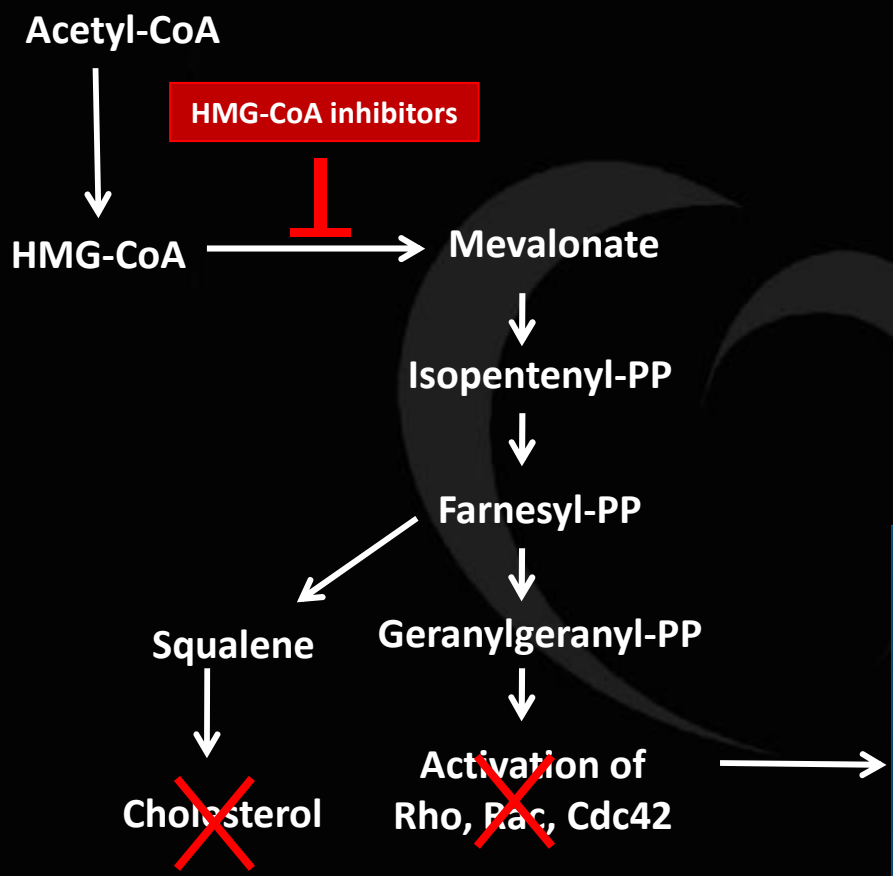
Epigenomic and transcriptomic approaches in the post-genomic era: path to novel targets for diagnosis and therapy of the ischaemic heart? Position Paper of the European Society of Cardiology Working Group on Cellular Biology of the Heart

Cinzia Perrino[1], Albert-Laszló Barabási[2,3,4,5], Gianluigi Condorelli[6,7], Sean Michael Davidson[8], Leon De Windt[9], Stefanie Dimmeler[10,11], Felix Benedikt Engel[12], Derek John Hausenloy[13,14,15,16,17,18], Joseph Addison Hill[19], Linda Wilhelmina Van Laake[20,21], Sandrine Lecour[22], Jonathan Leor[23,24], Rosalinda Madonna[25,26], Manuel Mayr[27], Fabrice Prunier[28], Joost Petrus Geradus Sluijter[29], Rainer Schulz[30], Thomas Thum[31], Kirsti Ytrehus[32], and Péter Ferdinandy[33,34,35*]

Cardiovascular Research June 2017



Test new strategies: HMG-CoA reductase inhibitors, Statins



Statin-related "pleiotropic effects"
Direct cardioprotective effects??

- Improvement endothelial function
- Atherosclerotic plaque stabilization
- Decreased inflammatory response
- Lower thrombotic risk

Badimon & Vilahur. Rev Esp Cardiol 2010

Clinical support…

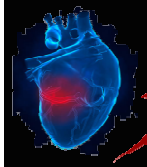
Better outcomes in ACS patients when oral LD of statins are administered early after revascularization
(Miracle, PROVE-IT, A to Z).

Cannon et al *N Eng J Med 2004*
Kinlay et al *Circulation 2004*
de Lemos et al *Eur Heart J 2004*

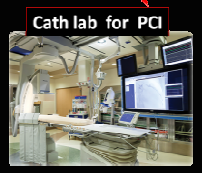
Decreased rates of peri-procedural complications in several small-scale studies where oral LD satins are administered before an elective or emergent PCI.

Patti et al *Circulation 2006*
Patti et al *J Am Col Cardiol 2007*
Cannon et al *N Eng J Med 2008*
Di Scieascio et al *J Am Col Cardiol 2009*

Statins, do they exert cardioprotection when administered intravenously prior reperfusion?



TRANSFER 2h

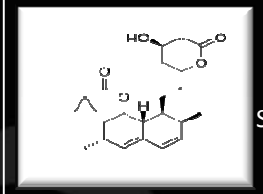


INTRAVENOUS
β-OH-SIMVASTATIN
(0.3mg/kg)

REPERFUSION

75 min | 15 min | 150 min

Simvastatin
P.O

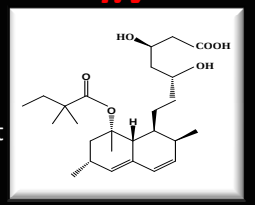


Lactone form
(closed)

Hydrolisis

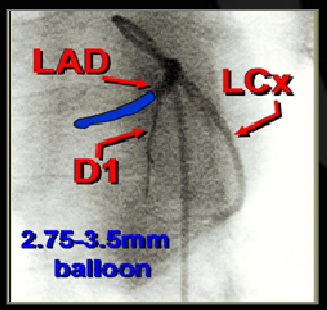
Sodium hydroxide + heat

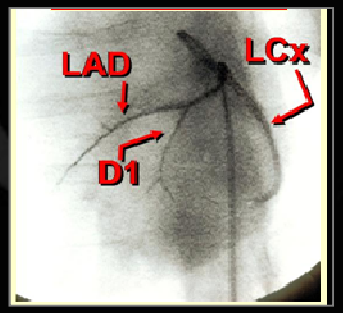
B-OH-Simvastatin
I.V



Hydroxiacid form
(open)

Fat: 24%
20% saturated fat
2% cholesterol
1% cholic acid
Protein: 20.2%
Carbohydrates: 35.3
Fiber: 5%
Minerals: 6%
Water: 9%



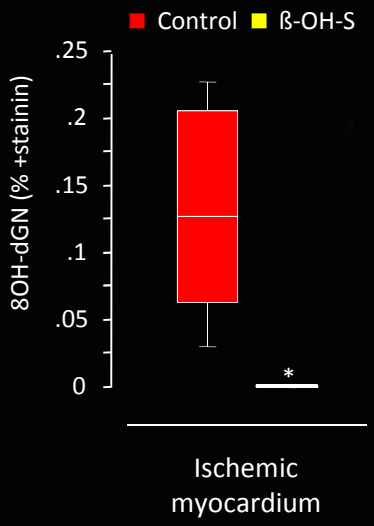


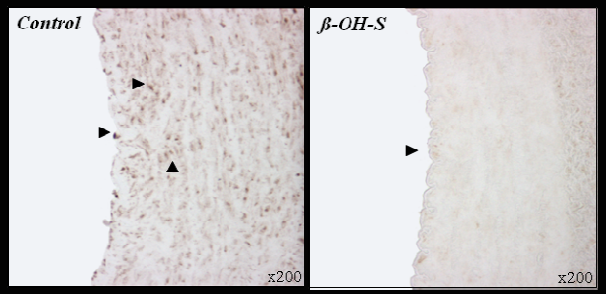
Echocardiography
Infarct size analysis
Molecular / Histological approaches **I/R injury**

G. Vilahur, et al. Int J Cardiol 2014

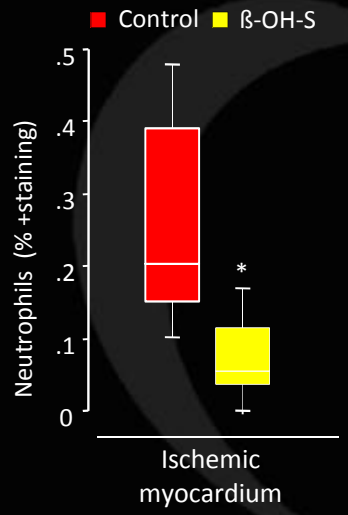
Iv Statin administration prior reperfusion protects against I/R injury

OXIDATIVE DAMAGE

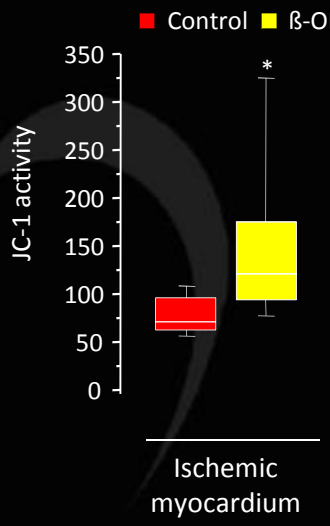




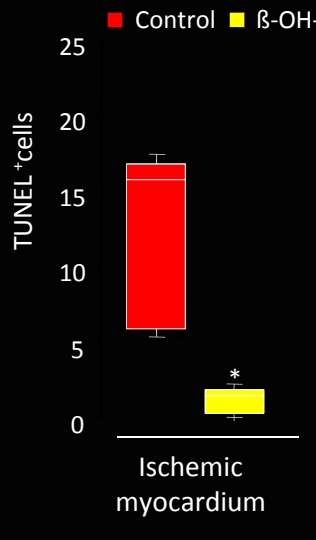
NEUTROPHILE INFILTRATION

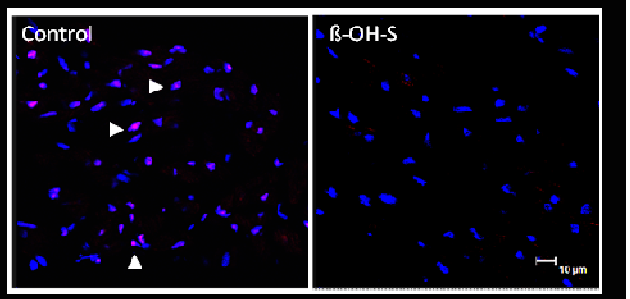


MITOCHONDRIAL FUNCTION



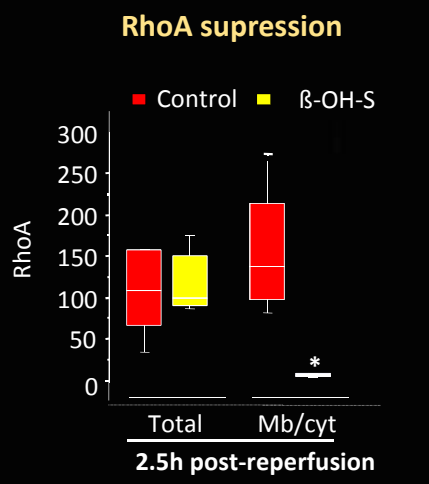
APOPTOSIS EXECUTION

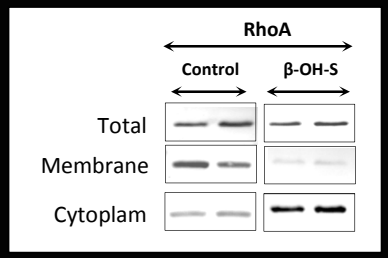


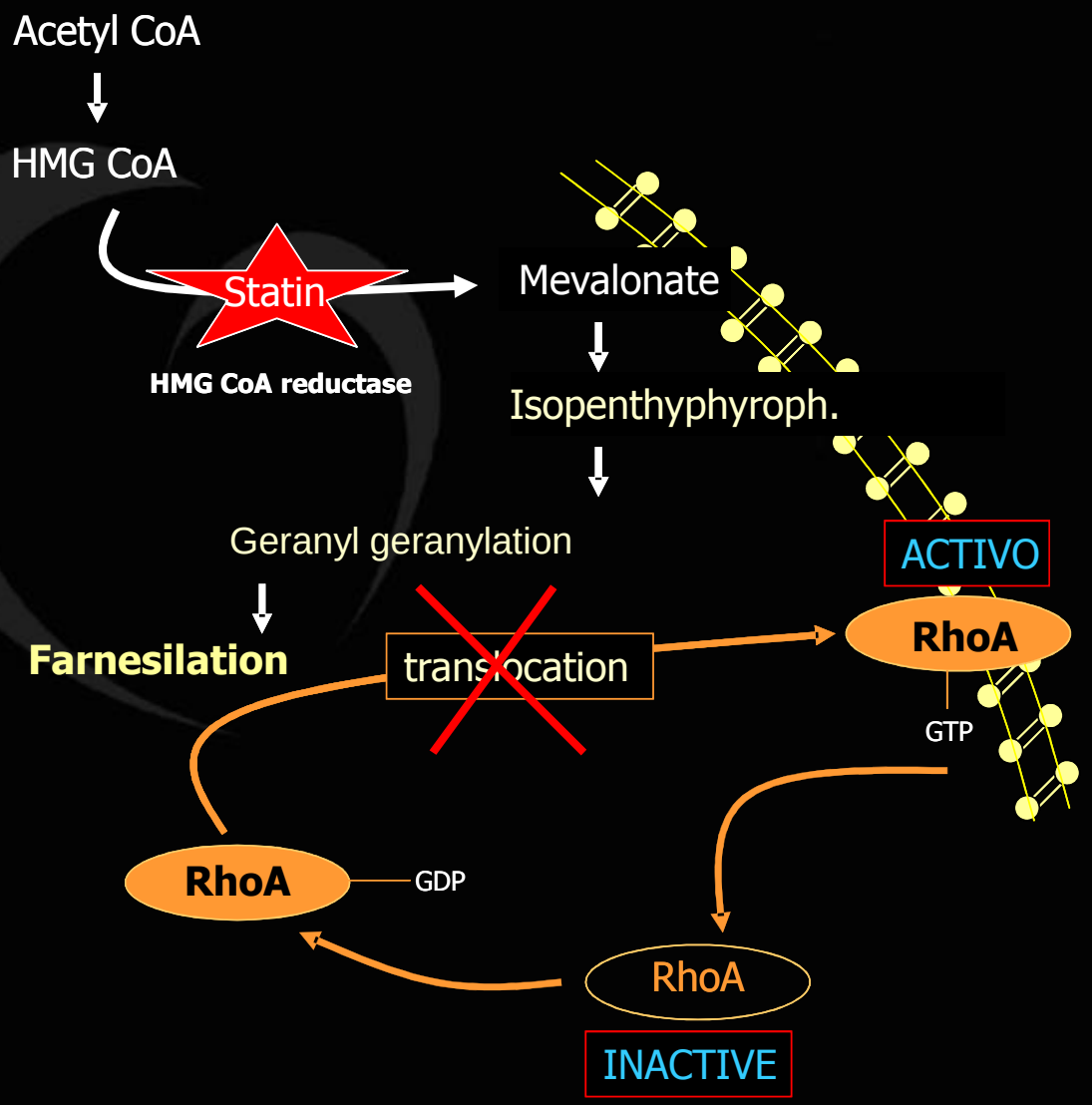


G. Vilahur, et al. Int J Cardiol 2014

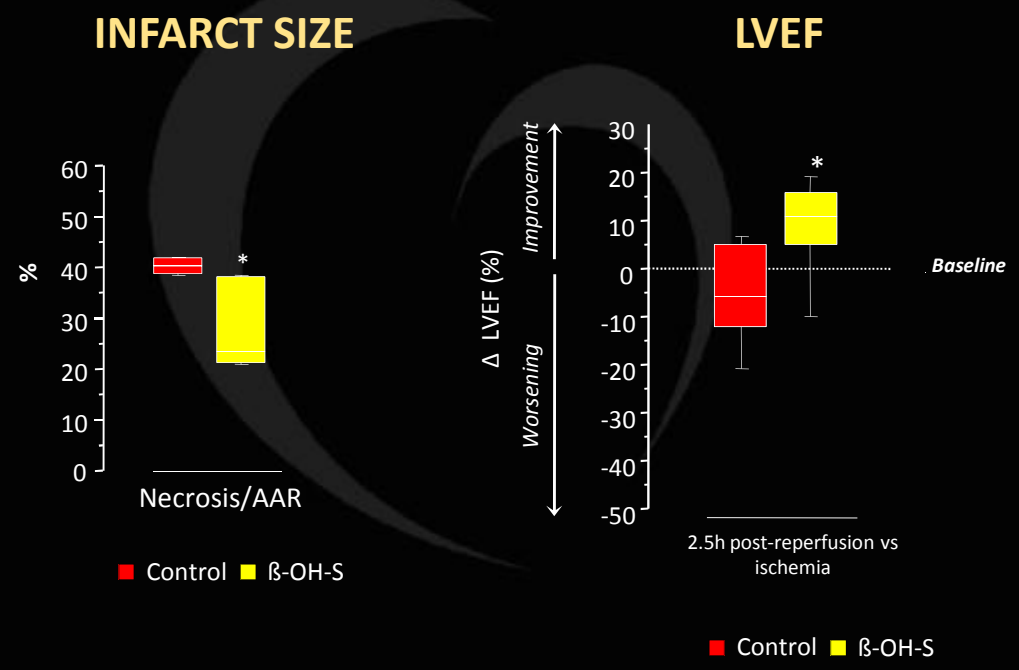
Intravenous statin administration supresses myocardial RhoA activation







Intravenous statin administration reduces infarct size and improves cardiac performance

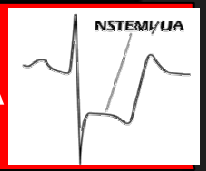


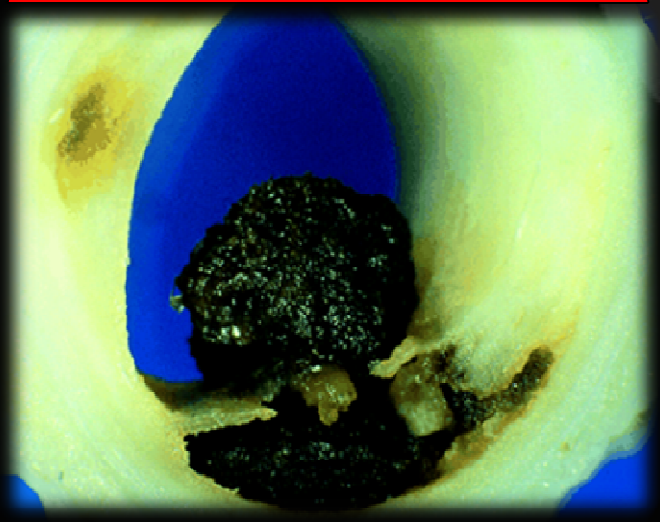
G. Vilahur, et al. Int J Cardiol 2014

Antiplatelet agents

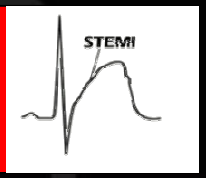
ACS

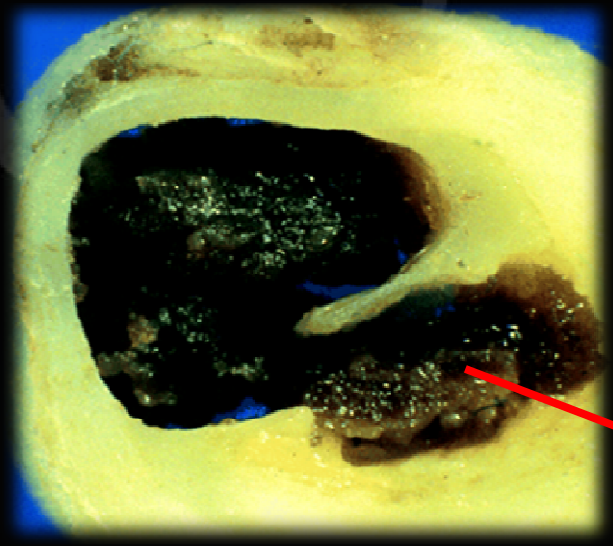
NSTEMI & UA

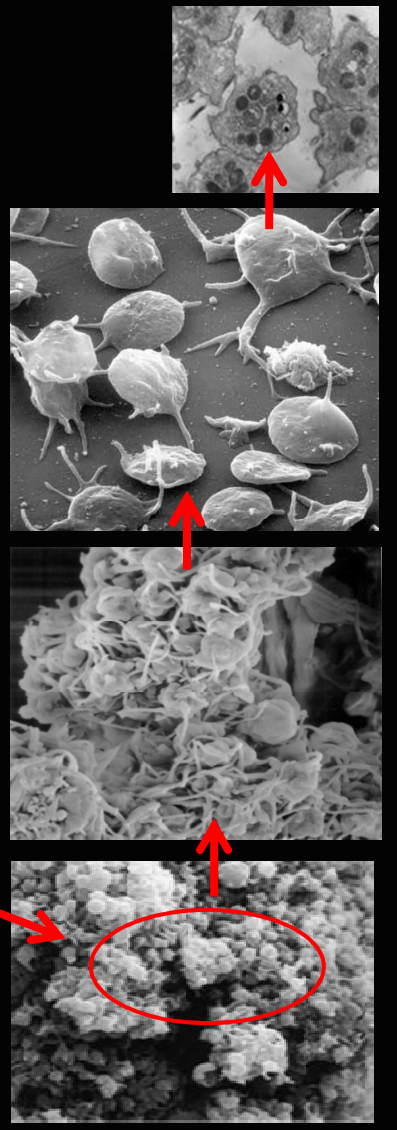




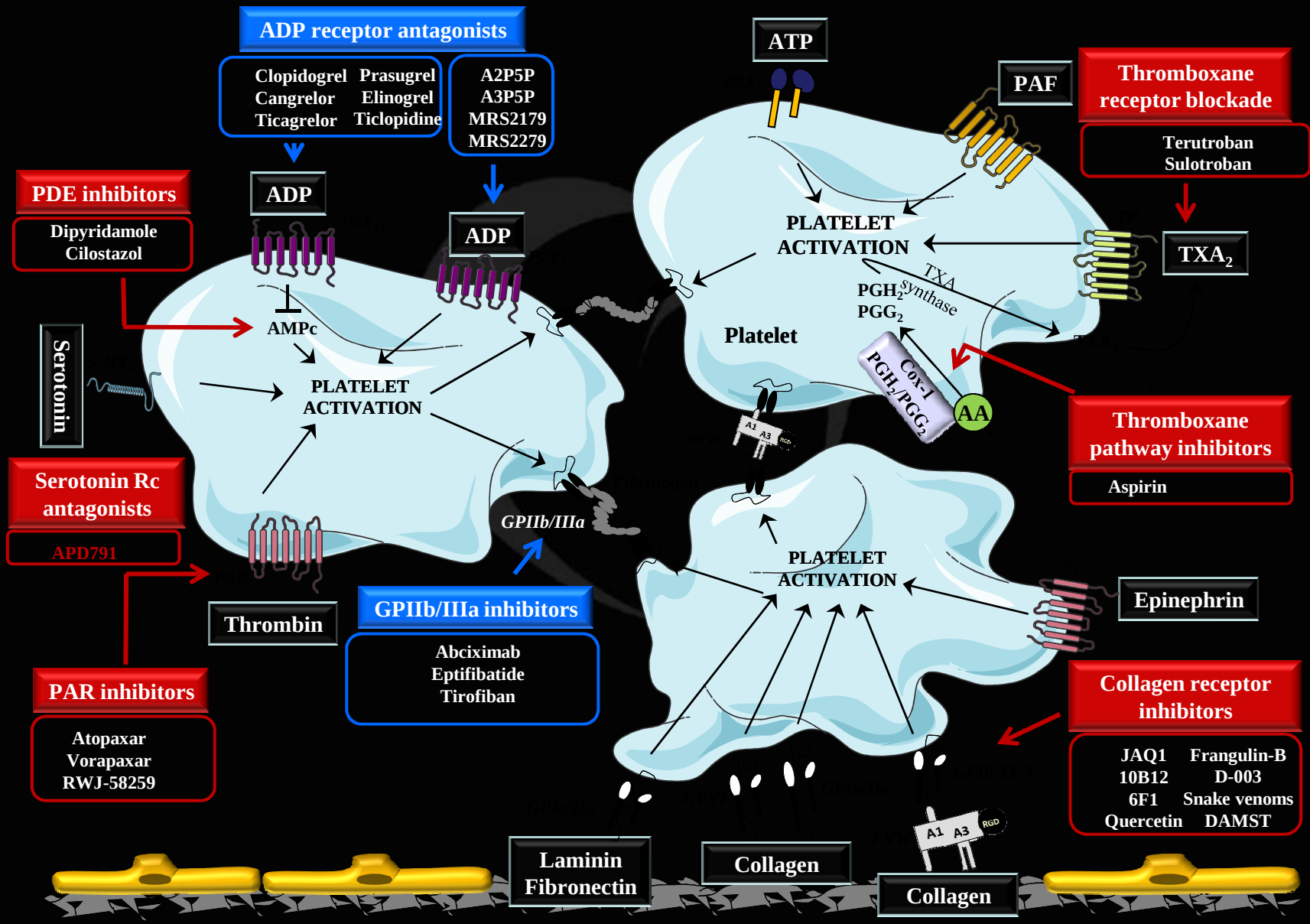
STEMI







Antiplatelet targets



L. Badimon & G. Vilahur Eur Heart J IACC 2014

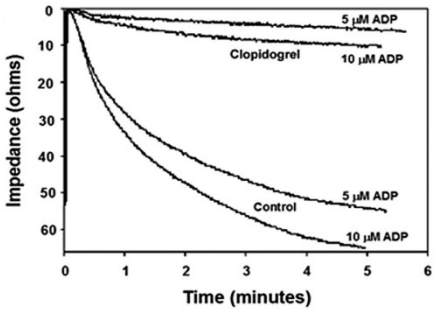
ADP-receptor antagonists: effect on infarct size

30min ischemia
+
3h reperfusion

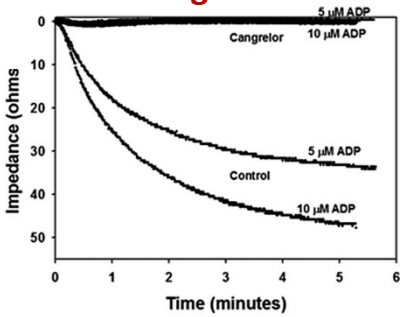
Clopidogrel
Cangrelor
Aspirin

Platelet aggregation

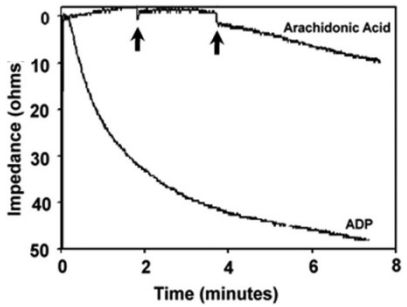
Clopidogrel



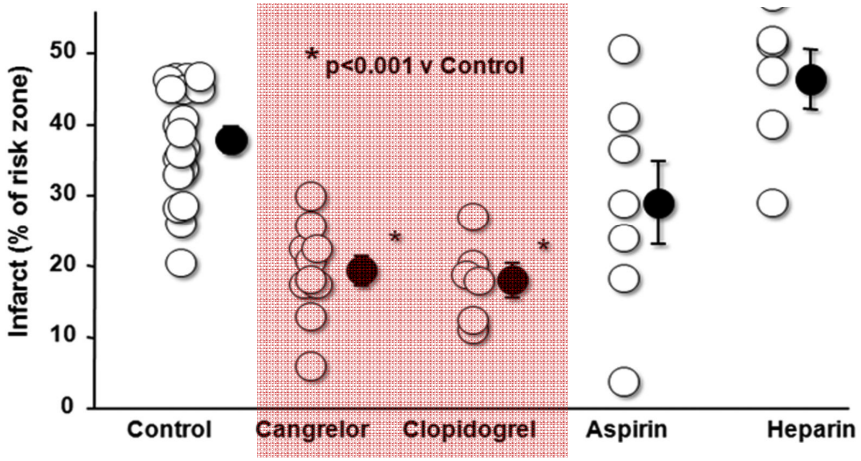
Cangrelor



Aspirin

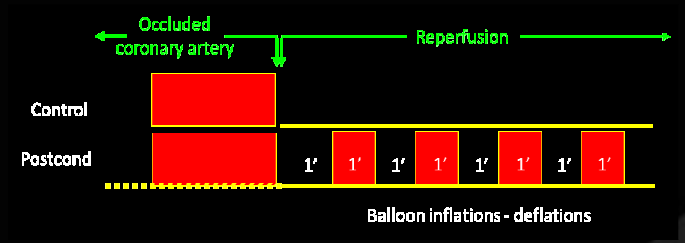


Infarct size

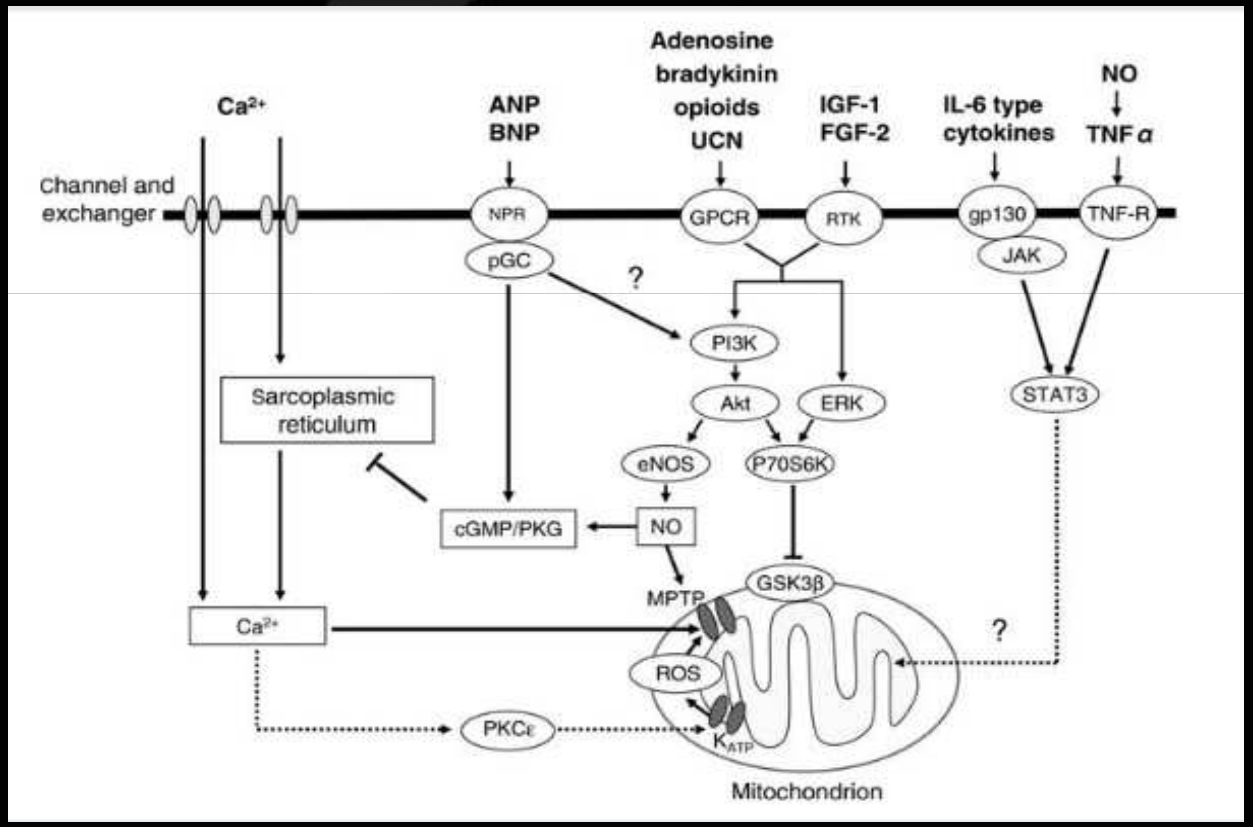


Yang X et al J Cardiovas Pharm & Therap 2013

Mechanisms of action: Ischemic Post-Conditioning



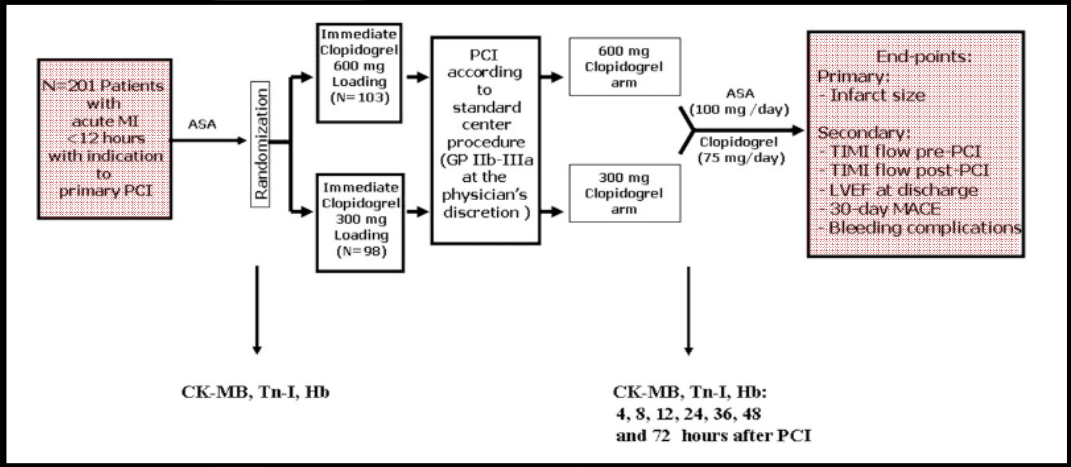
Ovize et al Cardiovasc Res 2010
Hausenloy D. Thrombosis Haemost 2009



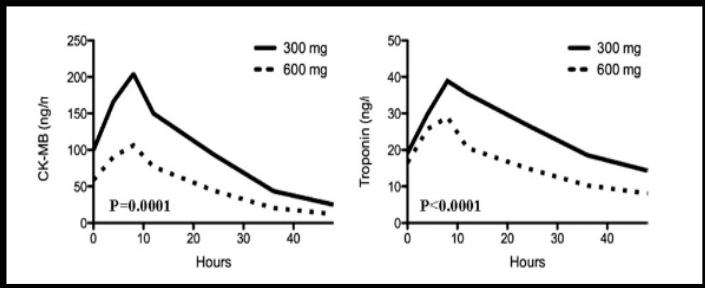
Clinical support…

Clopidogrel - ADP-receptor blockers

Barrabes et al *Thromb & Haemost 2010*
Yang X et al *J Cardiovas Pharm & Therap 2013*
Cohen M et al *Cardiovasc Drug Ther 2016*
Schäfer et al. *Basic Res Cardiol 2011*
Roubille et al. *Basic Res Cardiol 2012*
Patti et al *J Am Col Cardiol 2011 ARMYDA-6-MI*



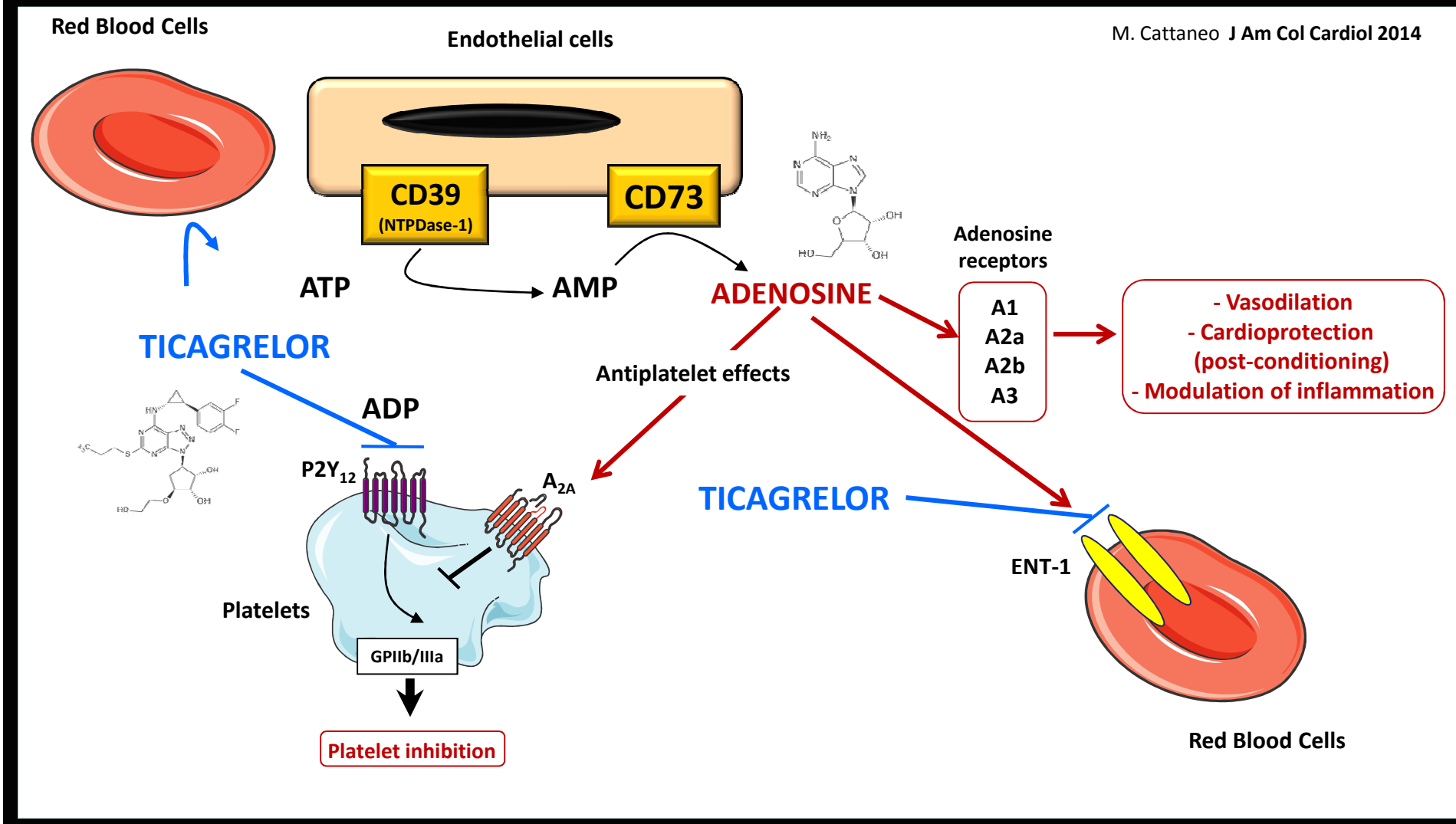
Infarct size – 24h



Potential explanations:

1) Improved coronary patency
2) Improved coronary flow

Effect of ticagrelor on infarct size : adenosine-related effect



Ticagrelor exerts direct cardioprotective effects

G. Vilahur, et al Circulation 2016

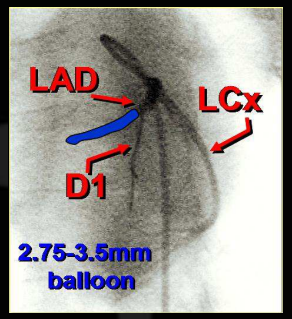
PLACEBO

CLOPIDOGREL
(LD:600mg; MD: 75mg)

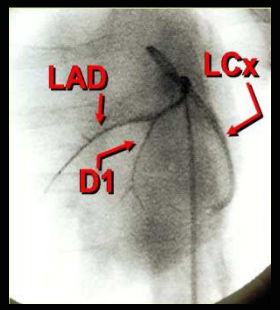
TICAGRELOR
(LD: 180mg; MD: 90 mb bid)

2h/4h

*Experimental pig model of **closed-chest acute MI** induction and reperfusion*

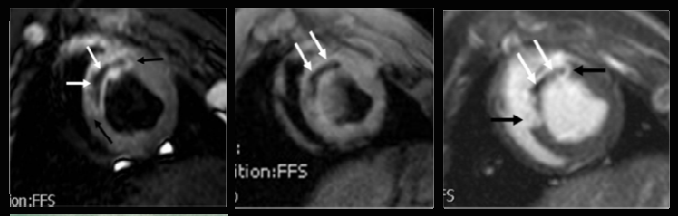


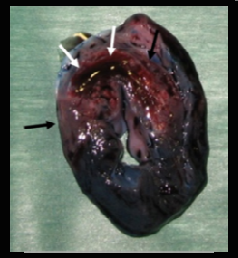
60min

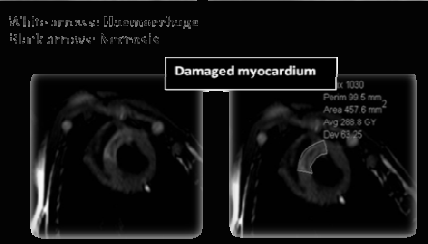


24h

3T - MRI







Outcome

- *Cardiac functional analysis*
- *No-reflow*
- *Necrosis*
- *Edema*

- *Local cardiac effects*
- *Systemic effects*
- *Thrombosis / coagulation*

Ticagrelor reduces infarct size to a greater extent than clopidogrel

CMR analyses	Treatment	*CMR*
LV mass (g)	Non-treated	70.0 [64.1-73.7]
	Clopidogrel	72.2 [69.3-74.7]
	Ticagrelor	70.6 [67.9-74.4]
Edema (g LV)	Non-treated	23.4 [20.9-31.1]
	Clopidogrel	21.6 [19.5-25.2]
	Ticagrelor	16.3 [14.2-19.9]*†
Edema (% LV)	Non-treated	36.2 [33.9-43.2]
	Clopidogrel	30.1 [26.6-34.5]
	Ticagrelor	23.1 [20.2-24.4]*†
Infact mass (g LV)	Non-treated	22.8 [17.3-25.8]
	Clopidogrel	**15.7 [14.2-16.2]***
	Ticagrelor	**12.0 [10.6-12.9]*†**
Necrosis (% LV)	Non-treated	31.1 [25.9-39.1]
	Clopidogrel	**20.9 [19.3-22.8]***
	Ticagrelor	**16.4 [15.5-17.9]*†**
No-reflow (gr LV)	Non-treated	4.6 [2.1-6.0]
	Clopidogrel	2.0 [1.5-2.8]*
	Ticagrelor	2.1 [1.8-3.0]*

	Treatment	*CMR*
Troponin (ng/mL)	Non-treated	19 [16.5-21.7]
	Clopidogrel	**13.4 [13.0-14.0]***
	Ticagrelor	**10.9 [9.3-11.4]*†**

	Treatment	*CMR*
LVEF (%)	Non-treated	43.0 [42.0-43.6]
	Clopidogrel	**47.2 [45.4-48.2] ***
	Ticagrelor	**47.2 [45.4-51.0]***
LVEDV (mL)	Non-treated	93.0 [87.6-98.1]
	Clopidogrel	**73.7 [68.9-81.3]***
	Ticagrelor	**77.4 [71.8-89.2]***
LVESV (mL)	Non-treated	54.0 [49.2-55.6]
	Clopidogrel	**39.5 [36.3-41.9]***
	Ticagrelor	**39.2 [37.3-46.0]***

* p<0.05 vs placebo-control animals
† p<0.05 vs clopidogrel-treated animals

G. Vilahur, et al Circulation 2016

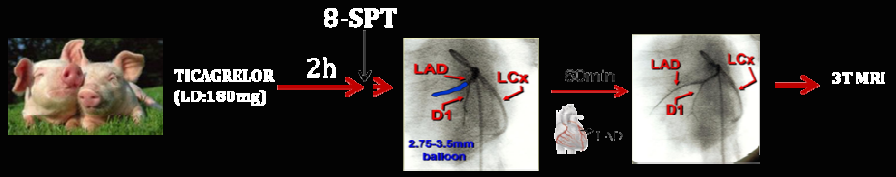
Ticagrelor reduces infarct size to a greater extent than clopidogrel and edema formation post-MI

CMR analyses	Treatment	*CMR*
LV mass (g)	Non-treated	70.0 [64.1-73.7]
	Clopidogrel	72.2 [69.3-74.7]
	Ticagrelor	70.6 [67.9-74.4]
Edema (g LV)	Non-treated	23.4 [20.9-31.1]
	Clopidogrel	21.6 [19.5-25.2]
	Ticagrelor	**16.3 [14.2-19.9]*†**
Edema (% LV)	Non-treated	36.2 [33.9-43.2]
	Clopidogrel	30.1 [26.6-34.5]
	Ticagrelor	**23.1 [20.2-24.4]*†**
Infact mass (g LV)	Non-treated	22.8 [17.3-25.8]
	Clopidogrel	15.7 [14.2-16.2]*
	Ticagrelor	12.0 [10.6-12.9]*†
Necrosis (% LV)	Non-treated	31.1 [25.9-39.1]
	Clopidogrel	20.9 [19.3-22.8]*
	Ticagrelor	16.4 [15.5-17.9]*†
No-reflow (gr LV)	Non-treated	4.6 [2.1-6.0]
	Clopidogrel	2.0 [1.5-2.8]*
	Ticagrelor	2.1 [1.8-3.0]*

	Treatment	*CMR*
Troponin (ng/mL)	Non-treated	19 [16.5-21.7]
	Clopidogrel	13.4 [13.0-14.0]*
	Ticagrelor	10.9 [9.3-11.4]*†

	Treatment	*CMR*
LVEF (%)	Non-treated	43.0 [42.0-43.6]
	Clopidogrel	**47.2 [45.4-48.2] ***
	Ticagrelor	**47.2 [45.4-51.0]***
LVEDV (mL)	Non-treated	93.0 [87.6-98.1]
	Clopidogrel	**73.7 [68.9-81.3]***
	Ticagrelor	**77.4 [71.8-89.2]***
LVESV (mL)	Non-treated	54.0 [49.2-55.6]
	Clopidogrel	**39.5 [36.3-41.9]***
	Ticagrelor	**39.2 [37.3-46.0]***

* p<0.05 vs placebo-control animals
† p<0.05 vs clopidogrel-treated animals



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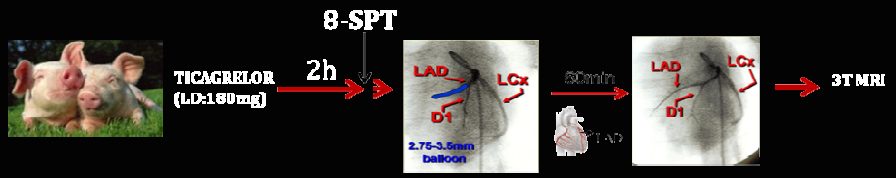
Ticagrelor reduces infarct size via adenosine-dependent mechanisms

CMR analyses	Treatment	*CMR*
LV mass (g)	Non-treated	70.0 [64.1-73.7]
	Clopidogrel	72.2 [69.3-74.7]
	Ticagrelor	70.6 [67.9-74.4]
	Ticagrelor+8SPT	66.5 [65.0-70.2]
Edema (g LV)	Non-treated	23.4 [20.9-31.1]
	Clopidogrel	21.6 [19.5-25.2]
	Ticagrelor	16.3 [14.2-19.9]*†
	Ticagrelor+8SPT	**24.6 [22.8-25.3]**
Edema (% LV)	Non-treated	36.2 [33.9-43.2]
	Clopidogrel	30.1 [26.6-34.5]
	Ticagrelor	23.1 [20.2-24.4]*†
	Ticagrelor+8SPT	**36.8 [33.6-39.4]**
Infact mass (g LV)	Non-treated	22.8 [17.3-25.8]
	Clopidogrel	15.7 [14.2-16.2]*
	Ticagrelor	12.0 [10.6-12.9]*†
	Ticagrelor+8SPT	**14.9 [14.6-16.1]***
Necrosis (% LV)	Non-treated	31.1 [25.9-39.1]
	Clopidogrel	20.9 [19.3-22.8]*
	Ticagrelor	16.4 [15.5-17.9]*†
	Ticagrelor+8SPT	**22.4 [21.8-23.9]***
No-reflow (gr LV)	Non-treated	4.6 [2.1-6.0]
	Clopidogrel	2.0 [1.5-2.8]*
	Ticagrelor	2.1 [1.8-3.0]*
	Ticagrelor+8SPT	2.2 [2.0-2.6]*

	Treatment	*CMR*
Troponin (ng/mL)	Non-treated	19 [16.5-21.7]
	Clopidogrel	13.4 [13.0-14.0]*
	Ticagrelor	10.9 [9.3-11.4]*†
	Ticagrelor+8SPT	**14.2 [12.2-16.1]***

	Treatment	*CMR*
LVEF (%)	Non-treated	43.0 [42.0-43.6]
	Clopidogrel	**47.2 [45.4-48.2] ***
	Ticagrelor	**47.2 [45.4-51.0]***
	Ticagrelor+8SPT	48.7 [46.6-51.0]*
LVEDV (mL)	Non-treated	93.0 [87.6-98.1]
	Clopidogrel	**73.7 [68.9-81.3]***
	Ticagrelor	**77.4 [71.8-89.2]***
	Ticagrelor+8SPT	84.4 [76.9-86.8]*
LVESV (mL)	Non-treated	54.0 [49.2-55.6]
	Clopidogrel	**39.5 [36.3-41.9]***
	Ticagrelor	**39.2 [37.3-46.0]***
	Ticagrelor+8SPT	44.2 [40.4-45.7]*

* p<0.05 vs placebo-control animals
† p<0.05 vs clopidogrel-treated animals



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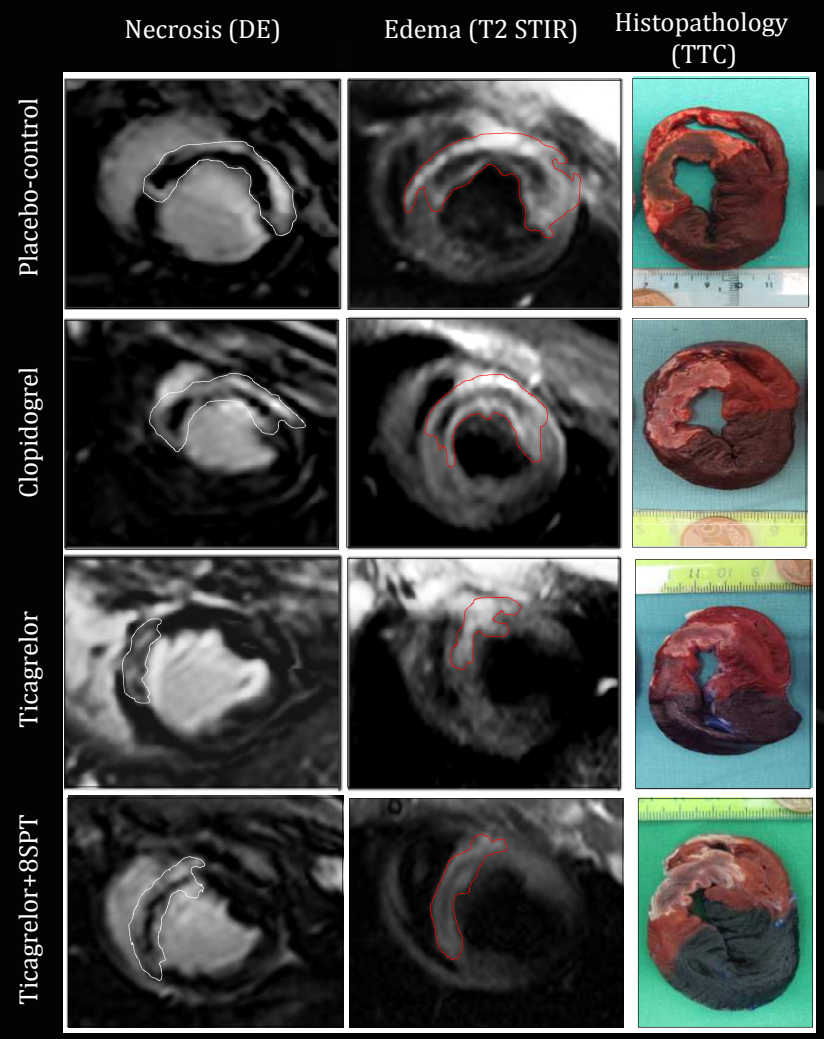
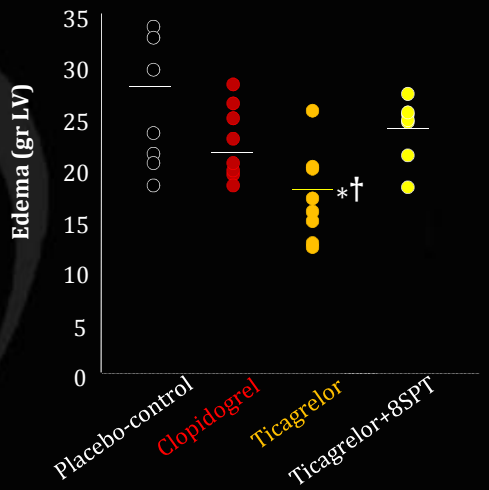
Edema reduction





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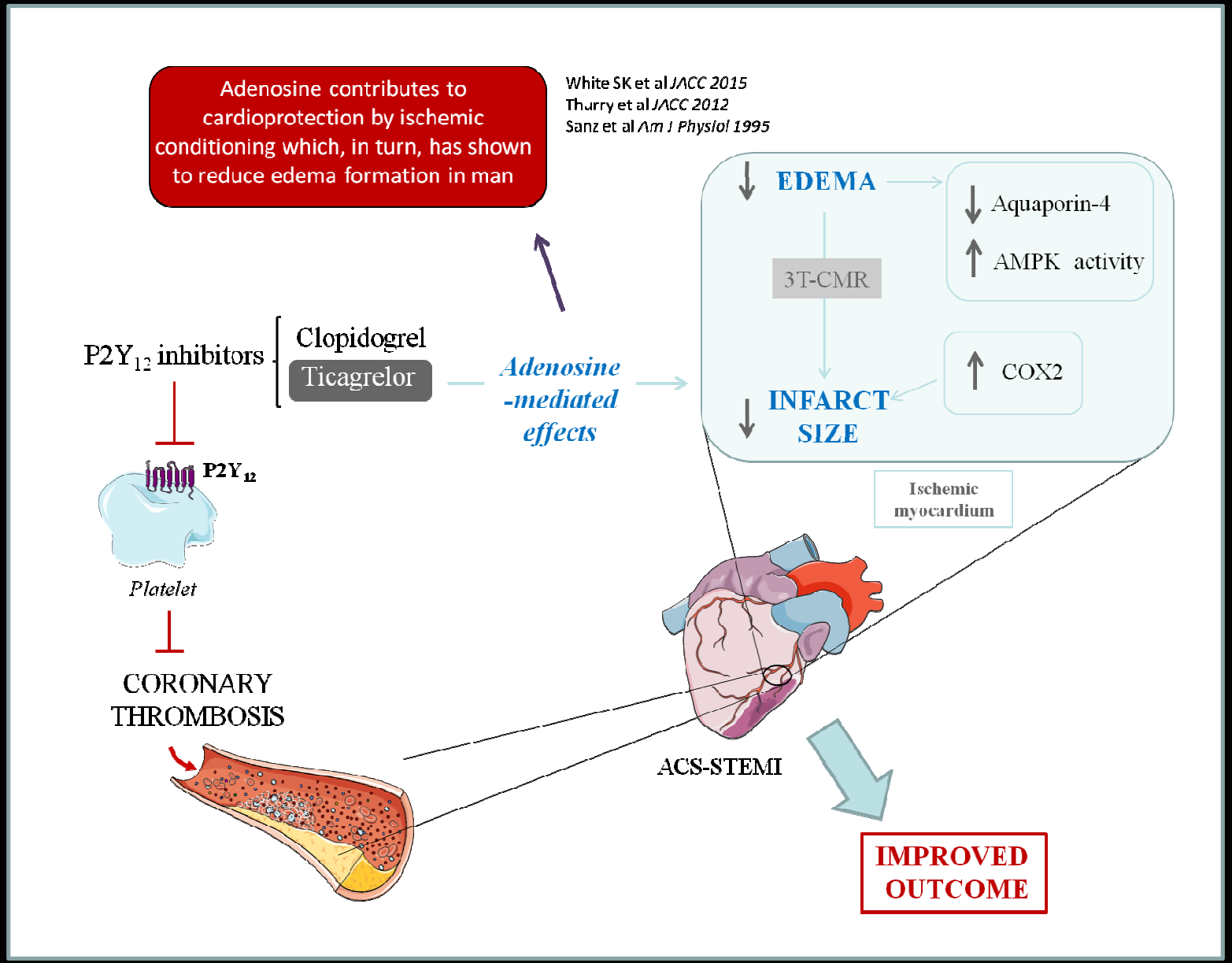
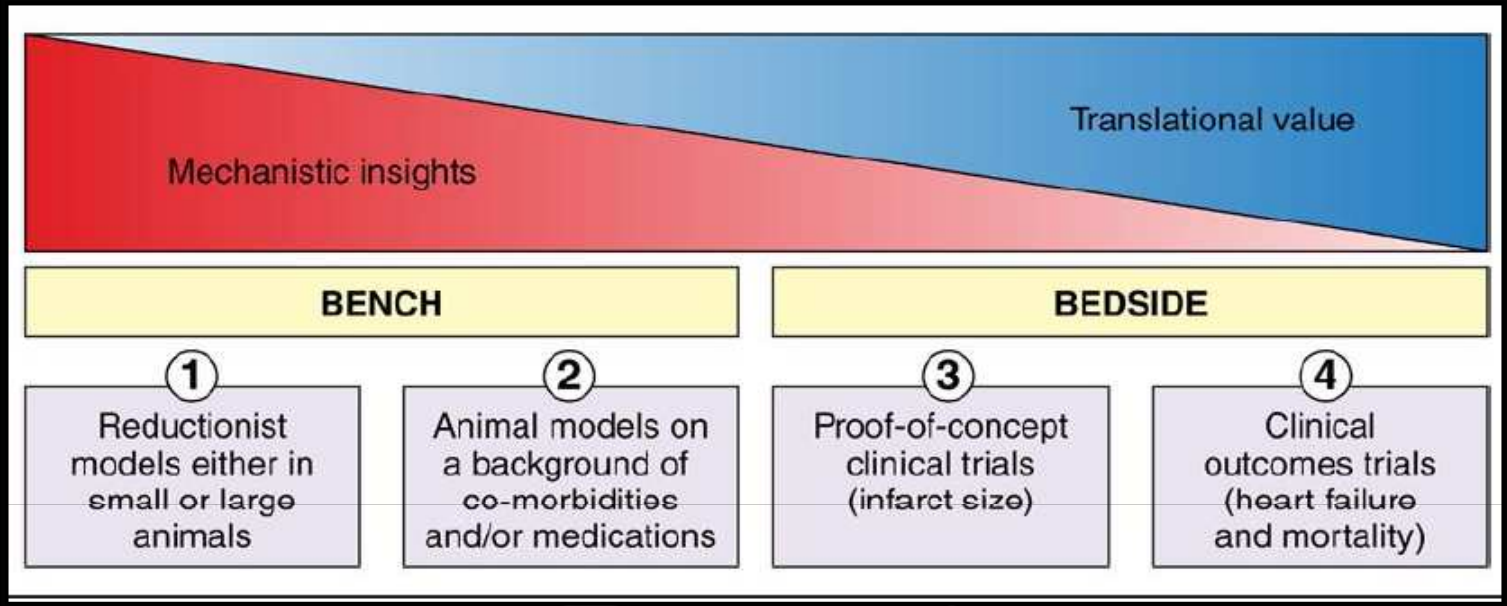


TAKE HOME MESSAGE: Opportunities and Challenge to successfully translate cardioprotection



Networks and procedures in analogy

Selection of agents with consistent preclinical/experimental data

Peform Phase II dose-finding studies

Selecting the optimal patient

Heush et al *Circulation Res 2017*

X. Rosselo & D. Yellon *Circulation 2016*

ICCC sant pau HOSPITAL DE LA SANTA CREU I SANT PAU UNIVERSITAT AUTÒNOMA DE BARCELONA CSIC CONSEJO SUPERIOR DE INVESTIGACIONES CIENTÍFICAS UAB Universitat Autònoma de Barcelona

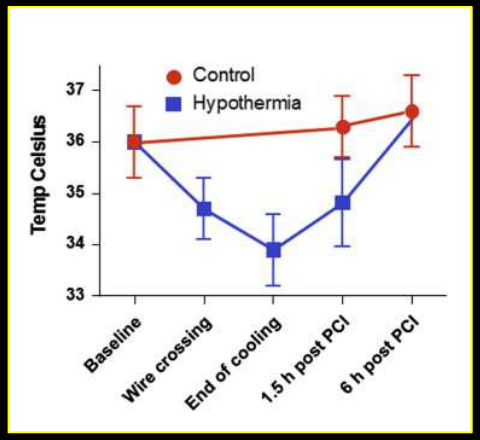
Therapies that show promise… mild hypothermia

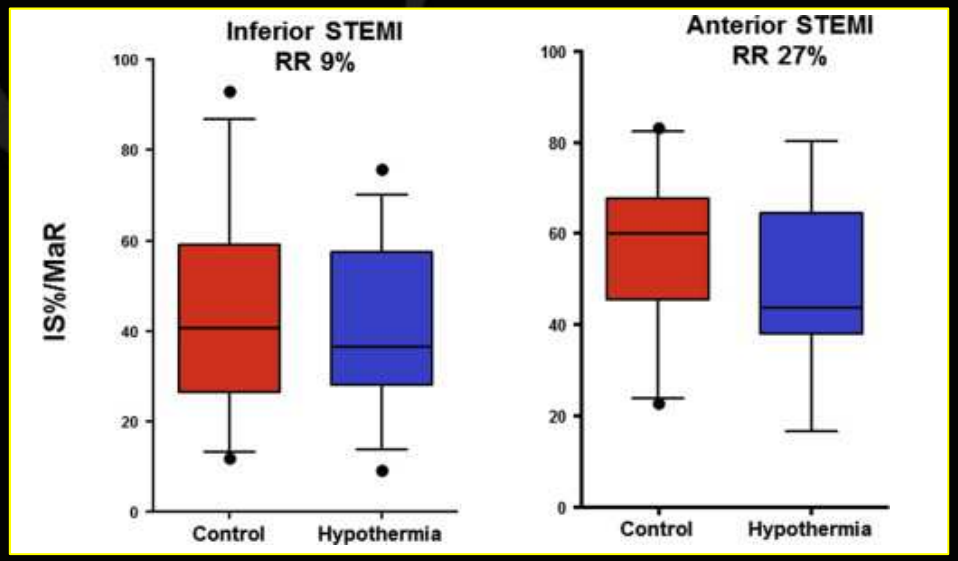
Severe hypothermia (20º C-28º C)
Moderate hypothermia (28º C-32º C) — Metabolic slowing

Mild hypothermia (32º C-35º C) — Erk activation (RISK)

Hale et al J Cardiovas Pharmacol 2011 *Tissier et al Basic Res Cardiol 2010* *Yang et al Basic Res Cardiol 2011*

The CHILL-MI Trial

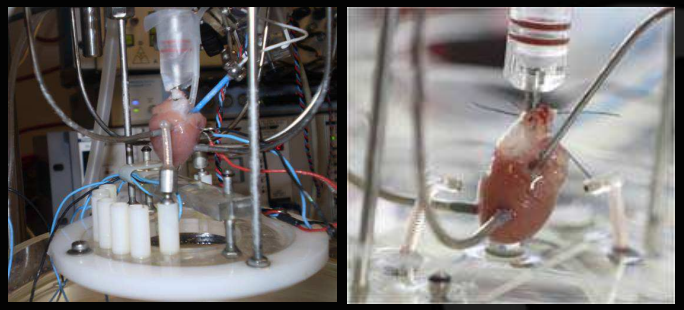


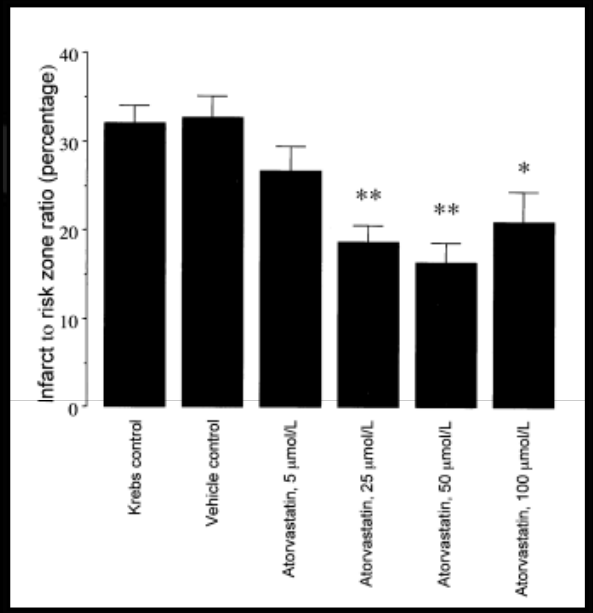


D. Erlinge et al JACC 2014

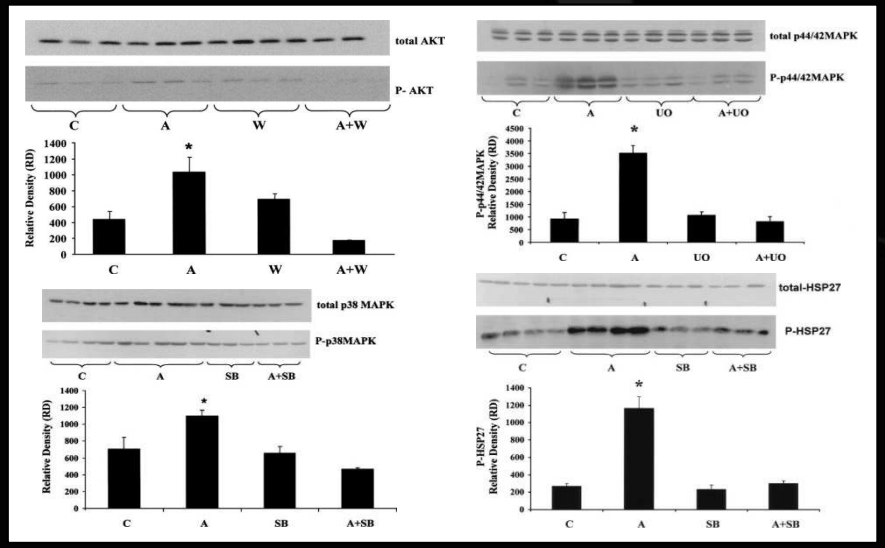
Atorvastatin, given at reperfusion, attenuates reperfusion injury *ex vivo* through multiple prosurvival signaling

30min global ischemia + 30 min resperfusion





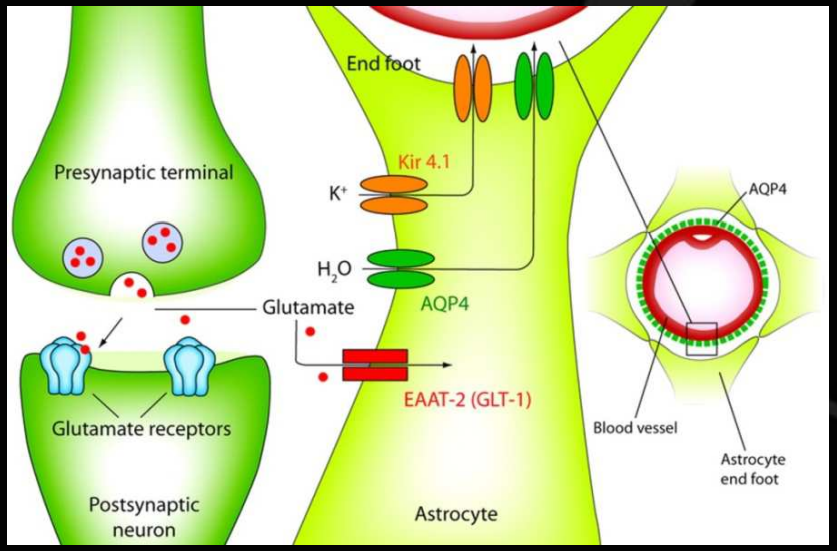
Bell & Yellon, *J Am Col Cardiol 2003*



Efthymiou,C et al *Journal of Cardiovascular Pharmacology. 2005*

Molecular analysis related to myocardial edema formation: AQUAPORIN-4

Aquaporin proteins are transmembrane channels critically involved in cellular water balance closely related to edema



Aquaporin-4 (AQP-4)?

Aquaporin-4 is responsible or cerebral ischemia (Yao et al 2014)

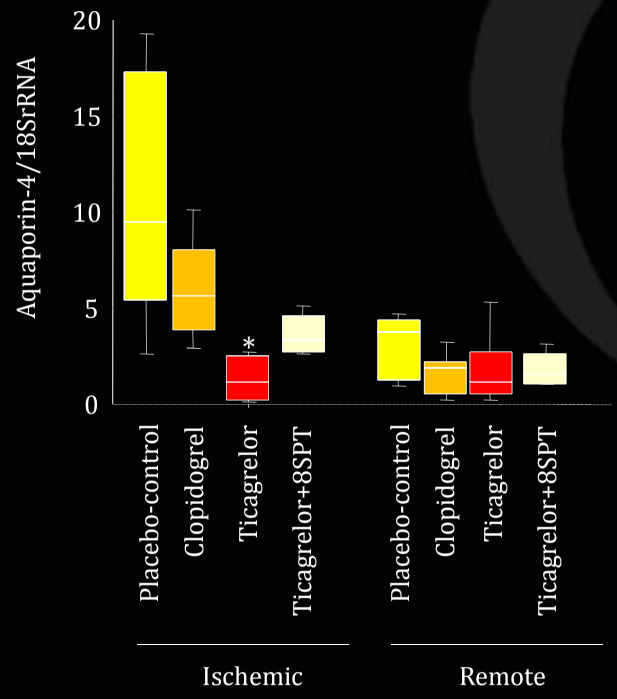
Aquaporin-4 increases after myocardial ischemia and is involved in myocyte swelling and infarct size (Rutkovskiy A et al 2012; Warth et al 2007)

Adenosine signaling regulates aquaporin-4 expression (Lee et al 2013)

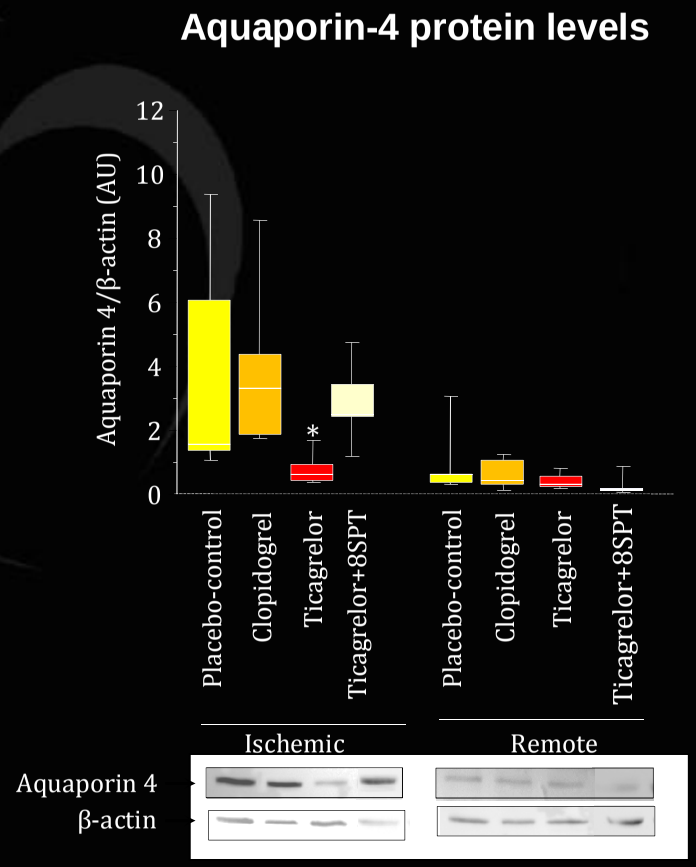
Aquaporin-4 expression is found to be reduced in ENT-$1^{-/-}$ mice (Hinton et al 2014)

Ticagrelor reduces aquaporin-4 transcription and protein expression

Aquaporin-4 mRNA



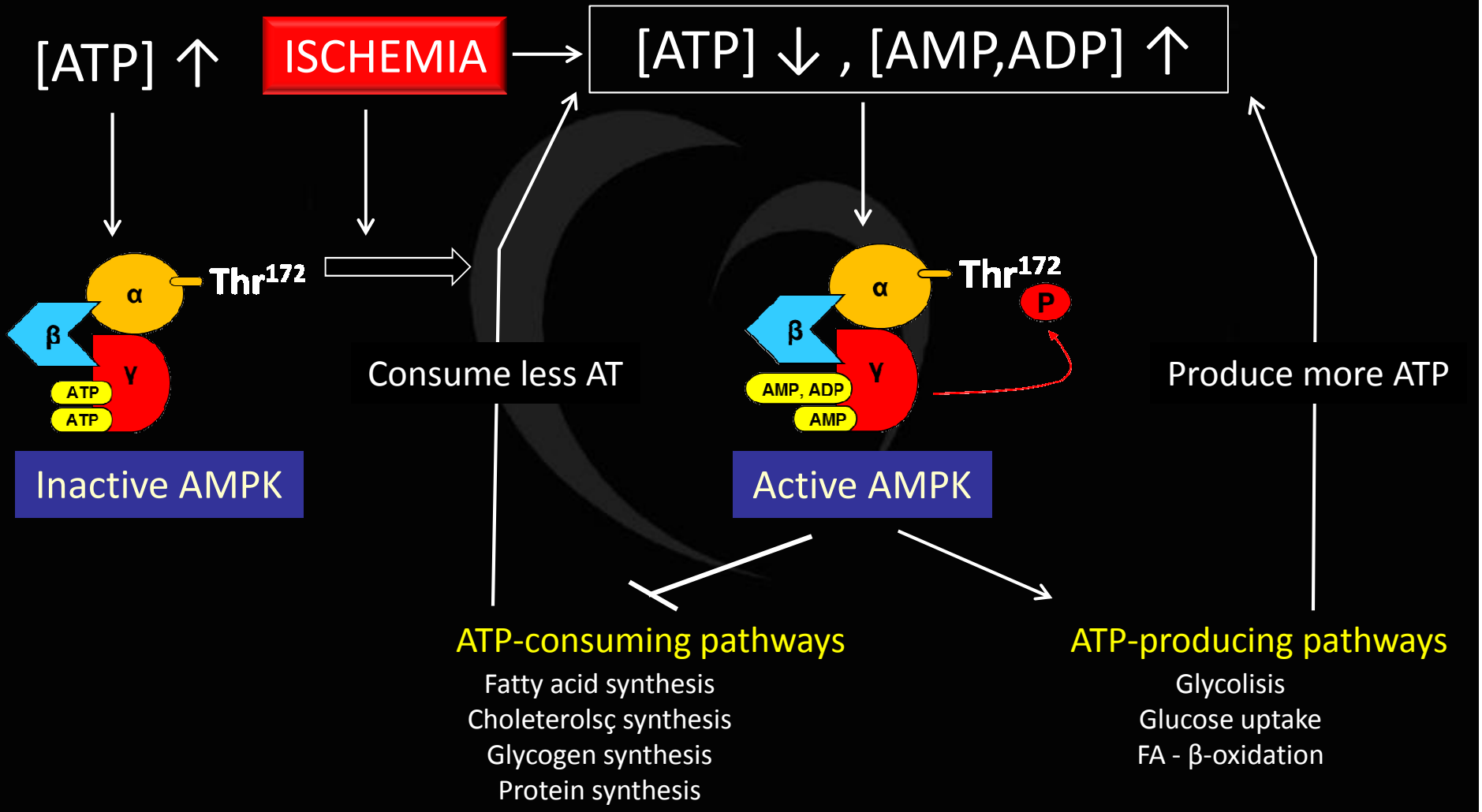
Aquaporin-4 protein levels



G. Vilahur, et al Circulation 2016

AMPK: a critical component of myocardial metabolism

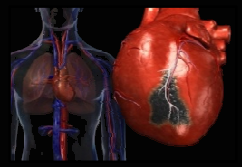
Neubauer S. *N Engl J Med 2007*



AMPK exerts cardioprotective properties

G. Heusch *Circulation Research 2015*

Ischemia-reperfusion



AMPK → K_{ATP}

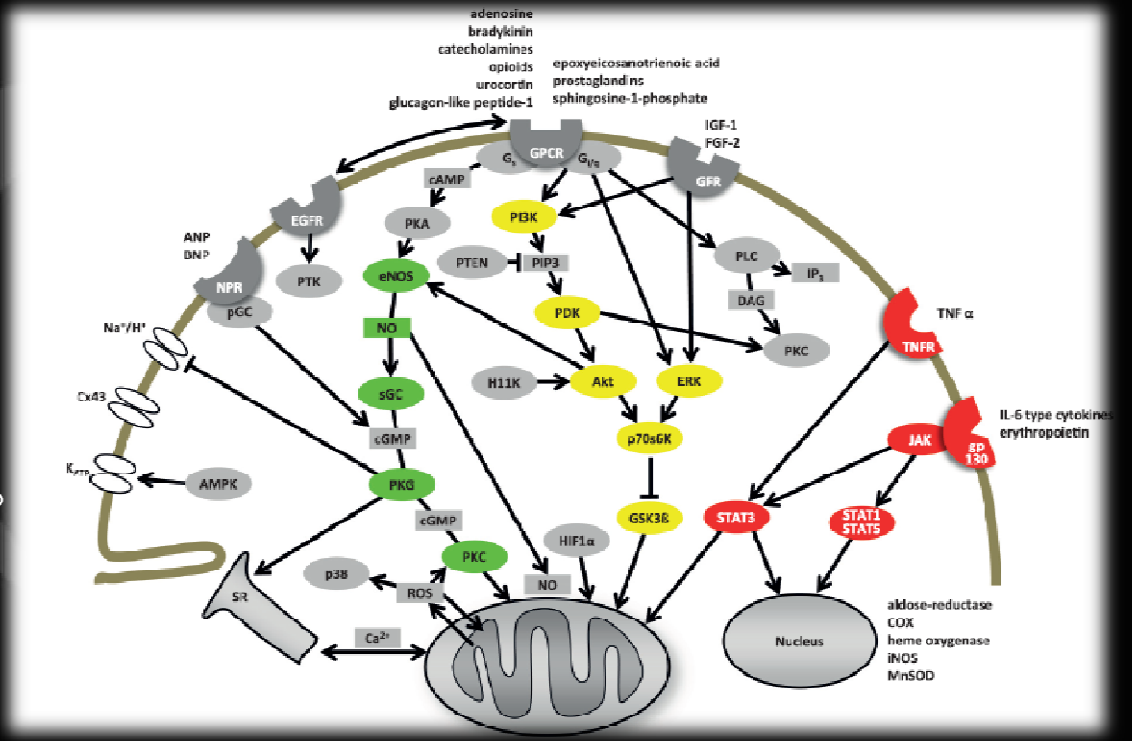
AMPK → eNOS

AMPK ⊣ ER Stress

AMPK ⊣ mPTP opening

AMPK ⊣ ROS production

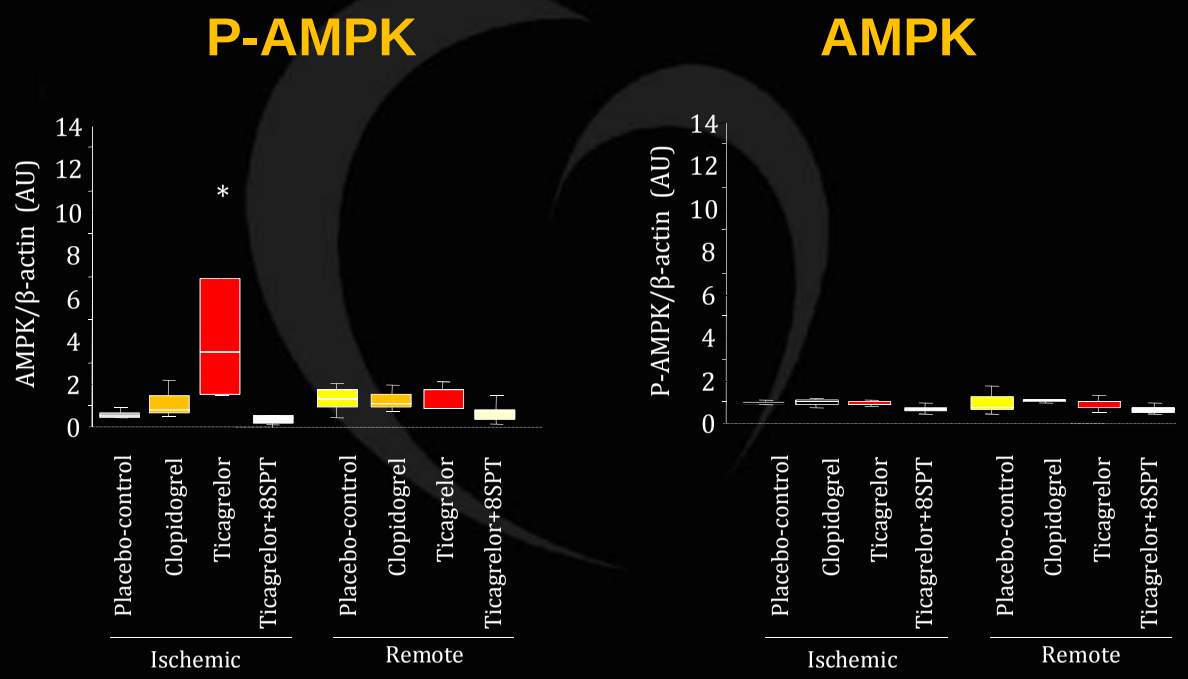
Cardioprotective signal transduction in conditioning



Castanares-Zapatero D et al. 2013

AMPK$^{-/-}$ mice: AMPK prevents ventricular edema formation

Ticagrelor increases AMPK signaling activation



G. Vilahur, et al Circulation 2016