

JUSTUS-LIEBIG-



UNIVERSITÄT  
GIESSEN

Physiologisches Institut



## Ischemia and Reperfusion: Pharmacological treatment options

Prof. Dr. Rainer Schulz



PROMISE  
IRTG  
GIESSEN  
BARCELONA



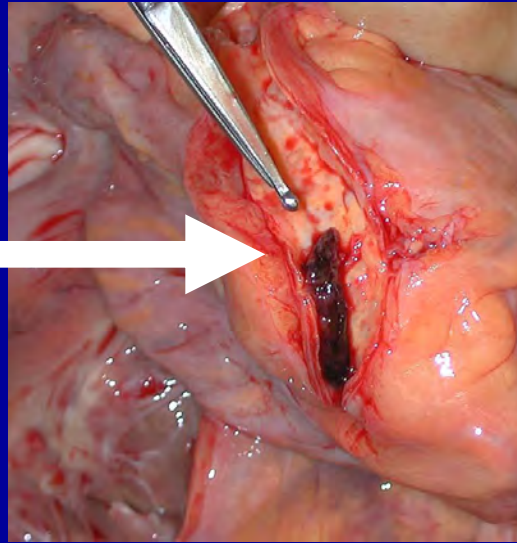
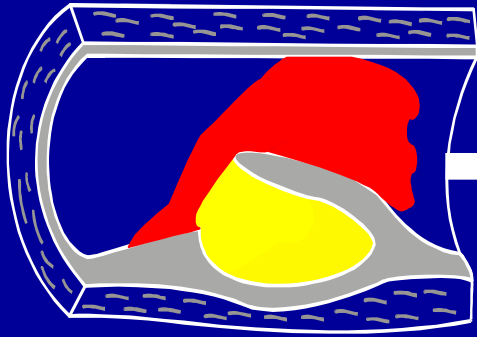
UGCVR  
UNIVERSITY  
OF GIESSEN  
CARDIOVASCULAR  
RESEARCH CENTER



# Plaque rupture and myocardial ischemia



Acute plaque rupture  
(Stary VI)



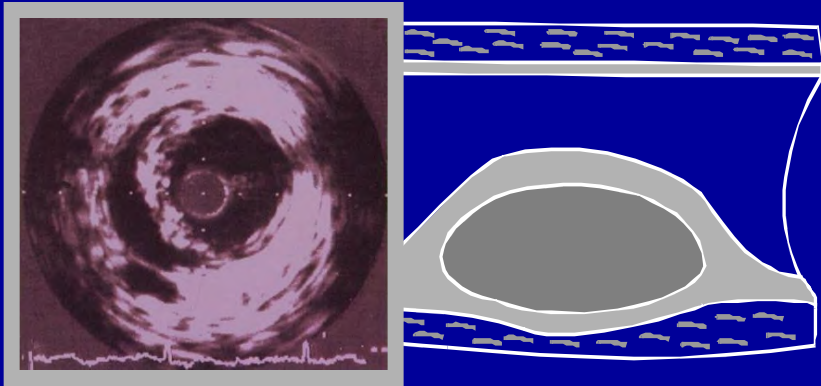
Ischemic myocardium  
(ACS, NSTEMI, STEMI)



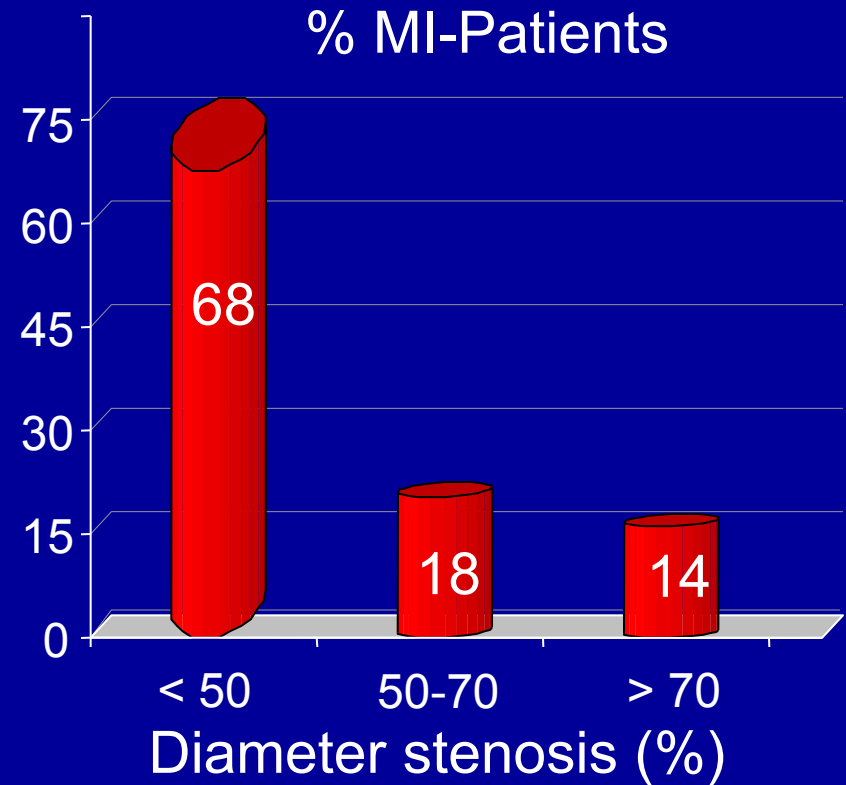
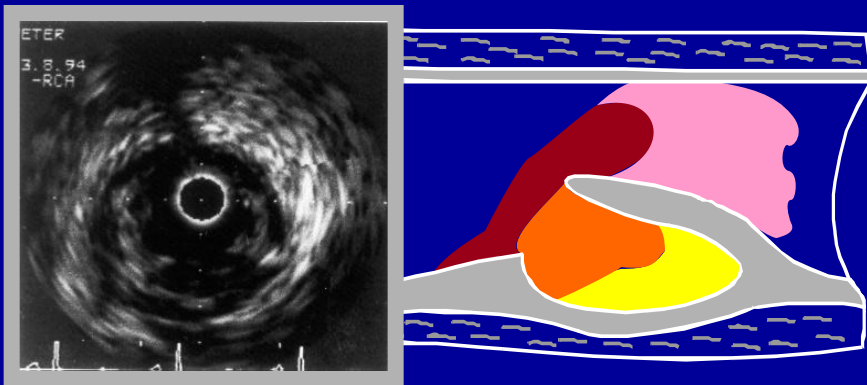
# Plaque ruptur and thrombosis



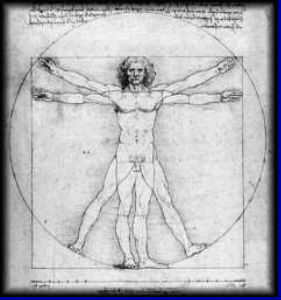
## Stable plaque



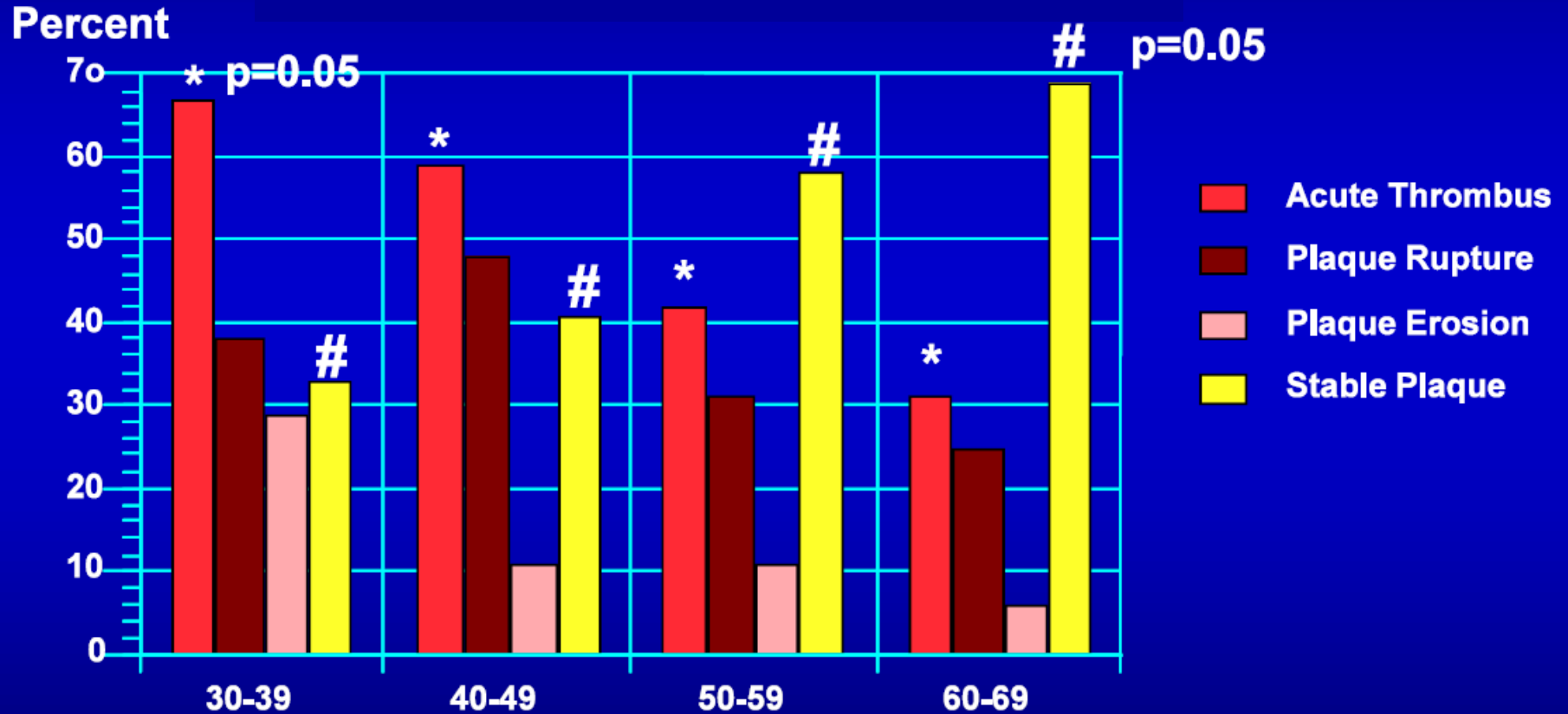
## Unstable plaque, plaque ruptur

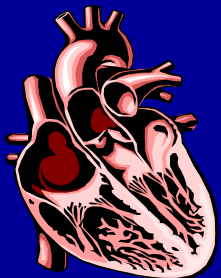


Falk et al., Circulation 92: 657-671, 1995

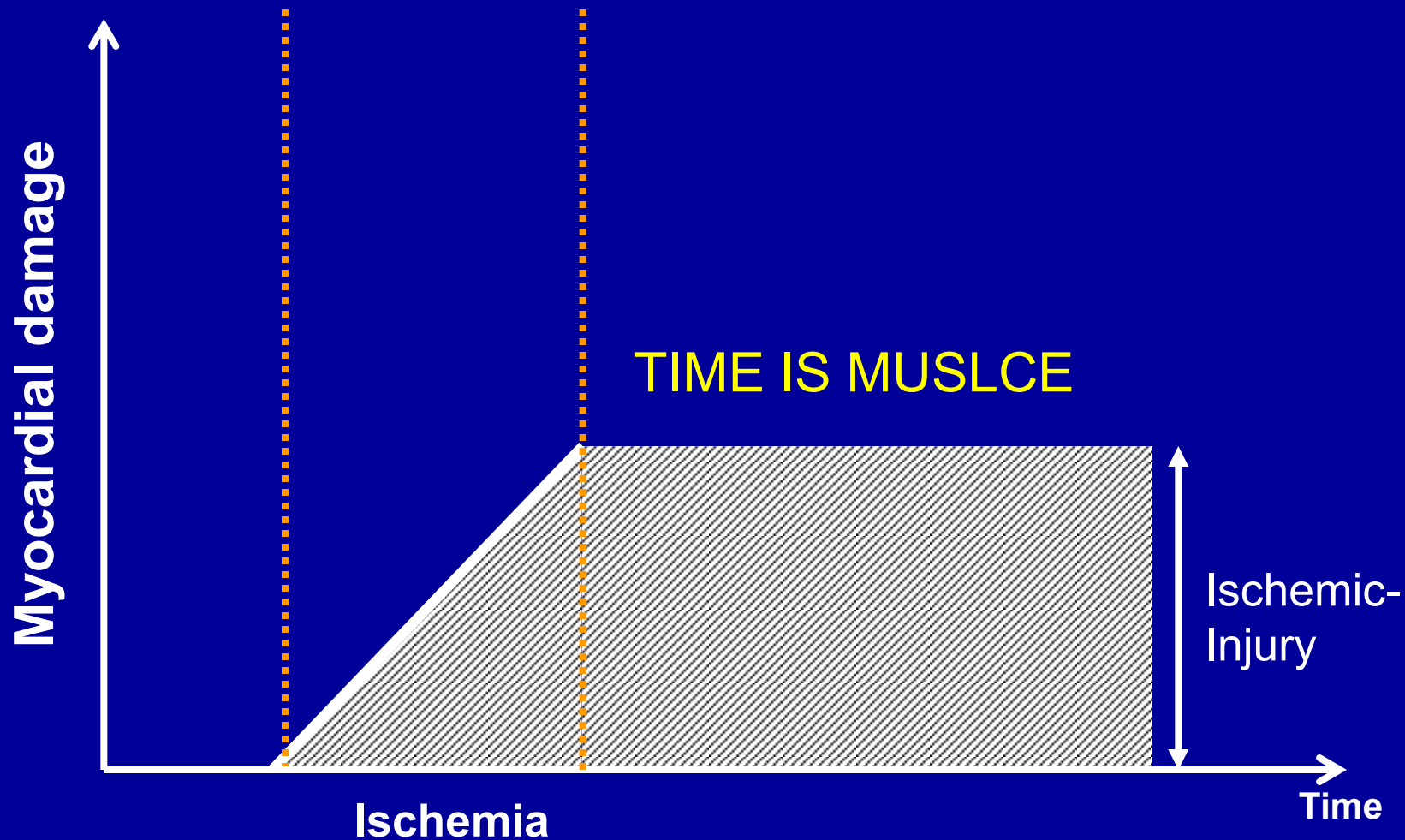


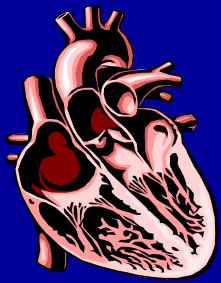
# Aging and plaque ruptur





# Ischemic injury



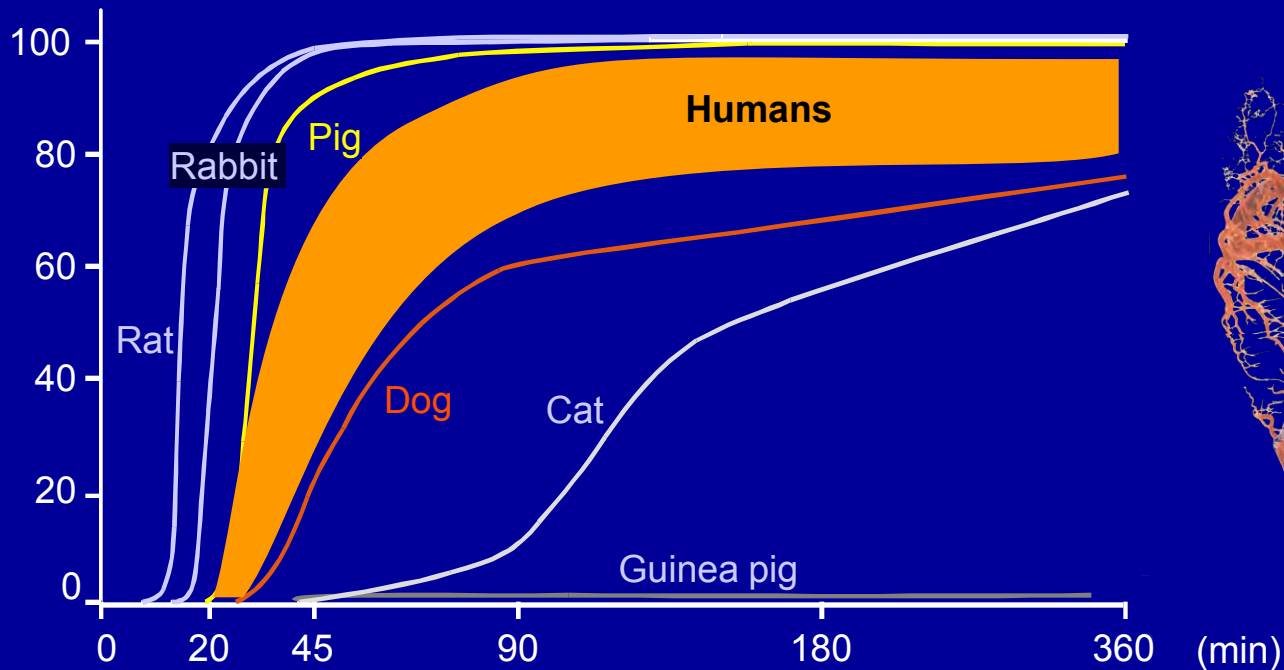


# Ischemia-reperfusion injury



## Ischemia

Infarct size  
(% area at risk)



Extent of collaterals



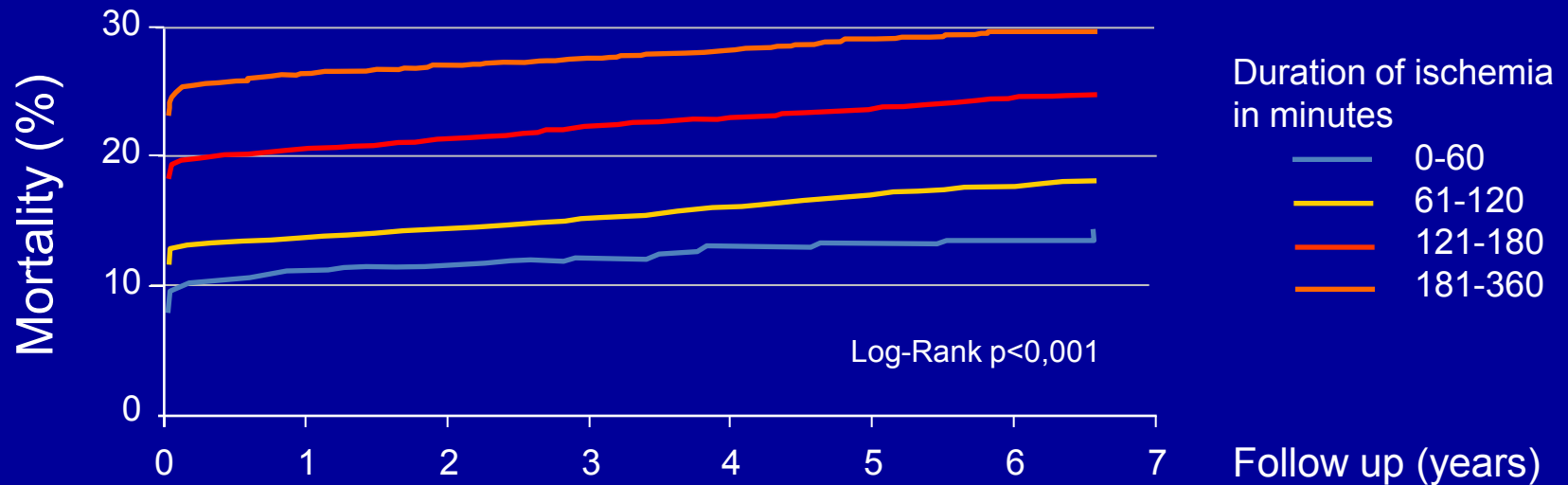


CHD

# Duration of ischemia and mortality

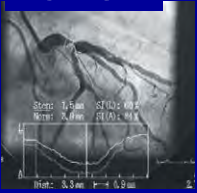


Cumulative mortality (Kaplan-Meier) in patients with STEMI and PCI (n=6.209)



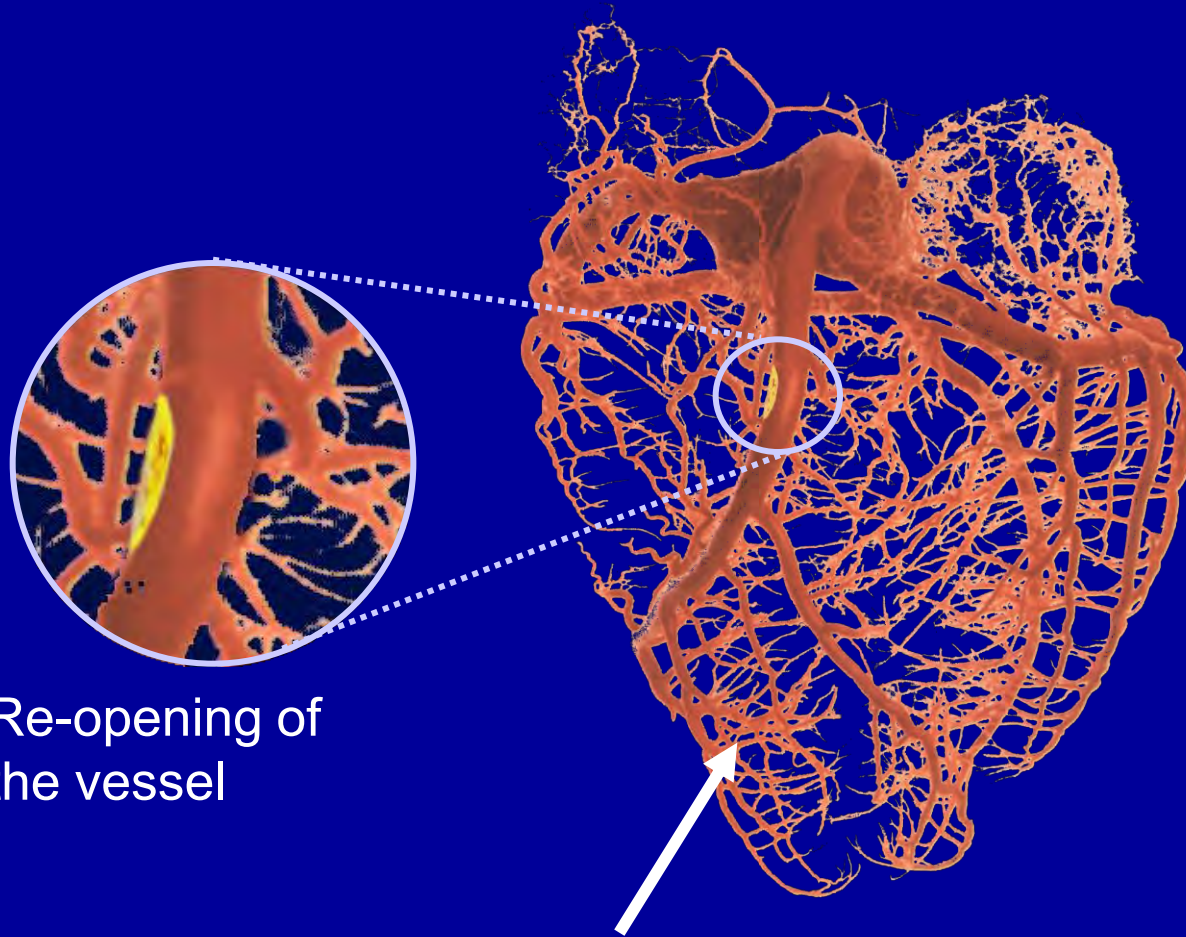
0-60	347	311	278	230	192	138	87
61-120	2643	2339	1906	1420	1006	667	375
121-180	2092	1836	1503	1183	843	533	278
181-360	1127	923	765	647	491	332	172

Patient



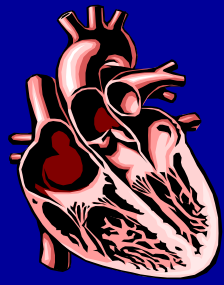
CHD

# Reperfusion

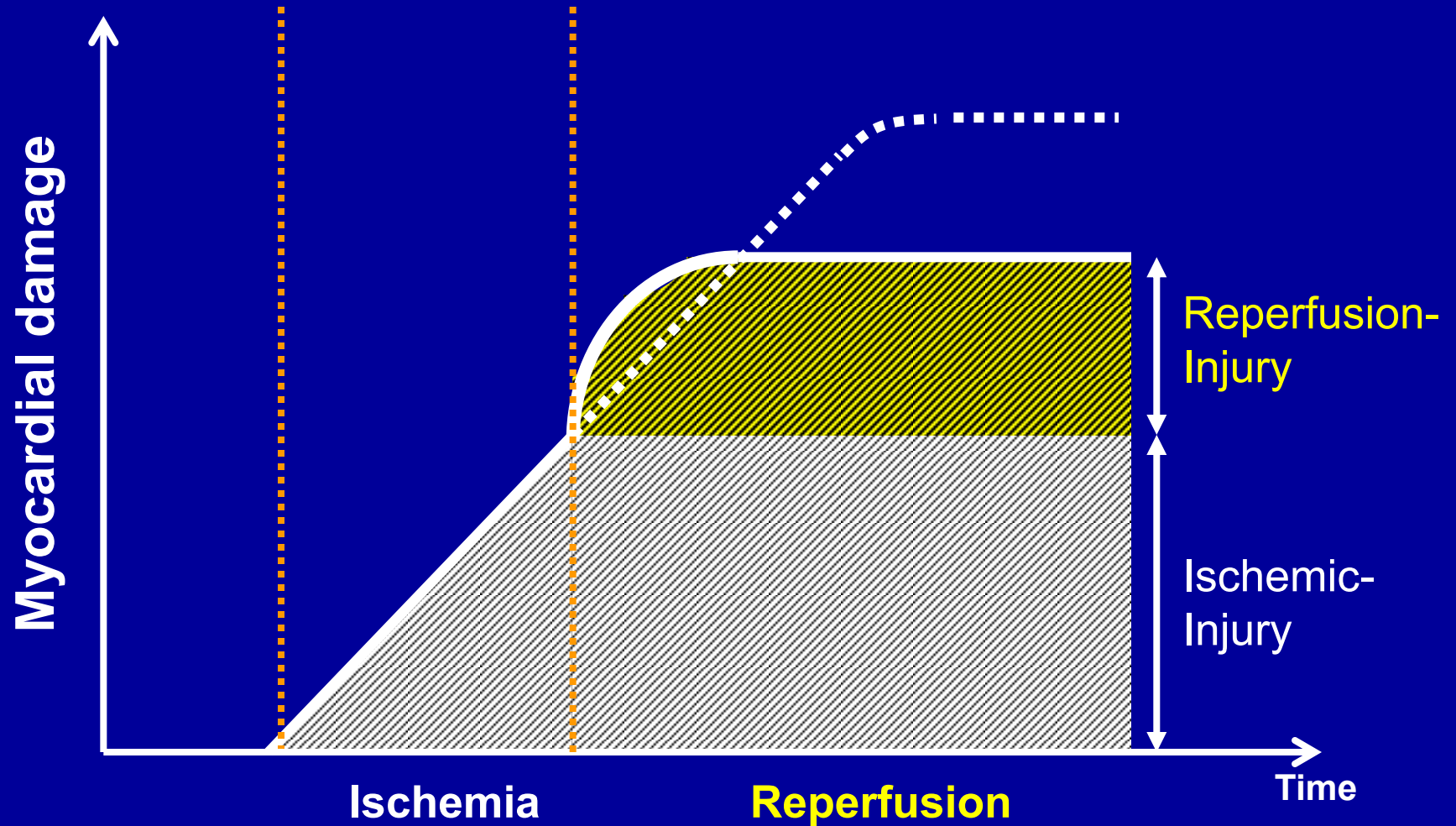


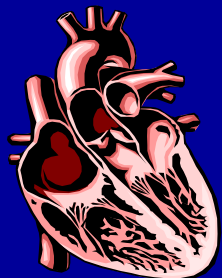
Re-opening of  
the vessel

Reperfused myocardium

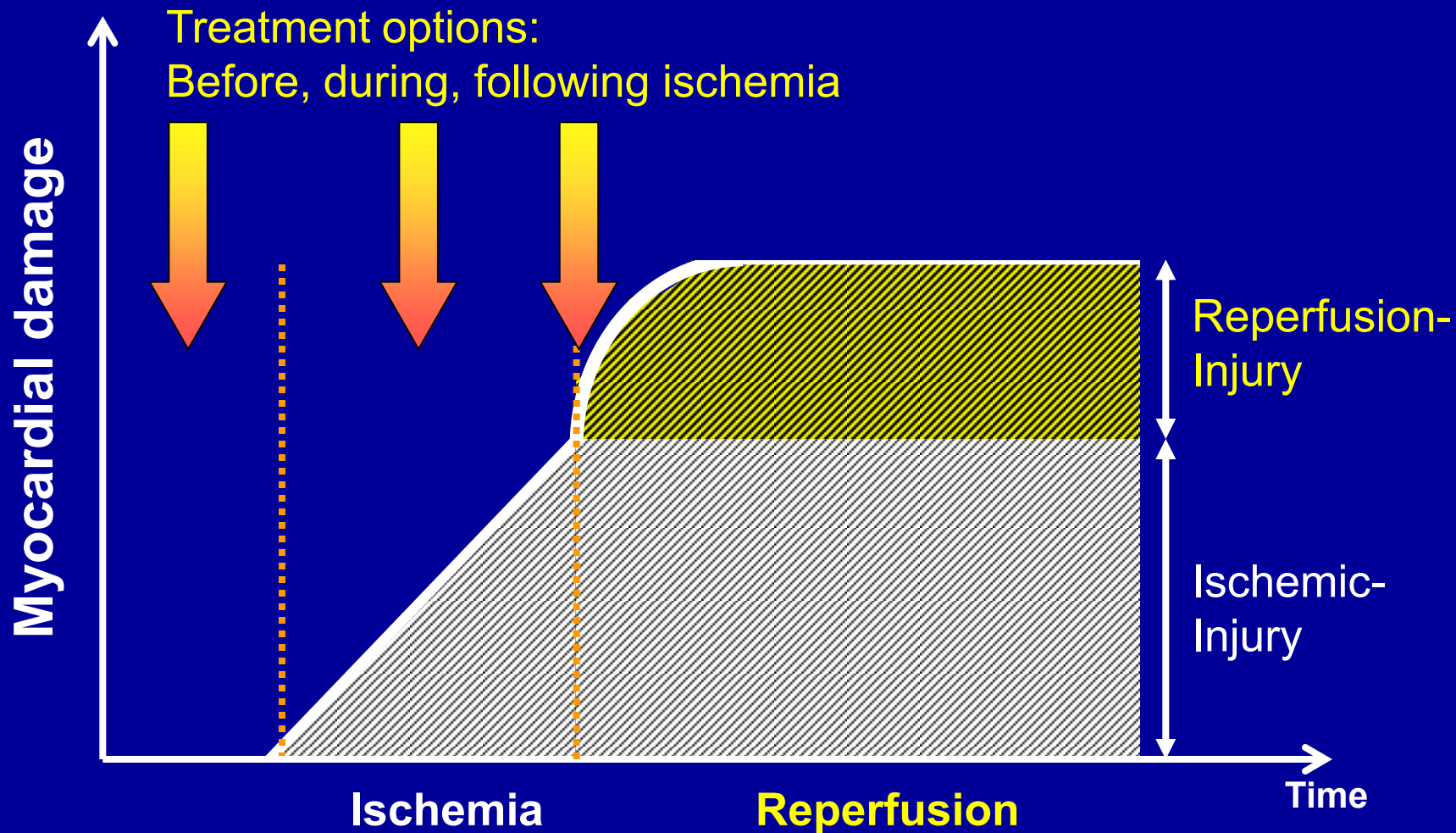


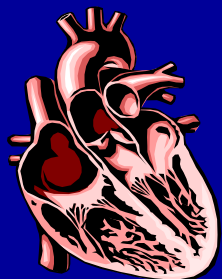
# Ischemia-reperfusion injury



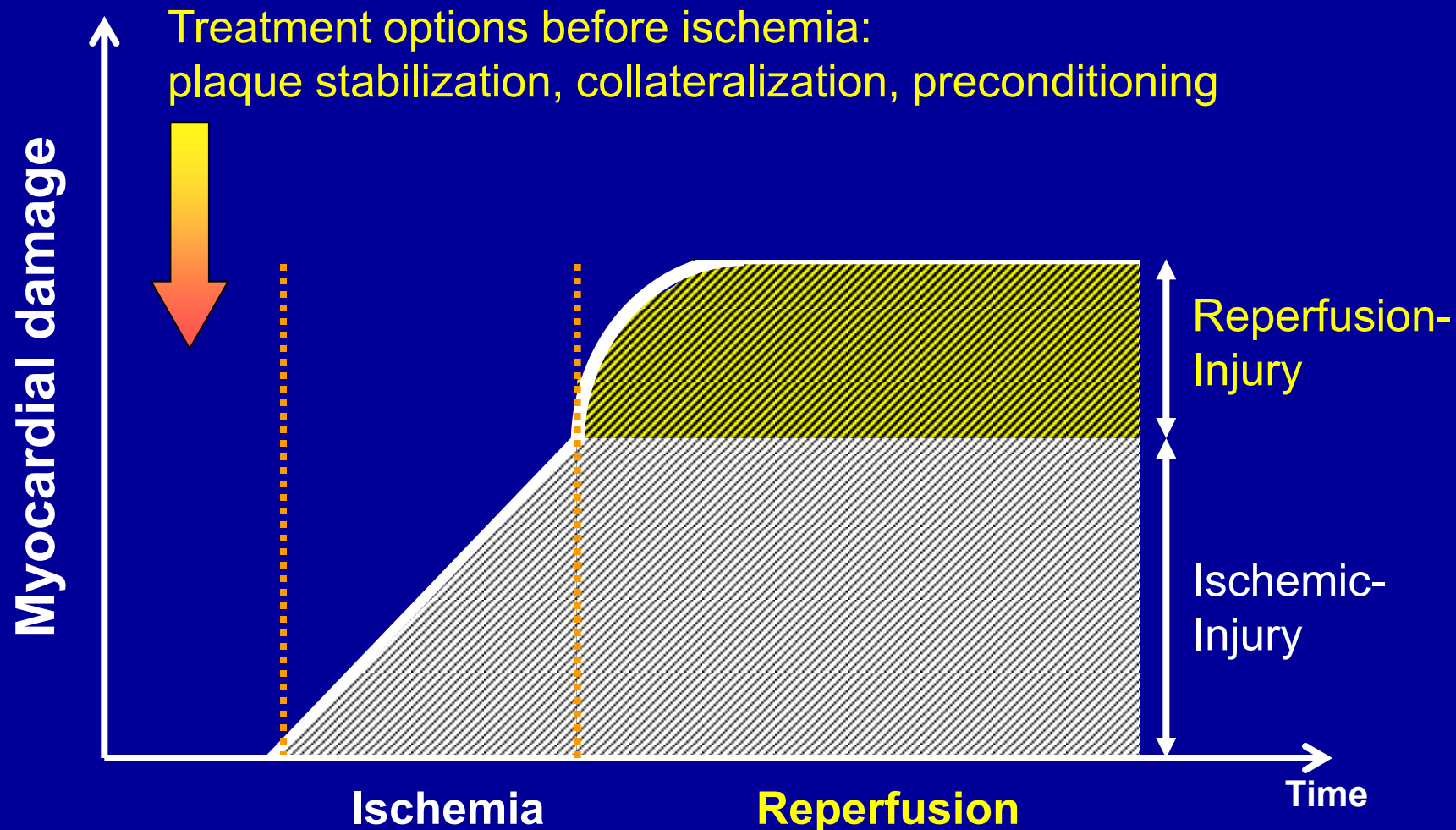


# Ischemia-reperfusion injury



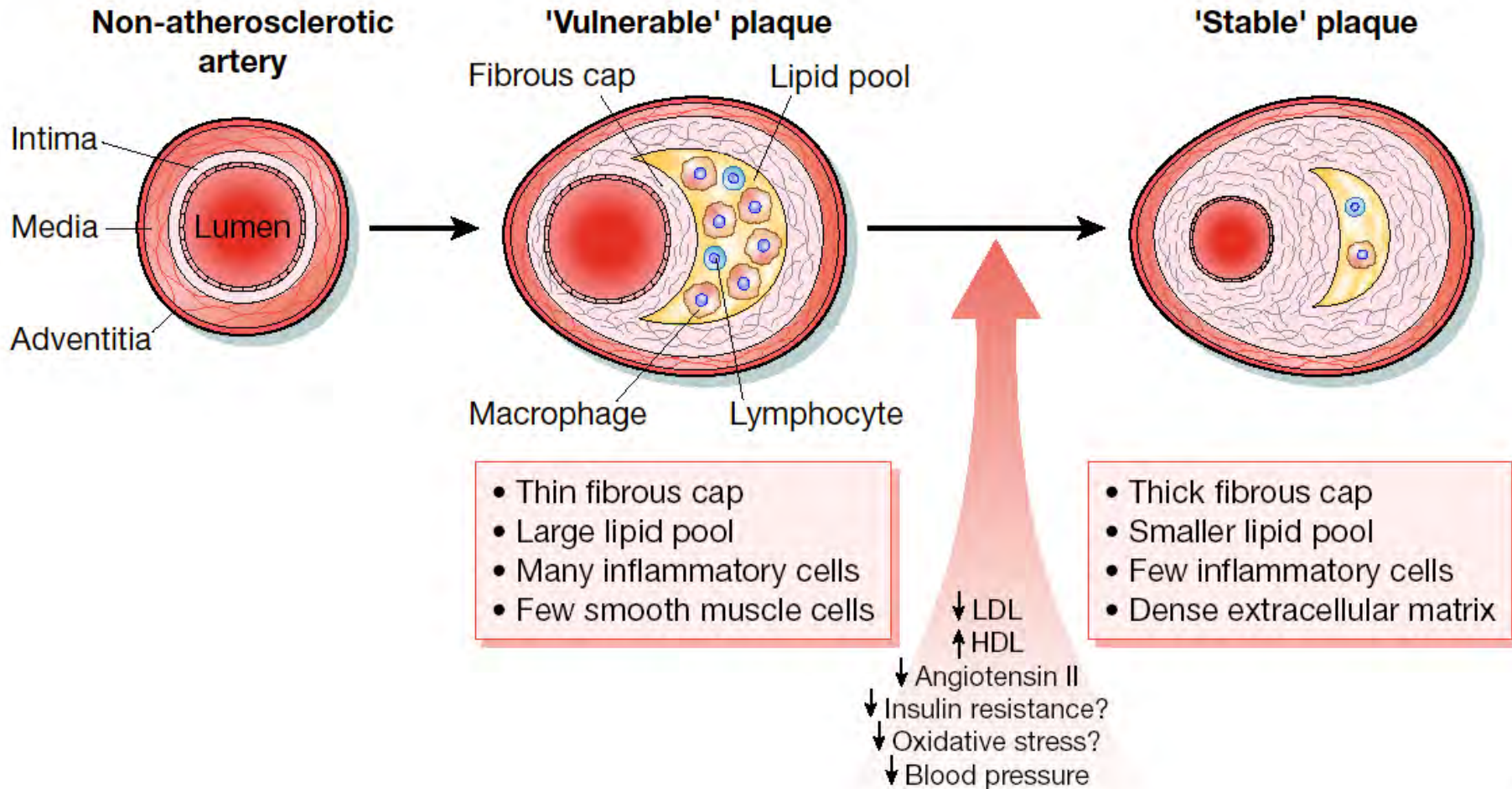


# Ischemia-reperfusion injury





# Development of an unstable plaque





# Avoiding plaque rupture: statins (1976)

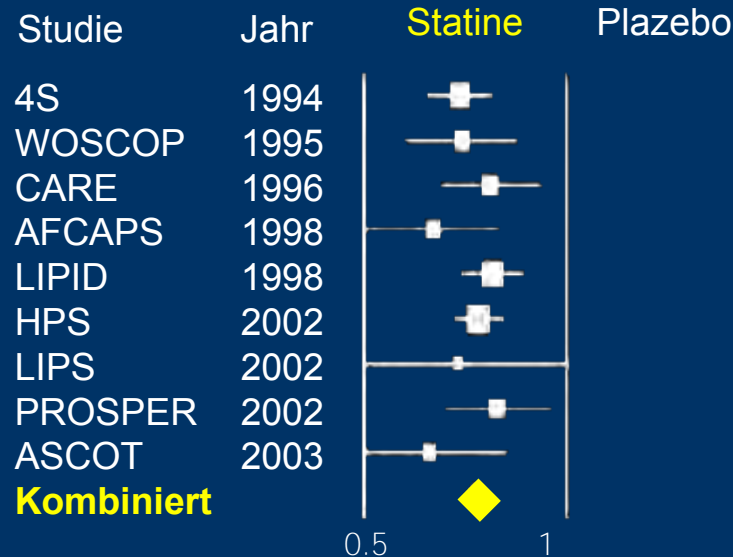


Akira Endo

## ML-236A, ML-236B, AND ML-236C, NEW INHIBITORS OF CHOLESTEROGENESIS PRODUCED BY *PENICILLIUM CITRINUM*

A. Endo, Journal of Antibiotics 29:1346-1348, 1976

Meta-Analysis: 69000 Patients  
Death or myocardial infarction

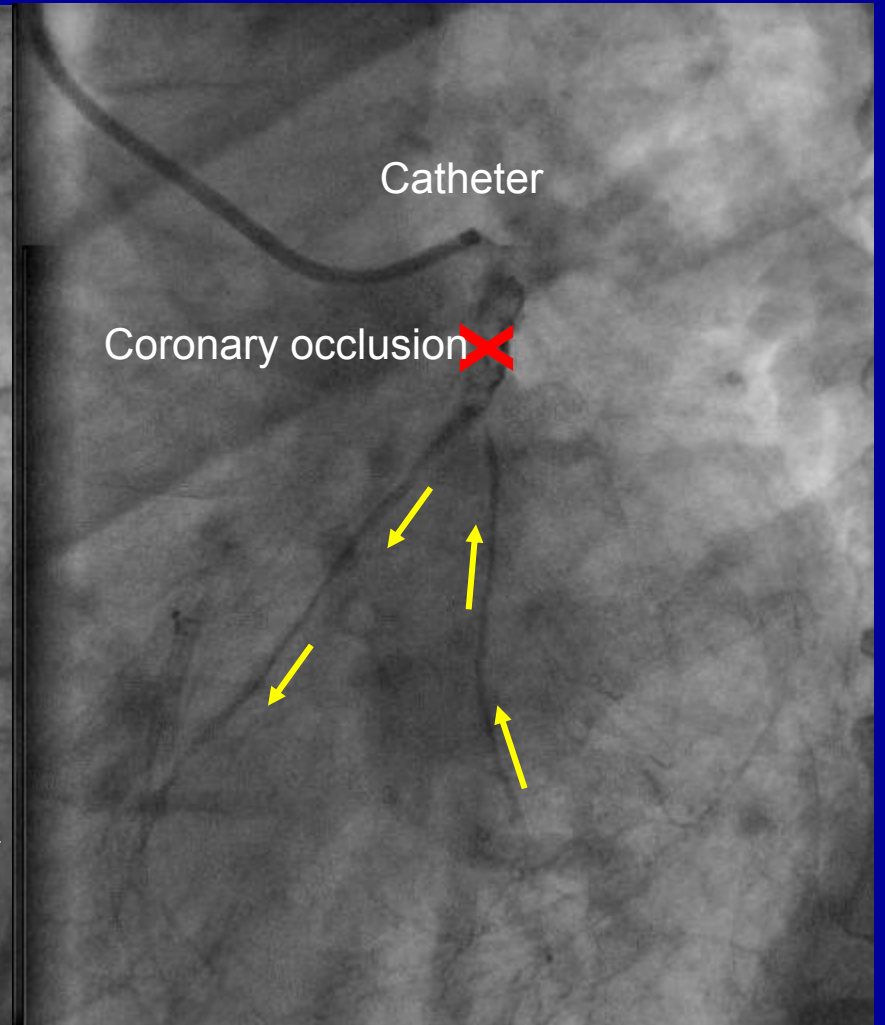
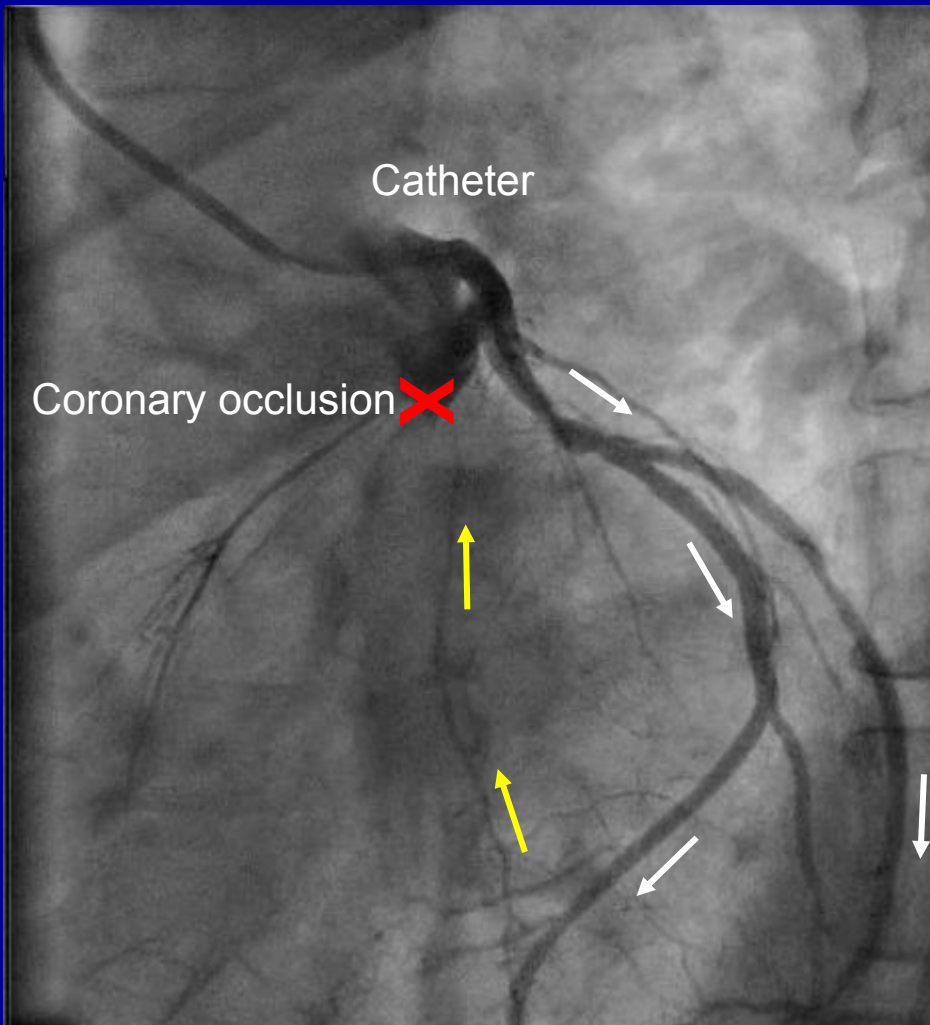


Patient



CHD

## Collateral vessel growth

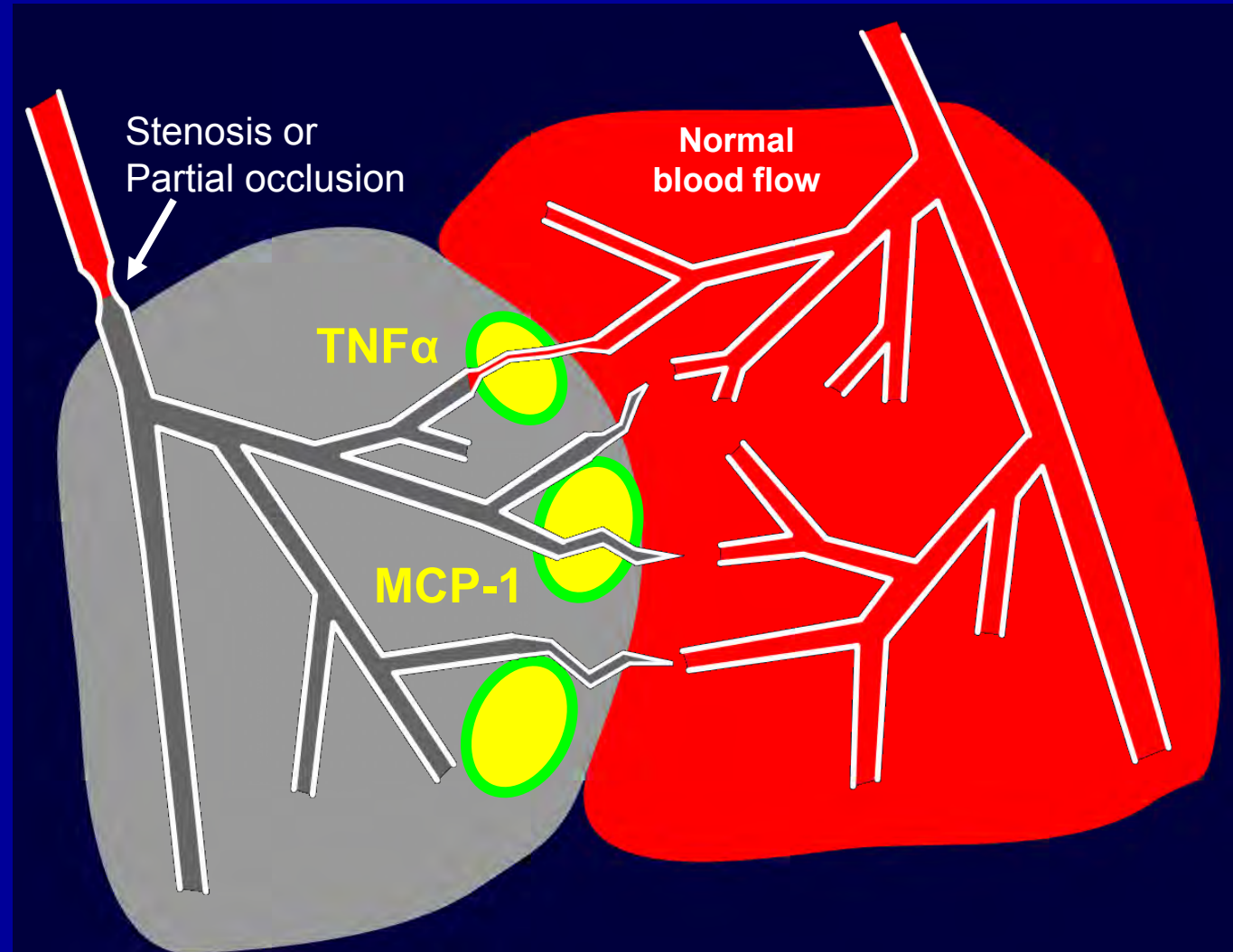
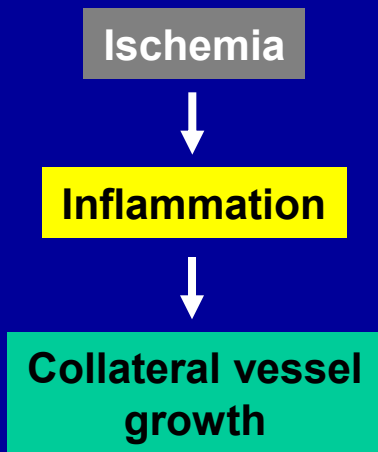


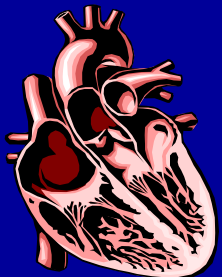
Patient



CHD

# Collateral vessel growth





# Endogenous cardioprotection: Ischemic Preconditioning



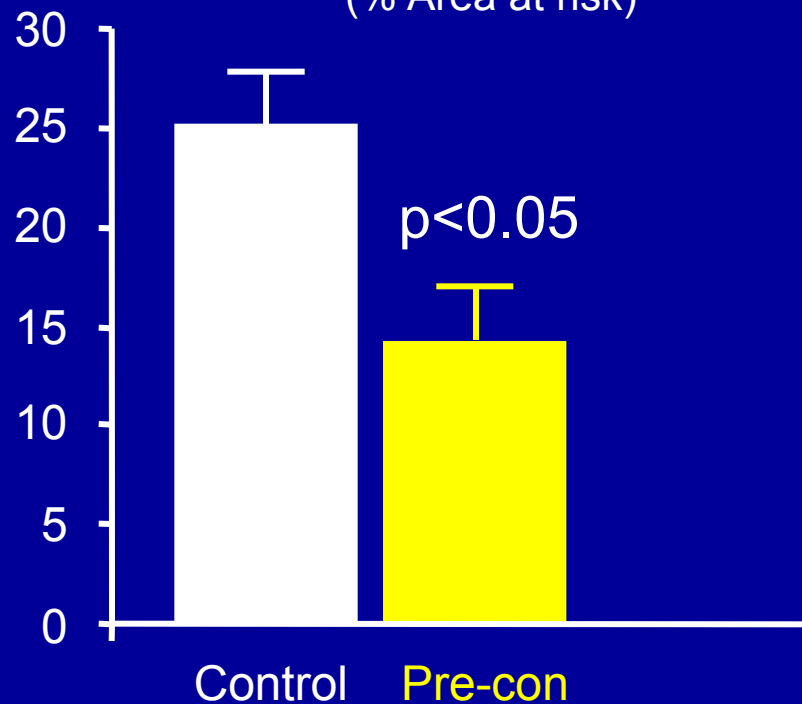
■ Coronary occlusion

First window (<2 hrs)  
Second window (>24hrs)  
Third window (>6hrs)

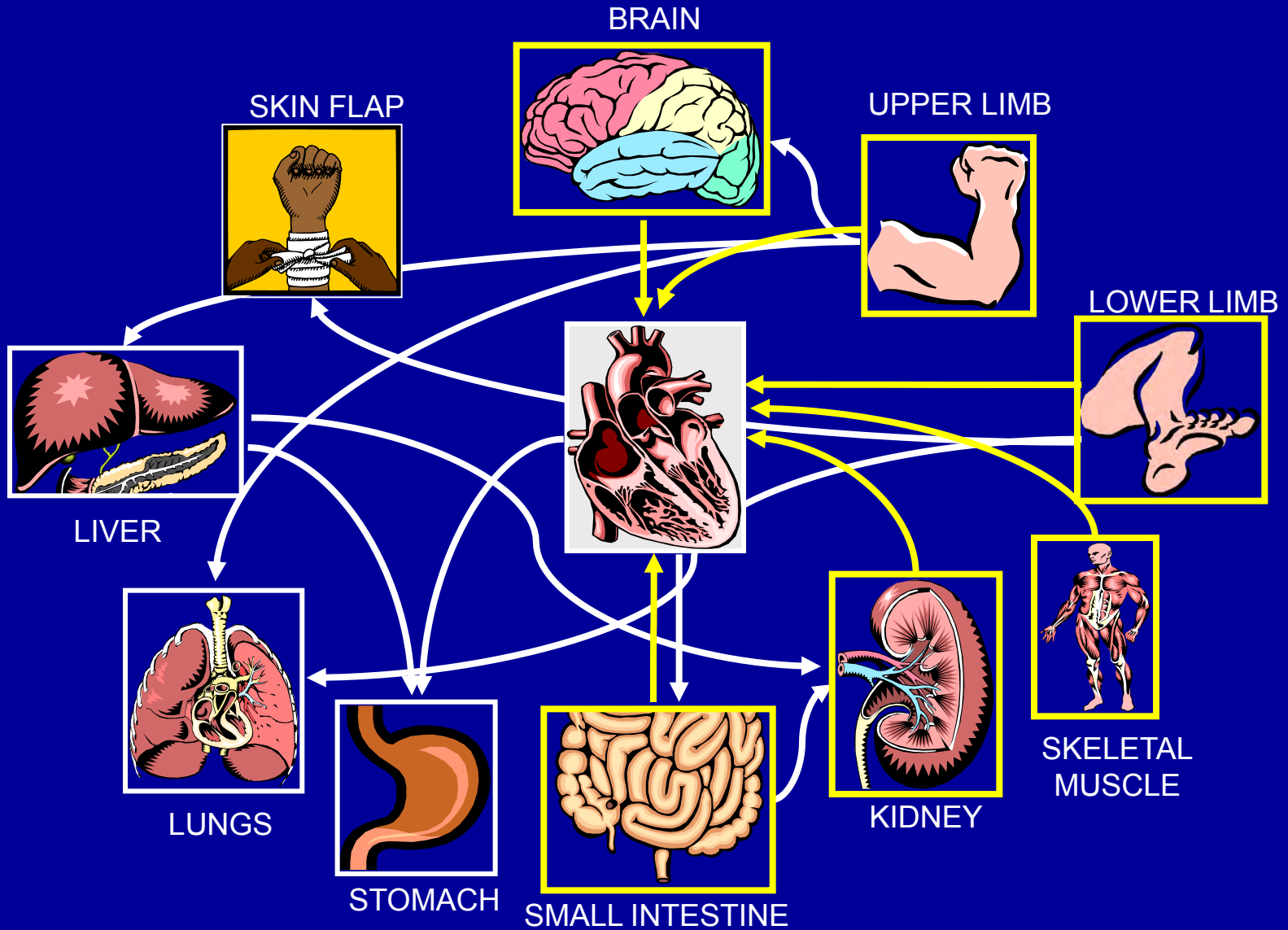
Pre-con  
(Ischemia/  
Drugs)

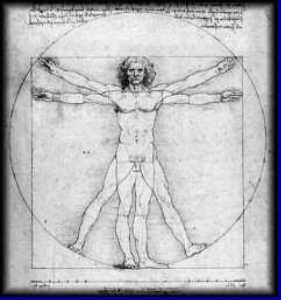


Infarct size  
(% Area at risk)



# Endogenous cardioprotection: Remote Preconditioning





# Endogenous cardioprotection: Ischemic Preconditioning



	Pre-infarction angina	
	Yes	No
Death	4/155 (3%)	18/254 (6%)
Heart failure/shock	1/155 (1%)	15/254 (6%)
Death/shock	4/155 (3%)	25/254 (10%)
CK-release (24 h)	115 U	151 U
Collaterals	8/85 (9%)	33/146 (23%)

# Endogenous cardioprotection: Ischemic Pre- and Postconditioning



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0002/3284440

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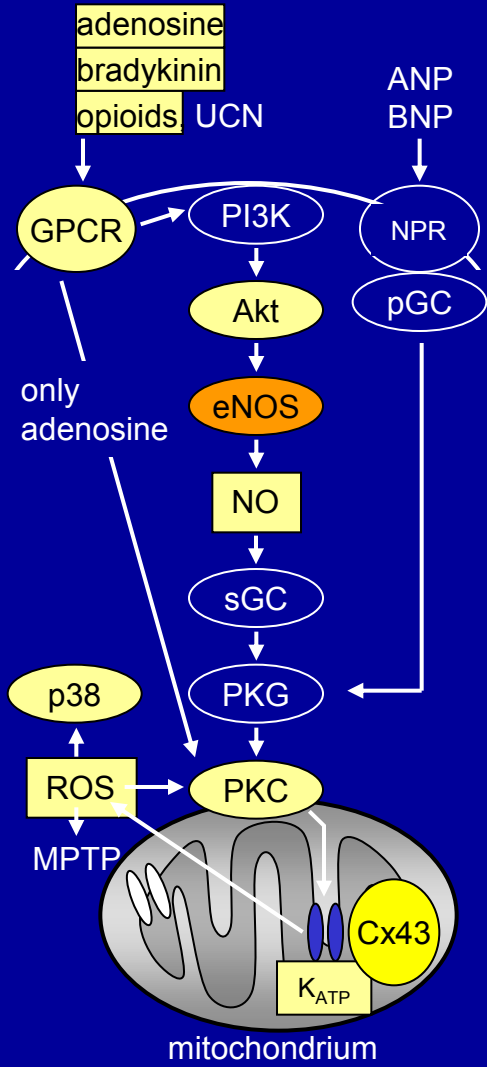
## Interaction of Cardiovascular Risk Factors with Myocardial Ischemia/Reperfusion Injury, Preconditioning, and Postconditioning

PETER FERDINANDY, RAINER SCHULZ, AND GARY F. BAXTER

*Cardiovascular Research Group, Department of Biochemistry, University of Szeged, Szeged, Hungary (P.F.); Pharmahungary Group, Szeged, Hungary (P.F.); Institut für Pathophysiologie, Zentrum für Innere Medizin, Universitätsklinikum Essen, Universität Duisburg-Essen, Essen, Germany (R.S.); and Division of Pharmacology, Welsh School of Pharmacy, Cardiff University, Cardiff, UK (G.F.B.)*

„ ... both phenomena work perfectly in healthy hearts,  
however, protection might be lost with co-morbidities...! “

# Preconditioning: Signal transduction



Heinzel et al., *Circ Res* 97:583-586, 2005

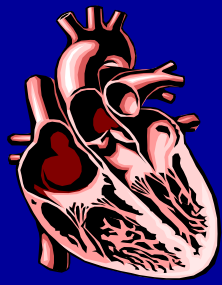
Boengler et al., *Cardiovasc Res* 67: 234-244, 2005

Rodriguez-Sinovas et al., *Circ Res* 99:93-101, 2006

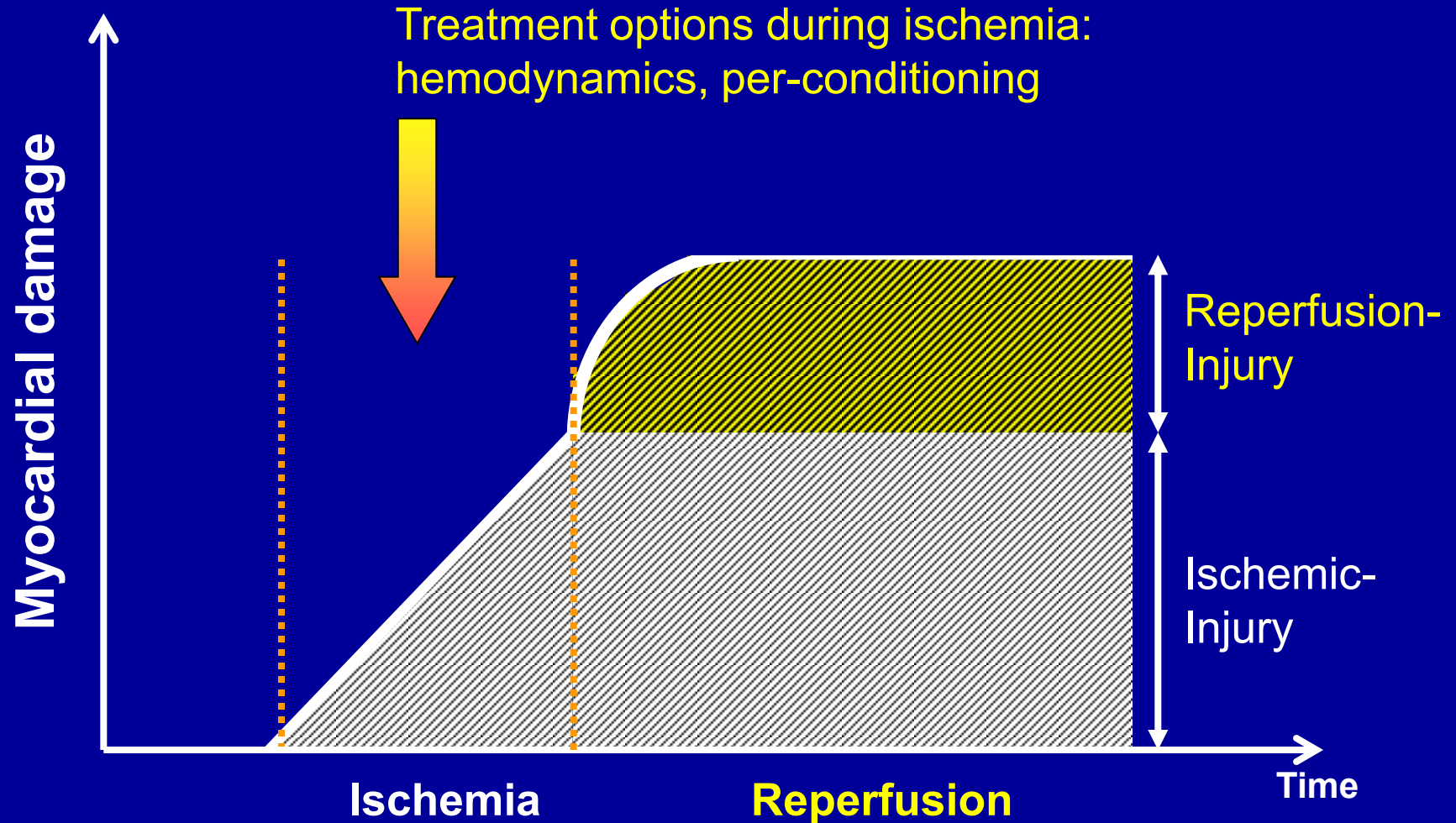
Boengler et al., *Basic Res Cardiol* 104: 141-147, 2009

Rottlaender et al., *J Clin Invest* 120:1441–1453, 2010

Görbe et al., *Am J Physiol Heart Circ Physiol*. 2011 Mar 11



# Ischemia-reperfusion injury



Patient



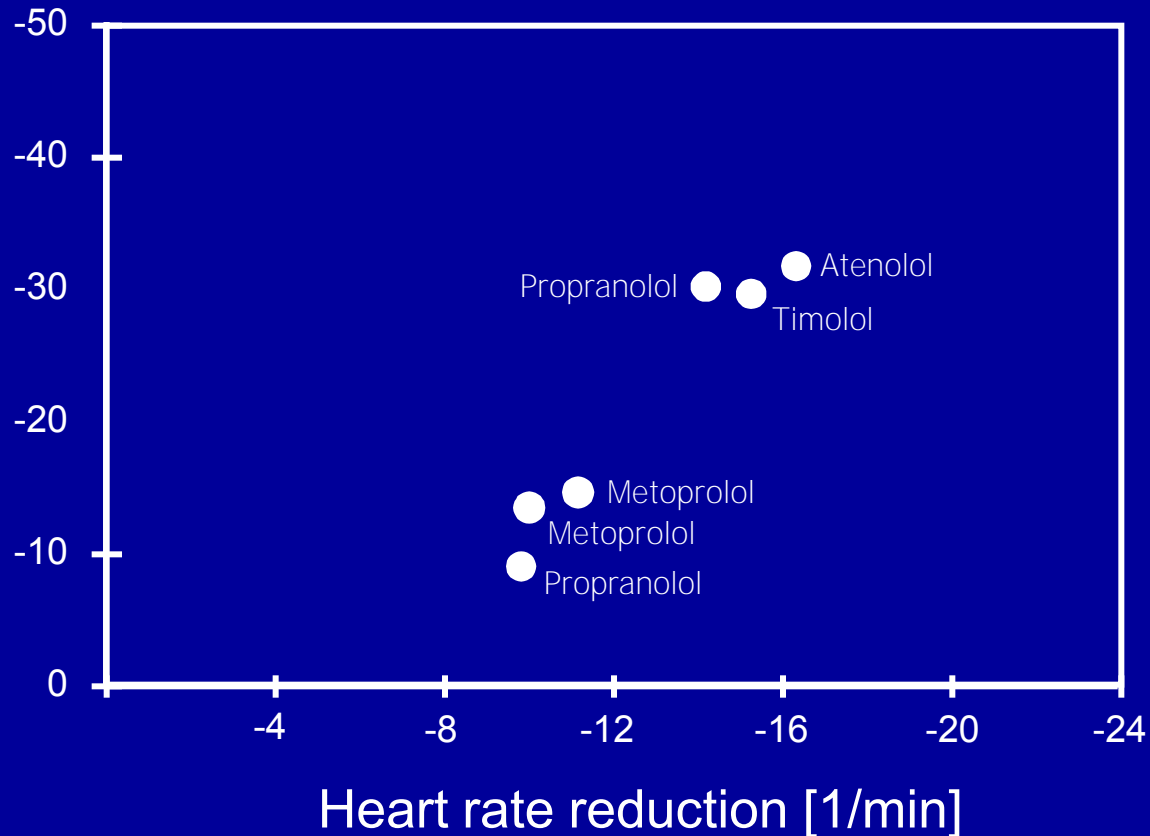
CHD

# Ischemia-reperfusion injury: $\beta$ -blockade



- Patient  
Creatine kinase release  
Kjekshus, Am J Cardiol 57: 43F-49F (1986)

Infarct size  
reduction [%]





# Endogenous cardioprotection: Perconditioning



## Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomised trial

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

*Lancet 2010; 375: 727–34*

JACC: CARDIOVASCULAR INTERVENTIONS  
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ISSN 1936-8798/10/\$36.00  
DOI: 10.1016/j.jcin.2009.10.015

## Cardioprotective Role of Remote Ischemic Perconditioning in Primary Percutaneous Coronary Intervention

Enhancement by Opioid Action

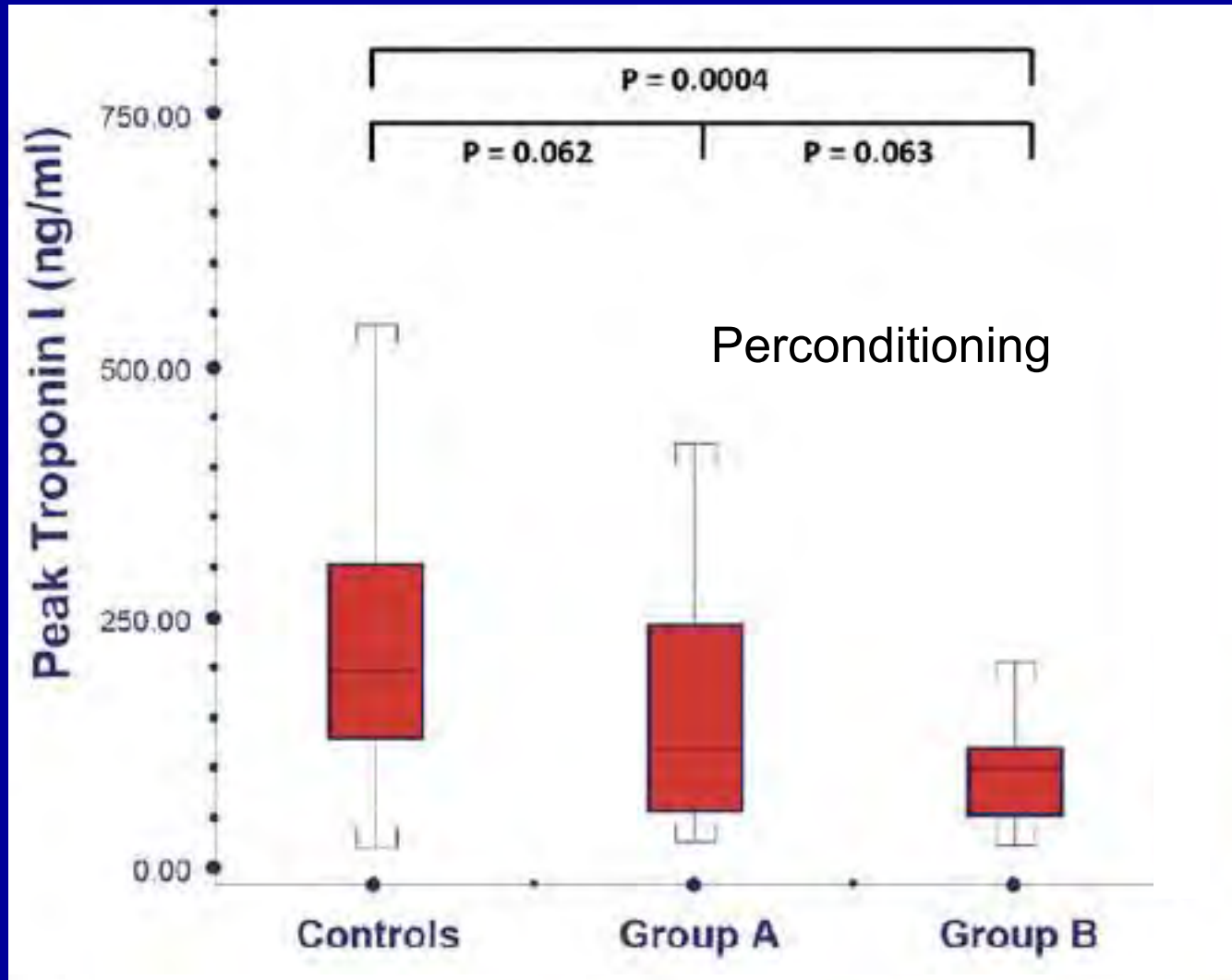
Ilias Rentoukas, MD,\* Georgios Giannopoulos, MD,† Andreas Kaoukis, MD,†

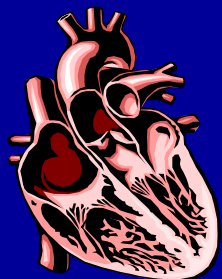
Patient



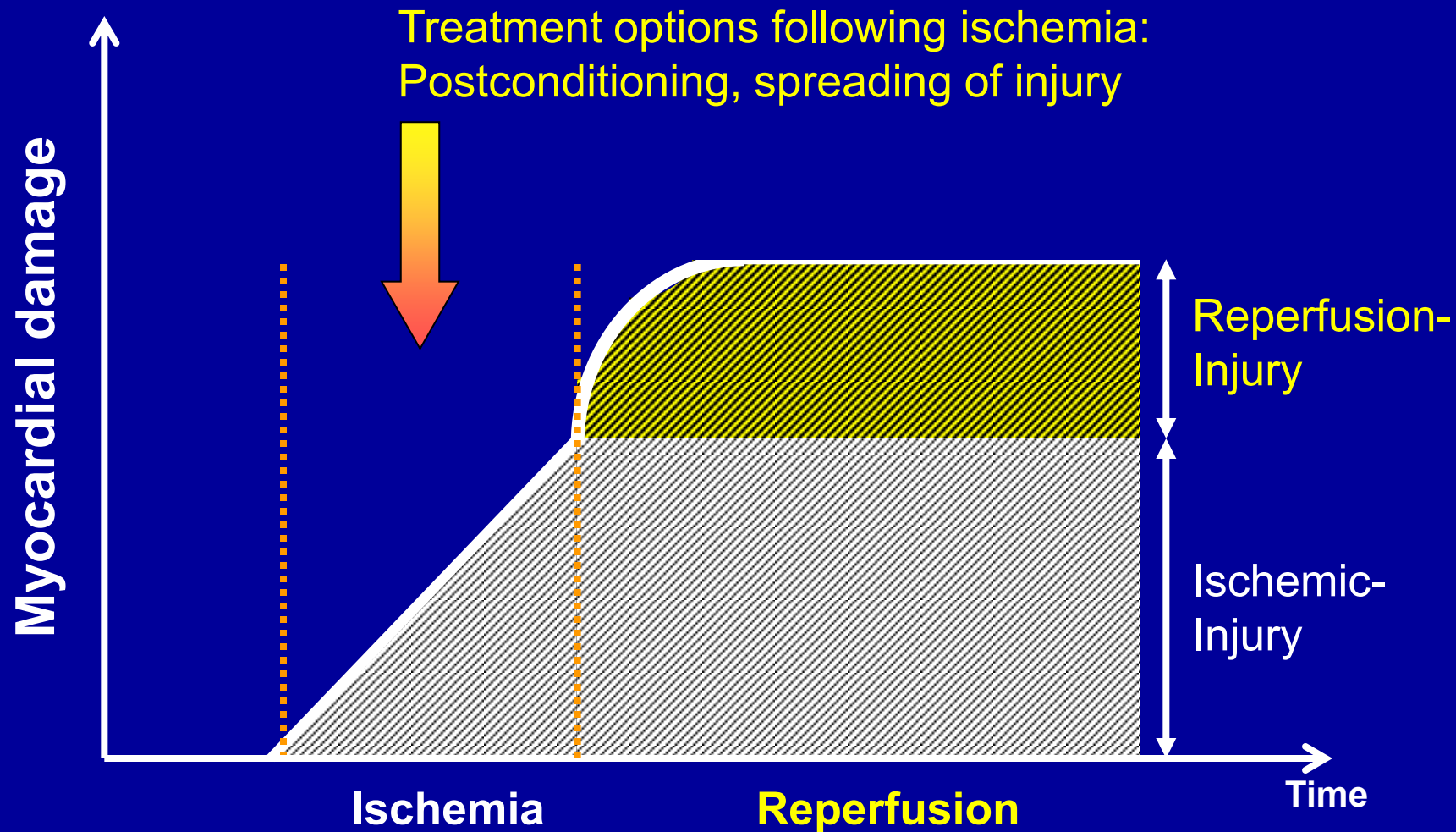
CHD

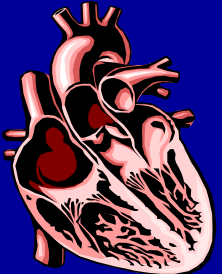
# Endogenous cardioprotection: Perconditioning



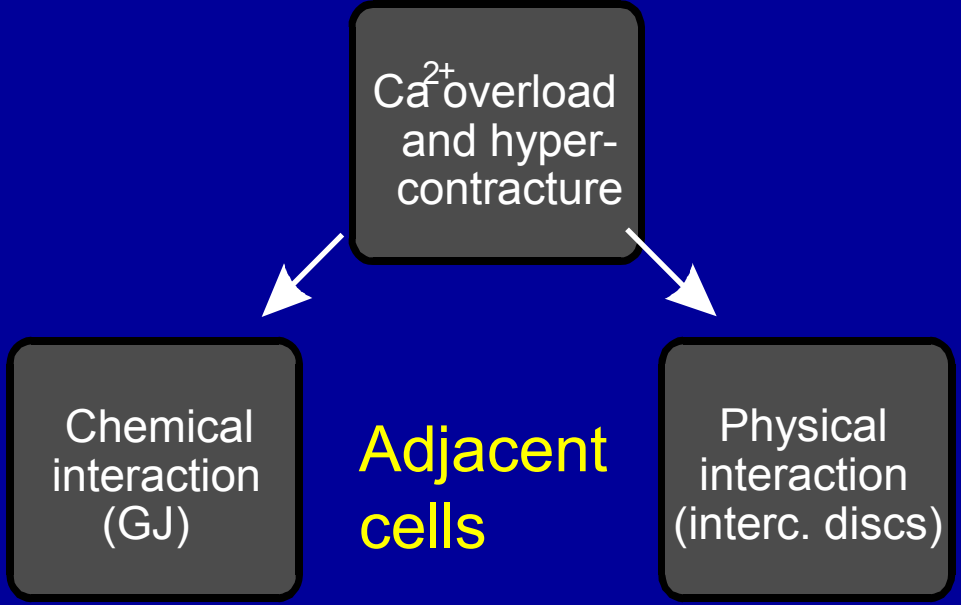


# Ischemia-reperfusion injury

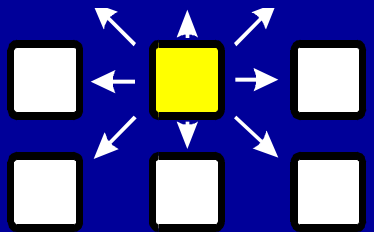




# Reperfusion injury



**BDM: Uncoupler of gap junctions (phosphatase inhibitor)**



**Spreading of injury**

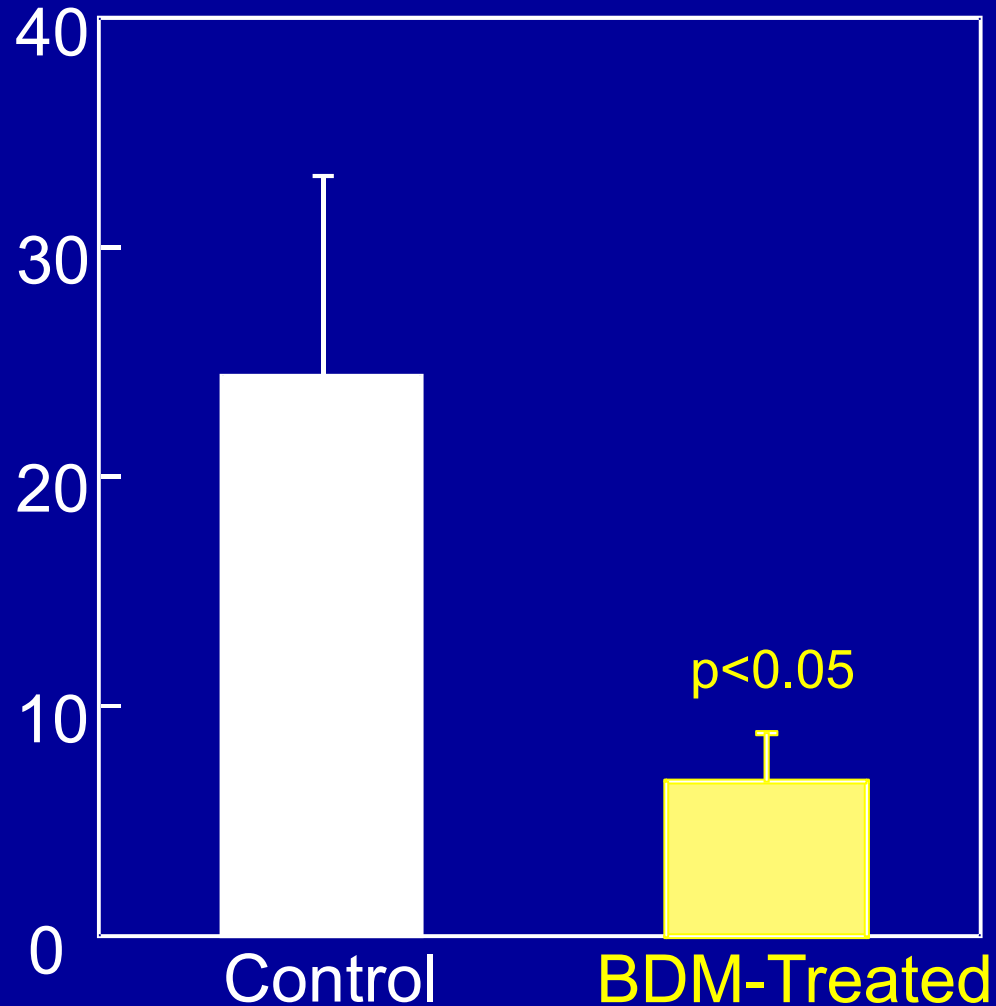


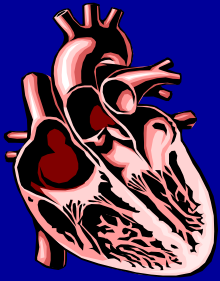
Anesthetized  
pig

# Reperfusion injury



Infarct size  
(% Area at  
risk)

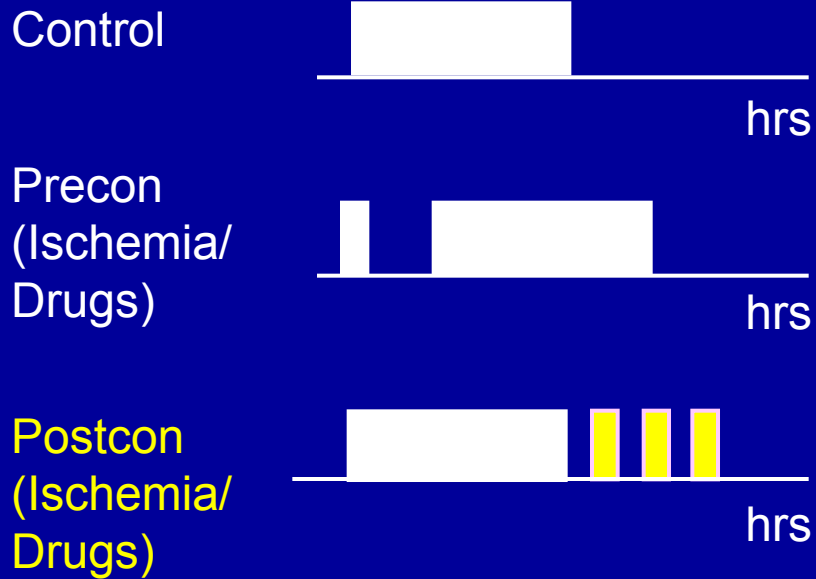




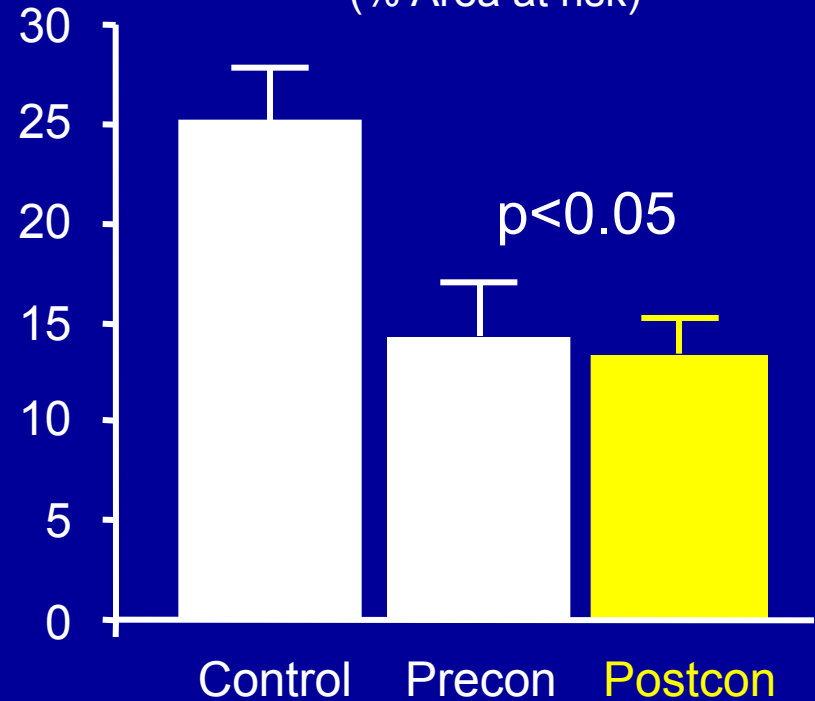
# Endogenous cardioprotection: Pre- and Post-conditioning

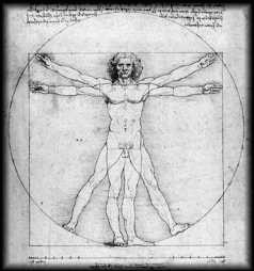


Coronary occlusion

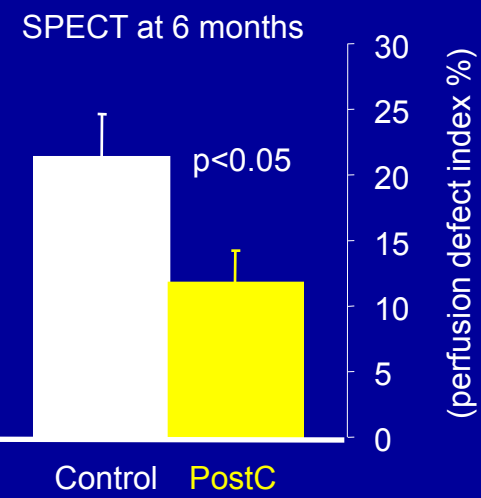
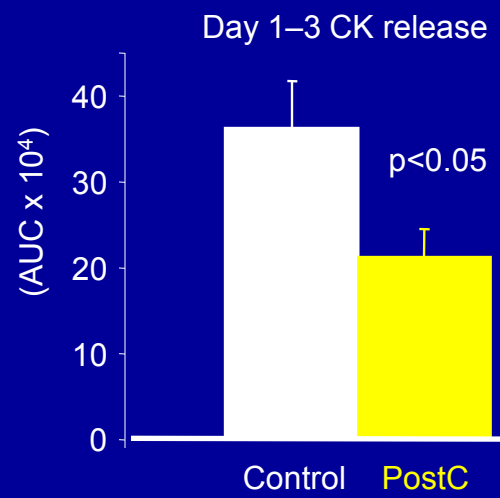
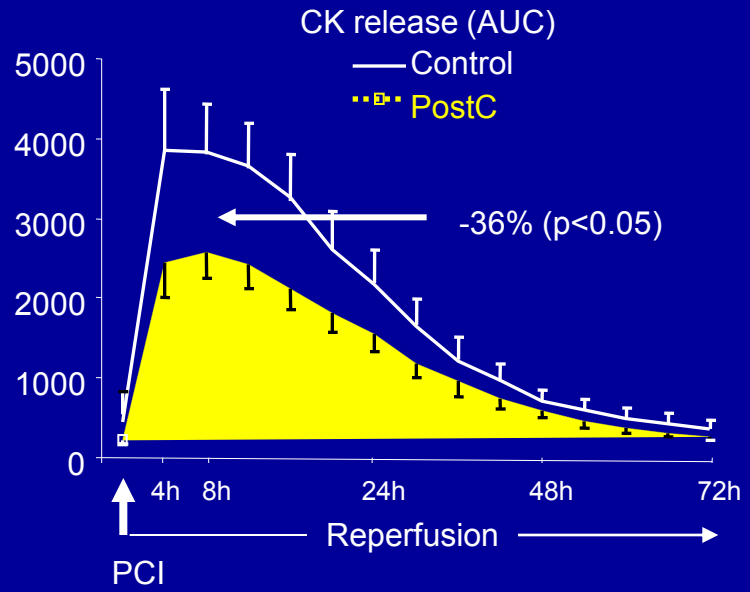
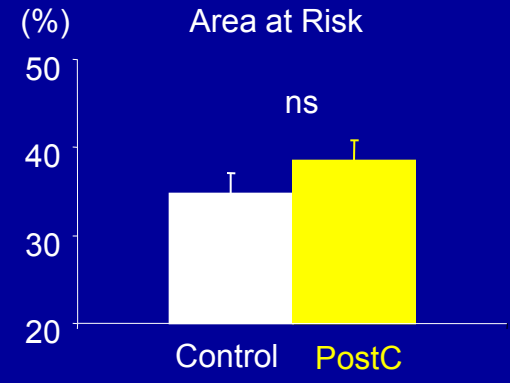
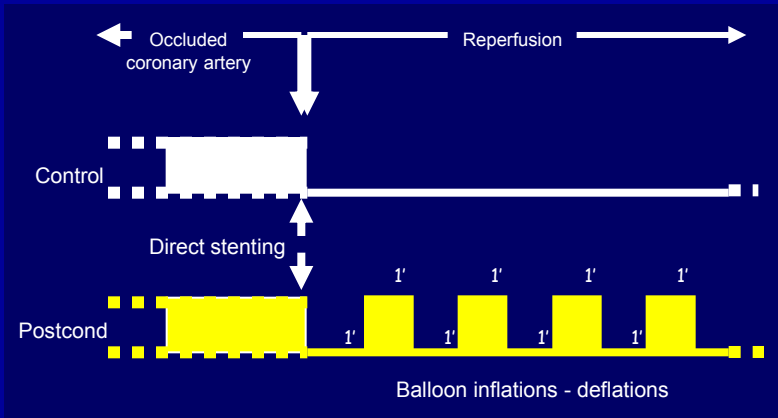
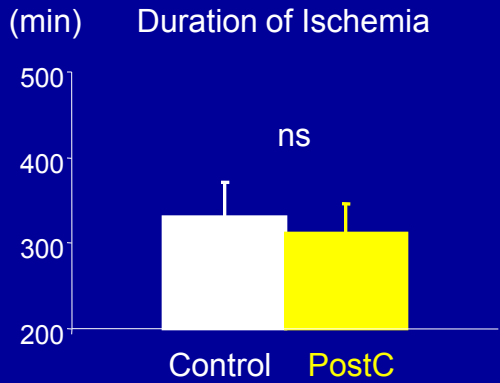


Infarct size  
(% Area at risk)

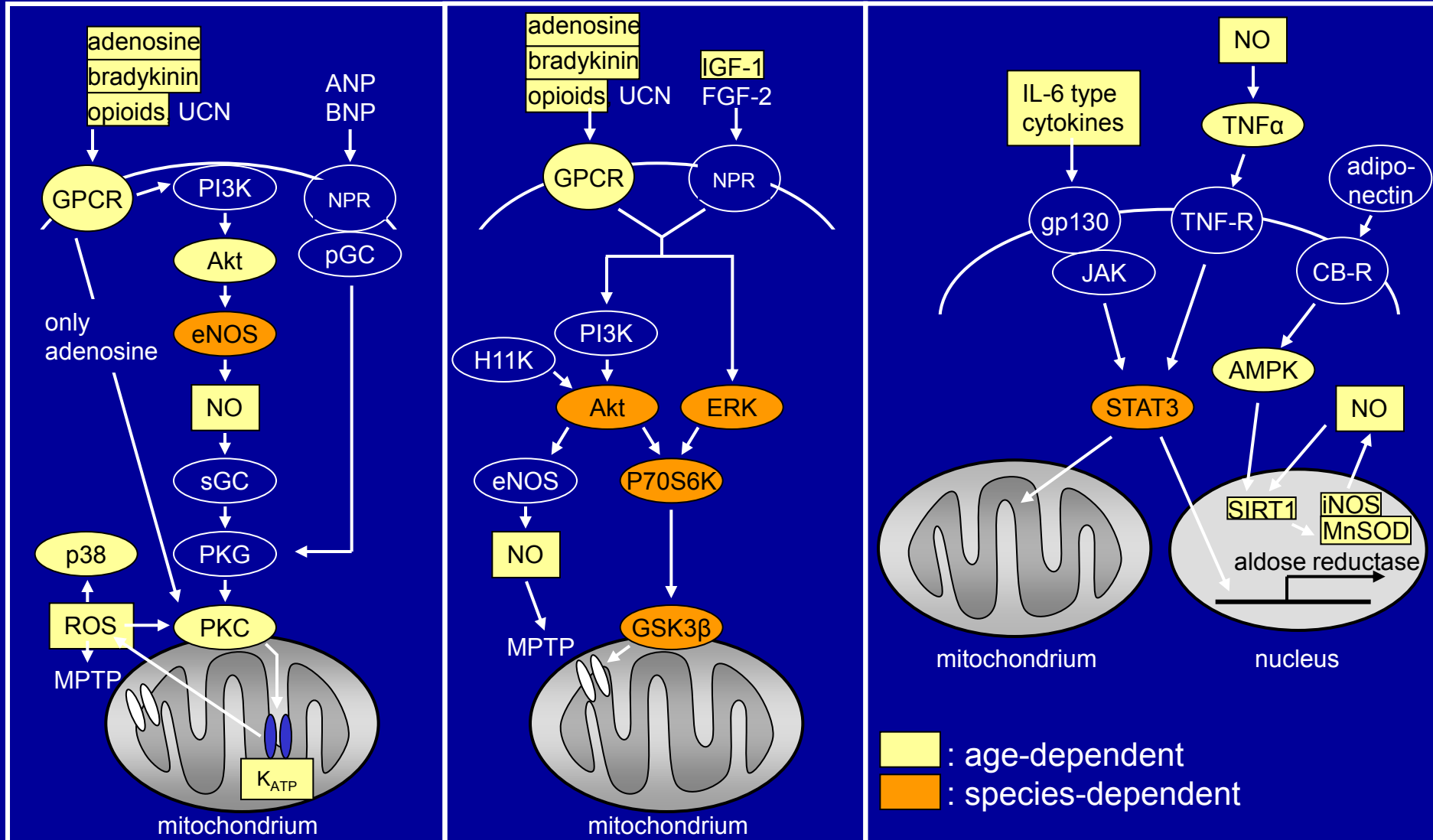




# Endogenous cardioprotection: Ischemic Postconditioning



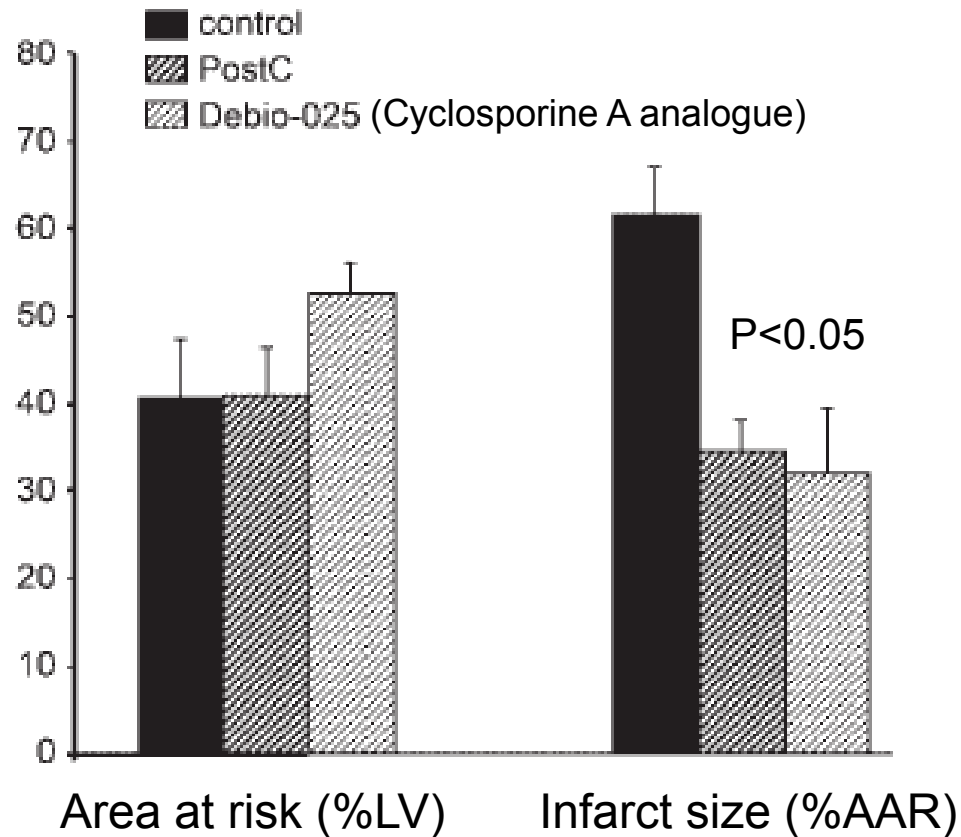
# Pre- and Post-conditioning: Signal transduction





Mice

# Ischemic Postconditioning: Signal transduction



Patient



# Pharmacological Postconditioning



CHD

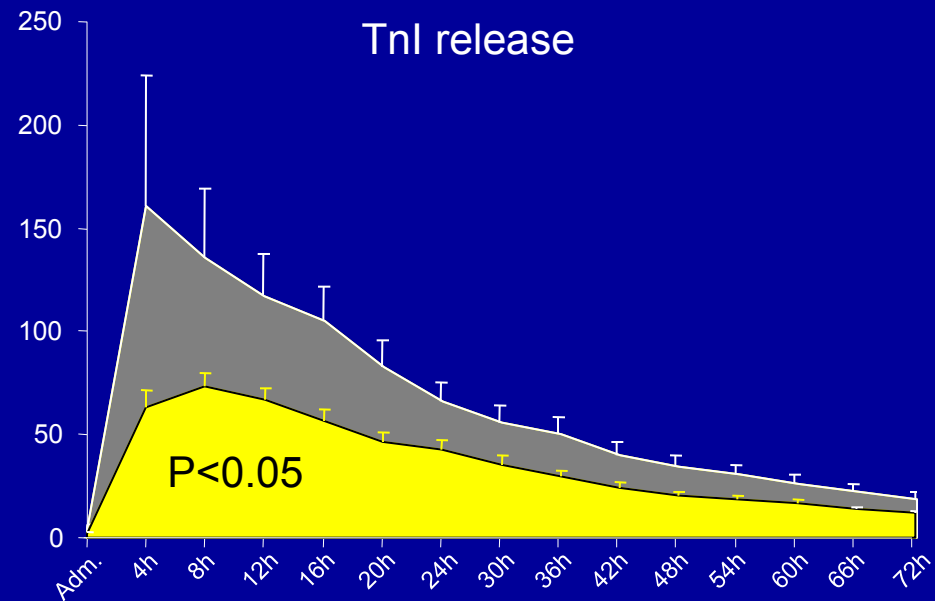
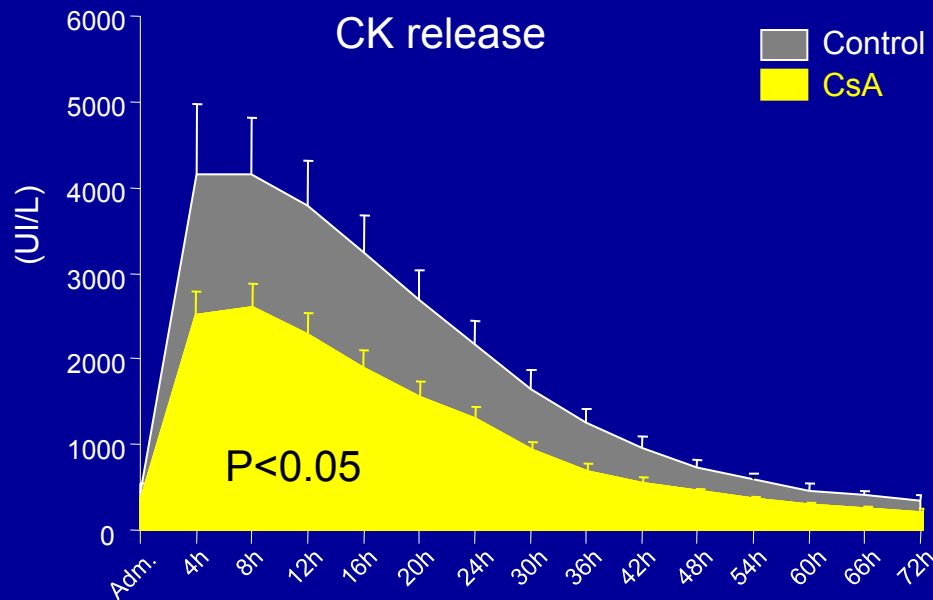
Cyclosporine A (or saline)  
(2.5 mg/kg, IV bolus)

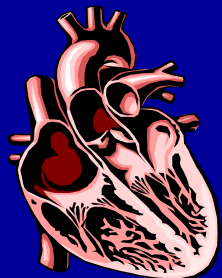
Coronary artery occlusion

Direct stenting

Day 1-3  
CK / Tnl release

**Infarct size**





# Ischemia-reperfusion injury

