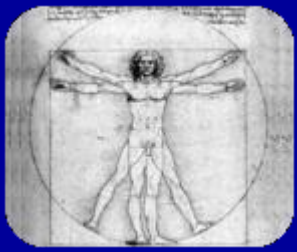




Ischemia/reperfusion injury: Pharmacological treatment options

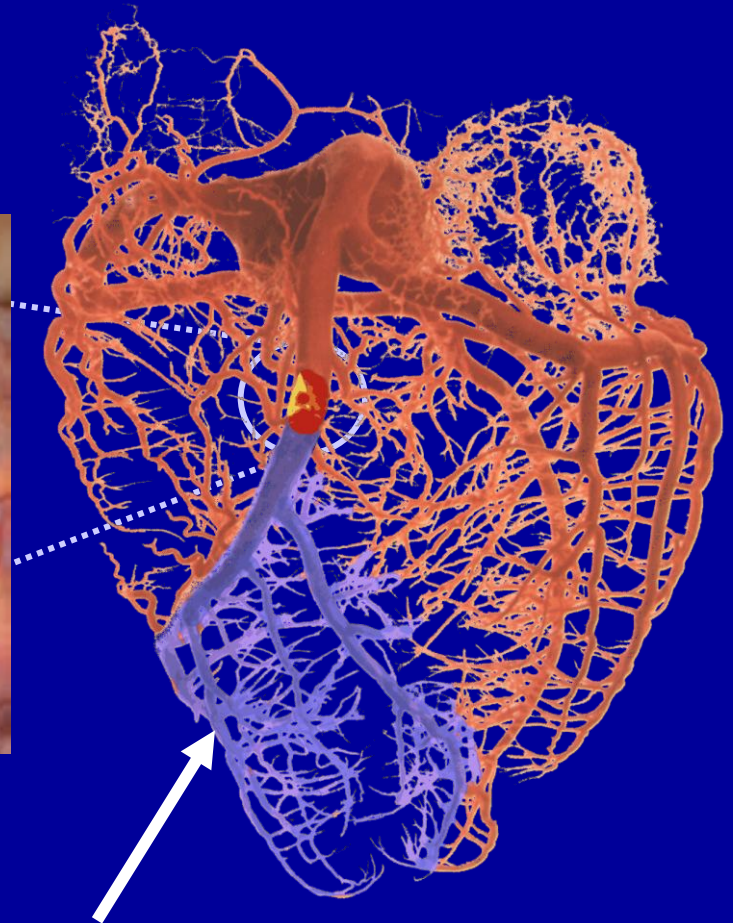
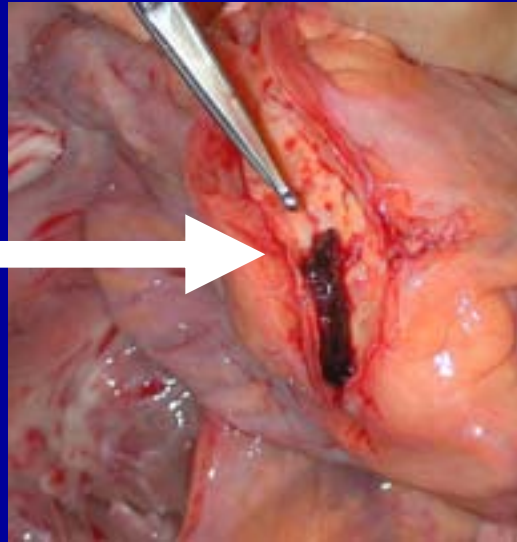
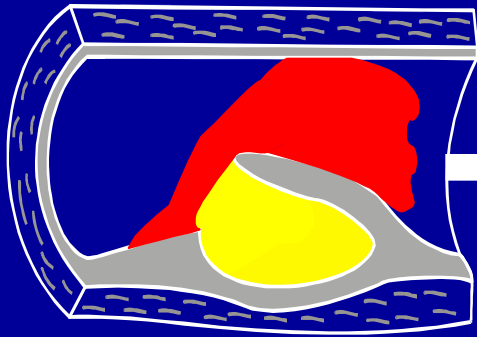
PD Dr. Kerstin Boengler



Plaque rupture and myocardial ischemia



Acute plaque rupture
(Stary VI)



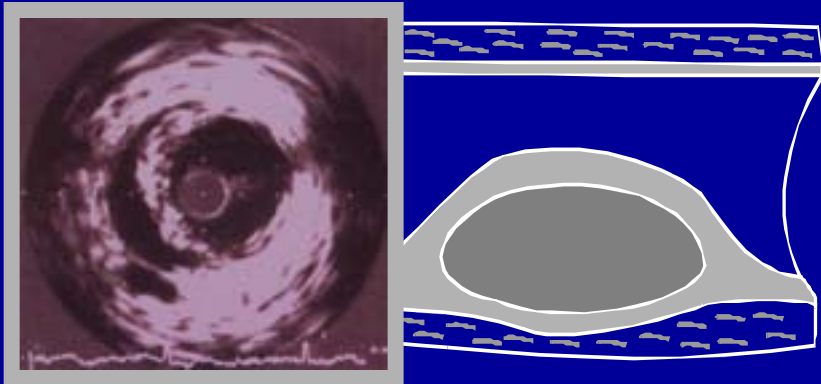
Ischemic myocardium
(ACS, NSTEMI, STEMI)



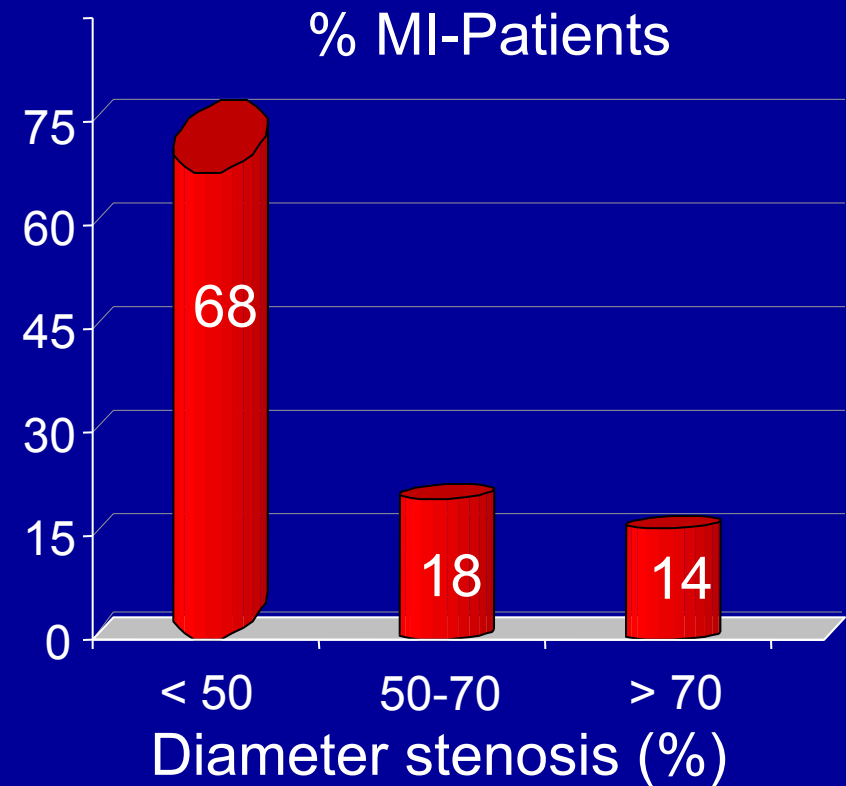
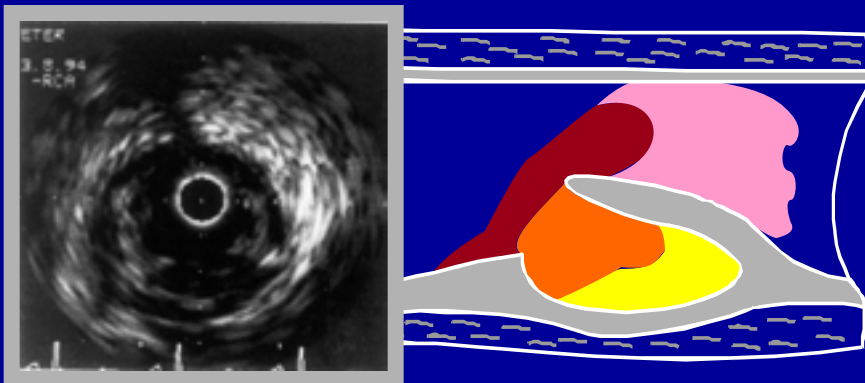
Plaque rupture, thrombosis and myocardial death



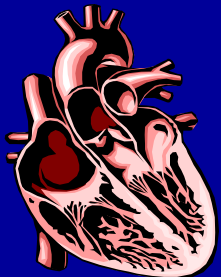
Stable plaque



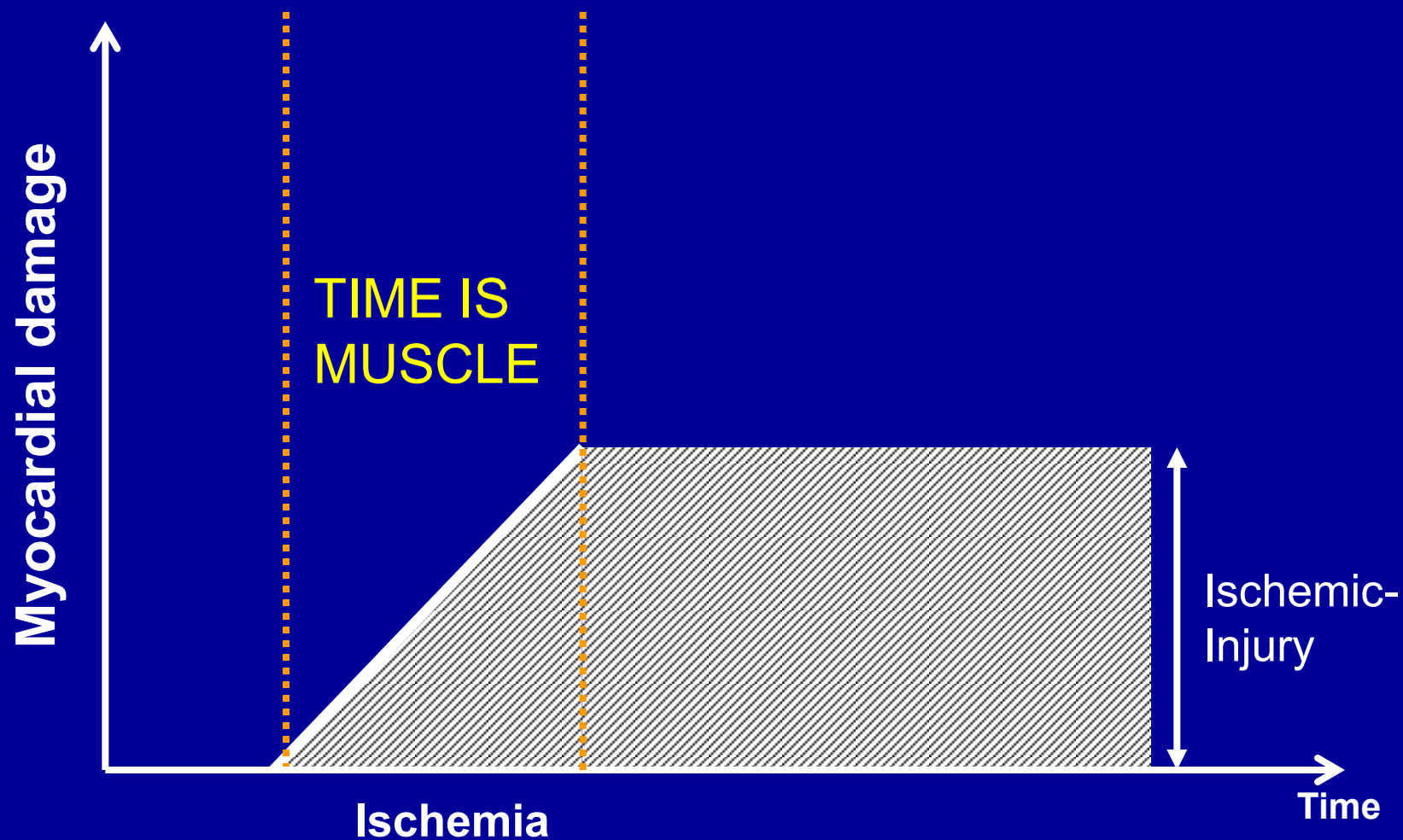
Unstable plaque, plaque rupture

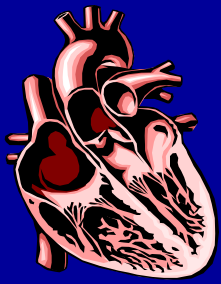


Falk et al., Circulation 92: 657-671, 1995



Ischemic injury



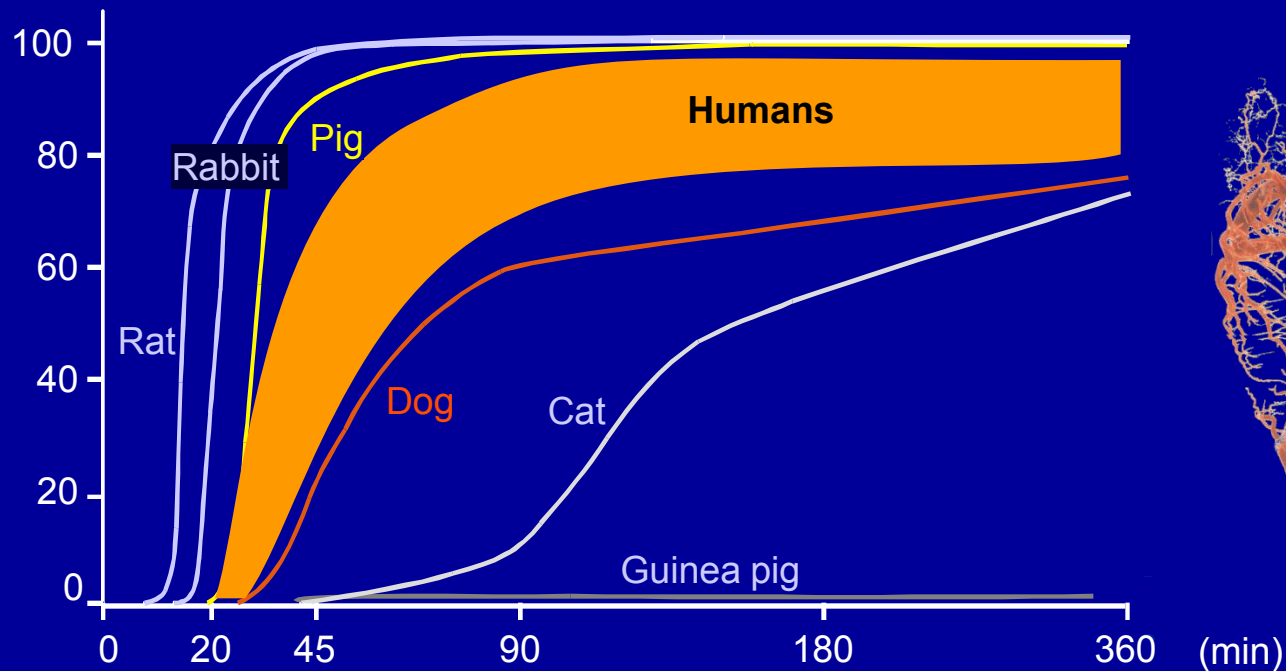


Ischemia-reperfusion injury



Ischemia

Infarct size
(% area at risk)



Extent of
collaterals

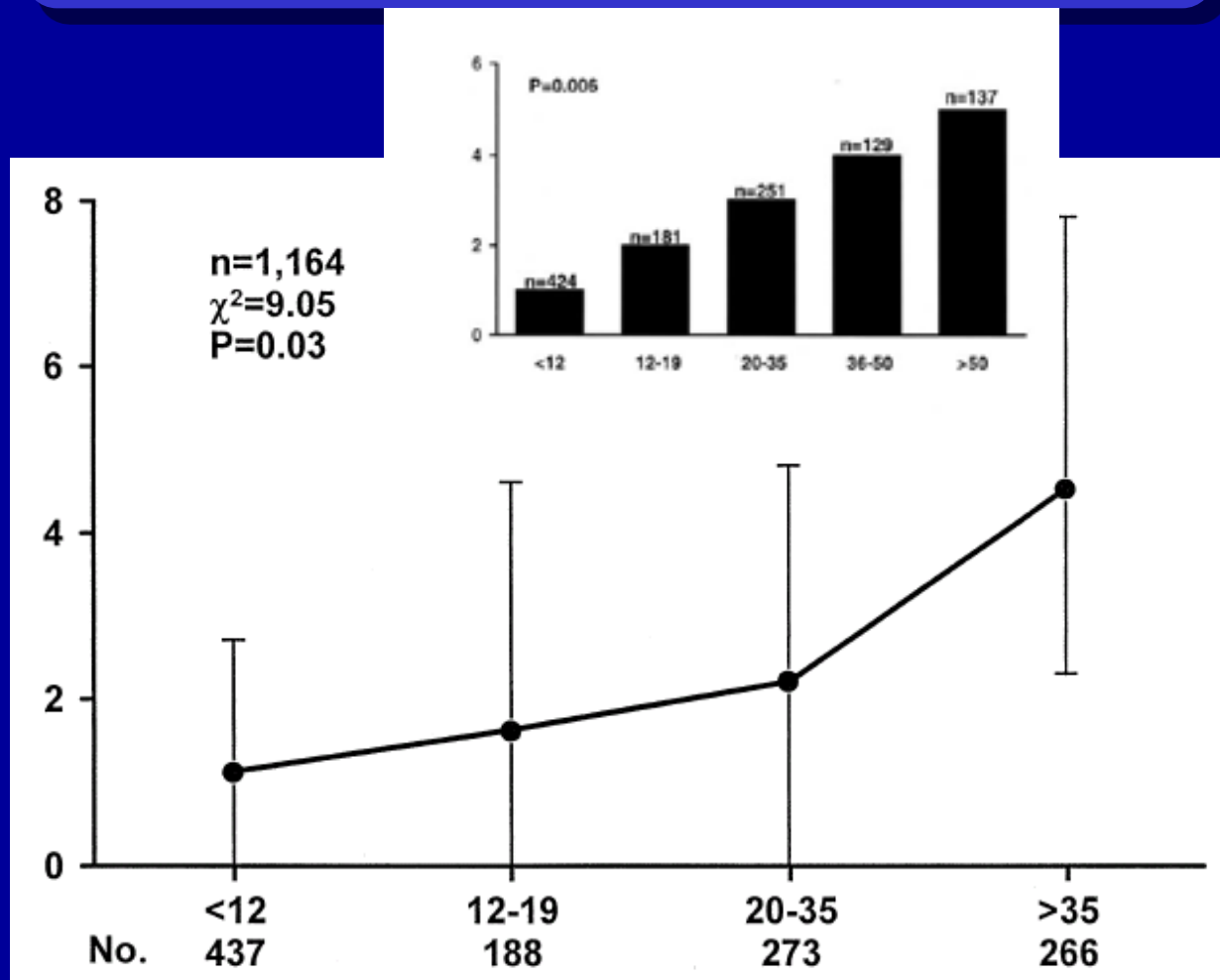




Myocardial infarction and prognosis



6 Month
mortality
(%)



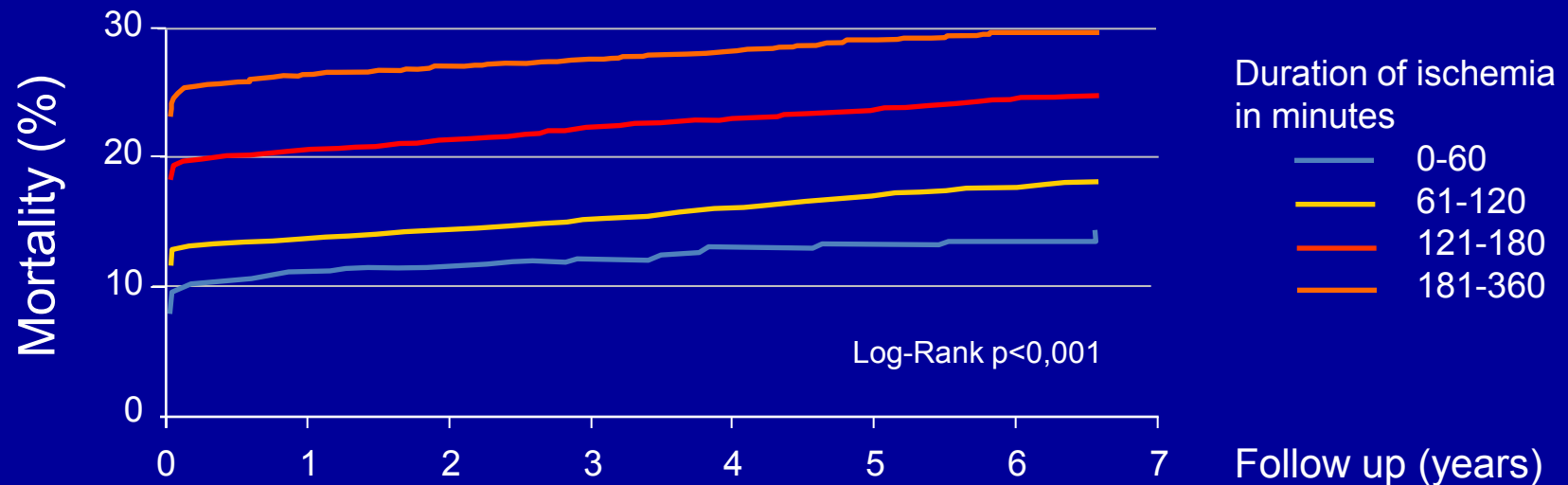
Infarct size (% area at risk)



Duration of ischemia and mortality



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



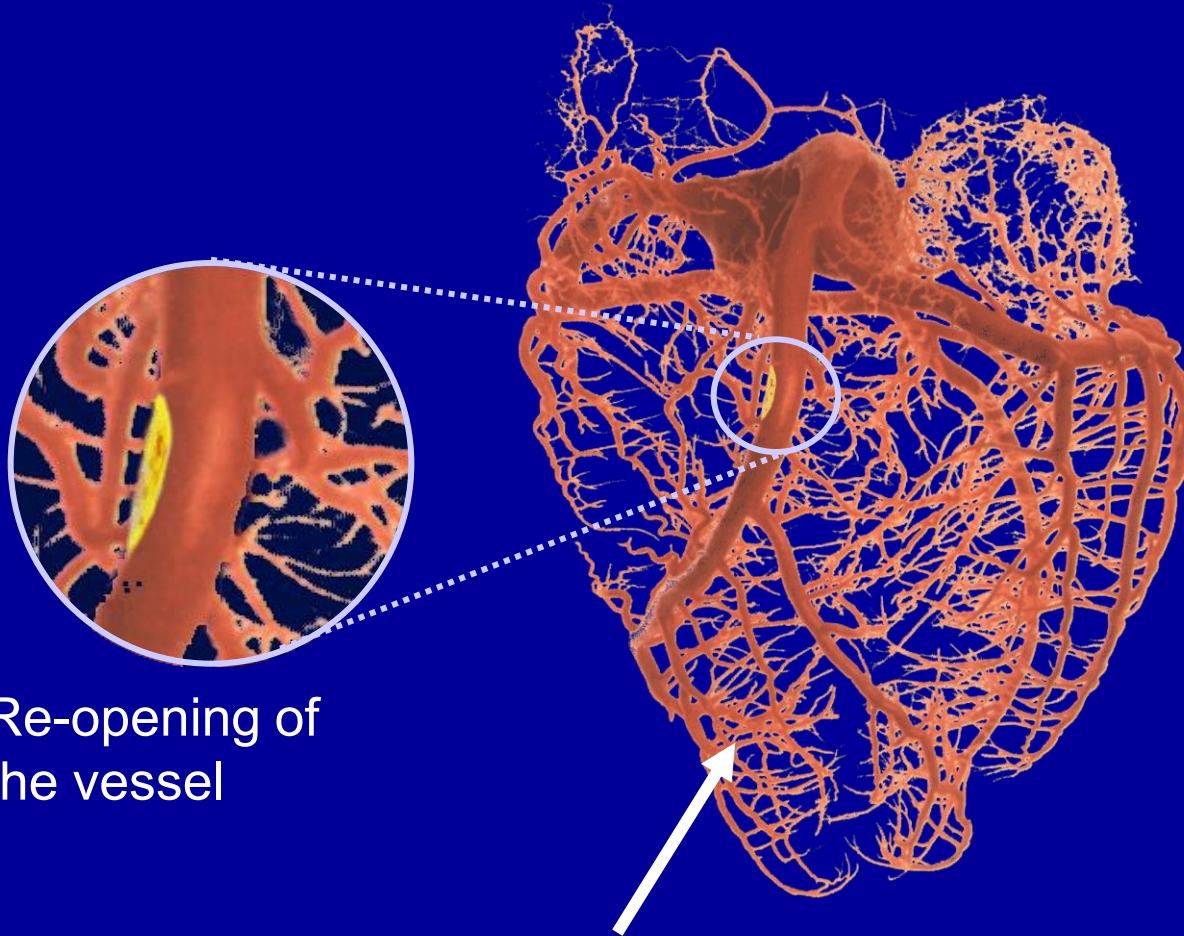
0-60	347	311	278	230	192	138	87
61-120	2643	2339	1906	1420	1006	667	375
121-180	2092	1836	1503	1183	843	533	278
181-360	1127	923	765	647	491	332	172

Patient



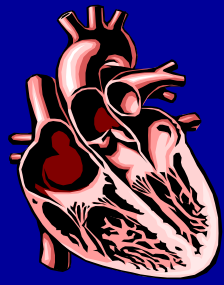
CHD

Reperfusion

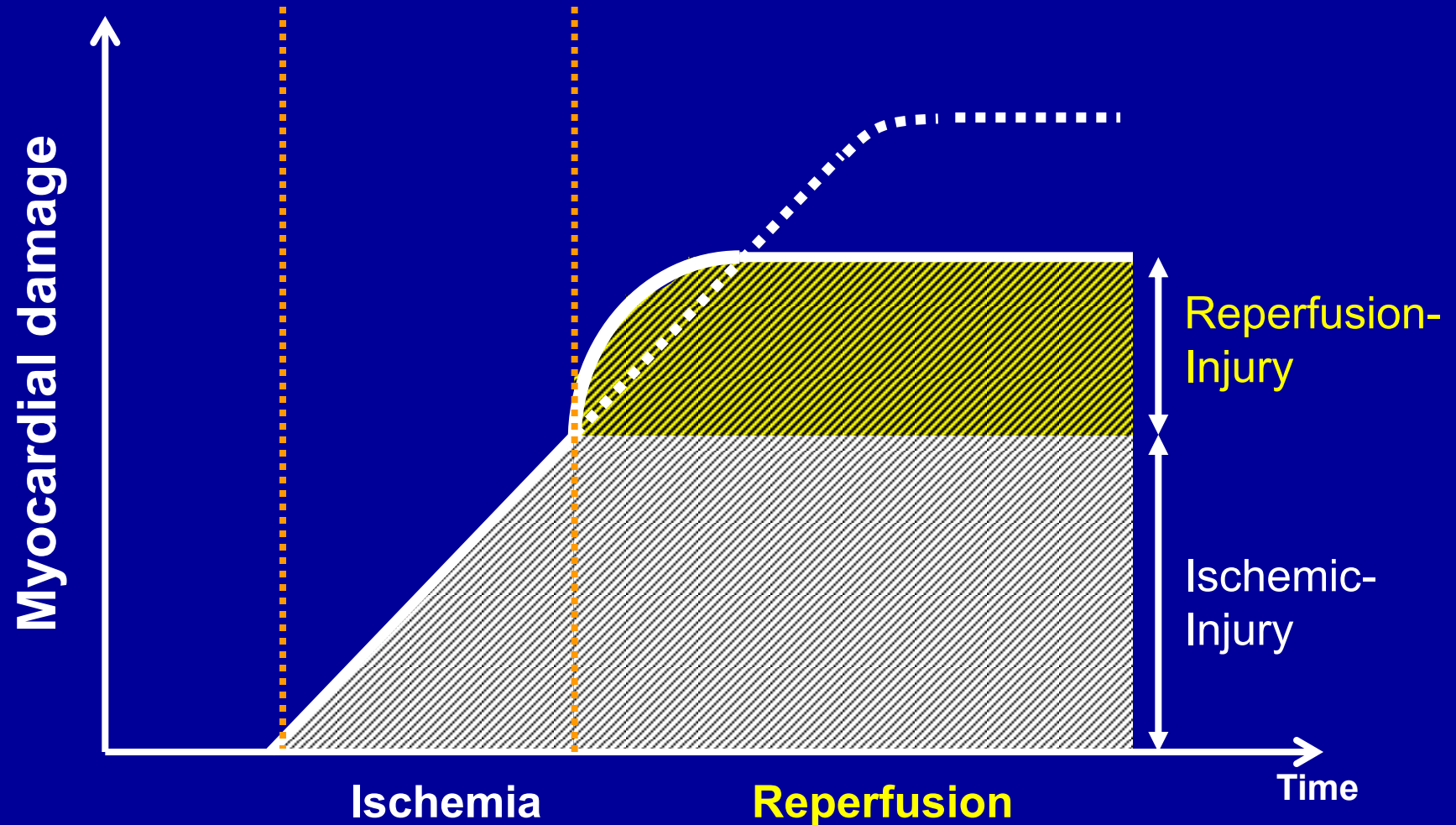


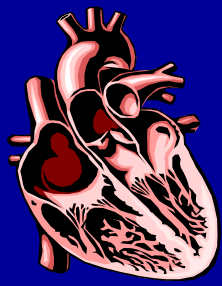
Re-opening of
the vessel

Reperfused myocardium

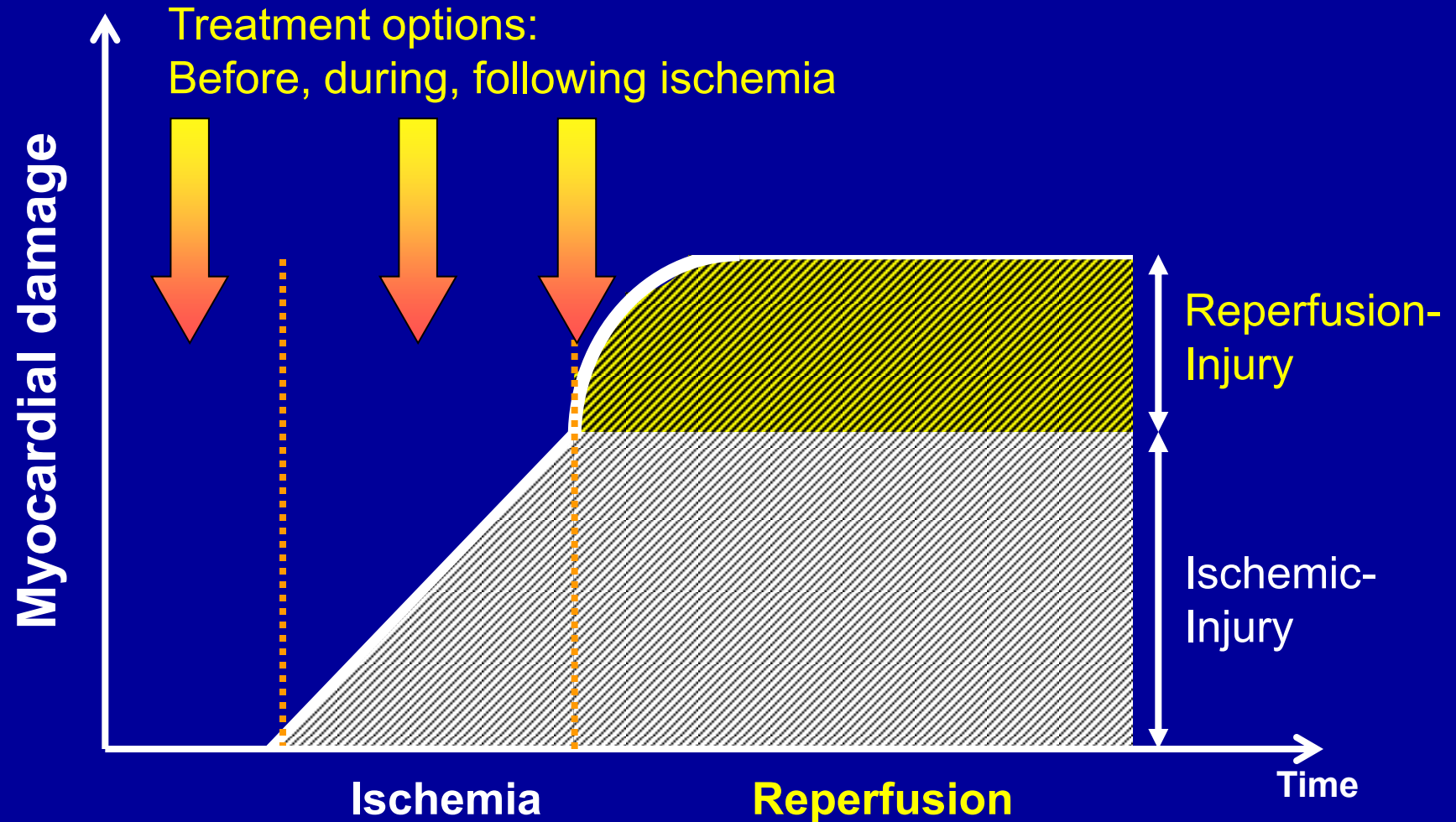


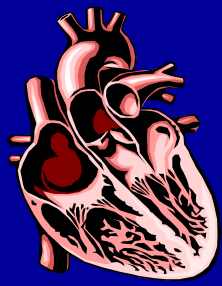
Ischemia-reperfusion injury



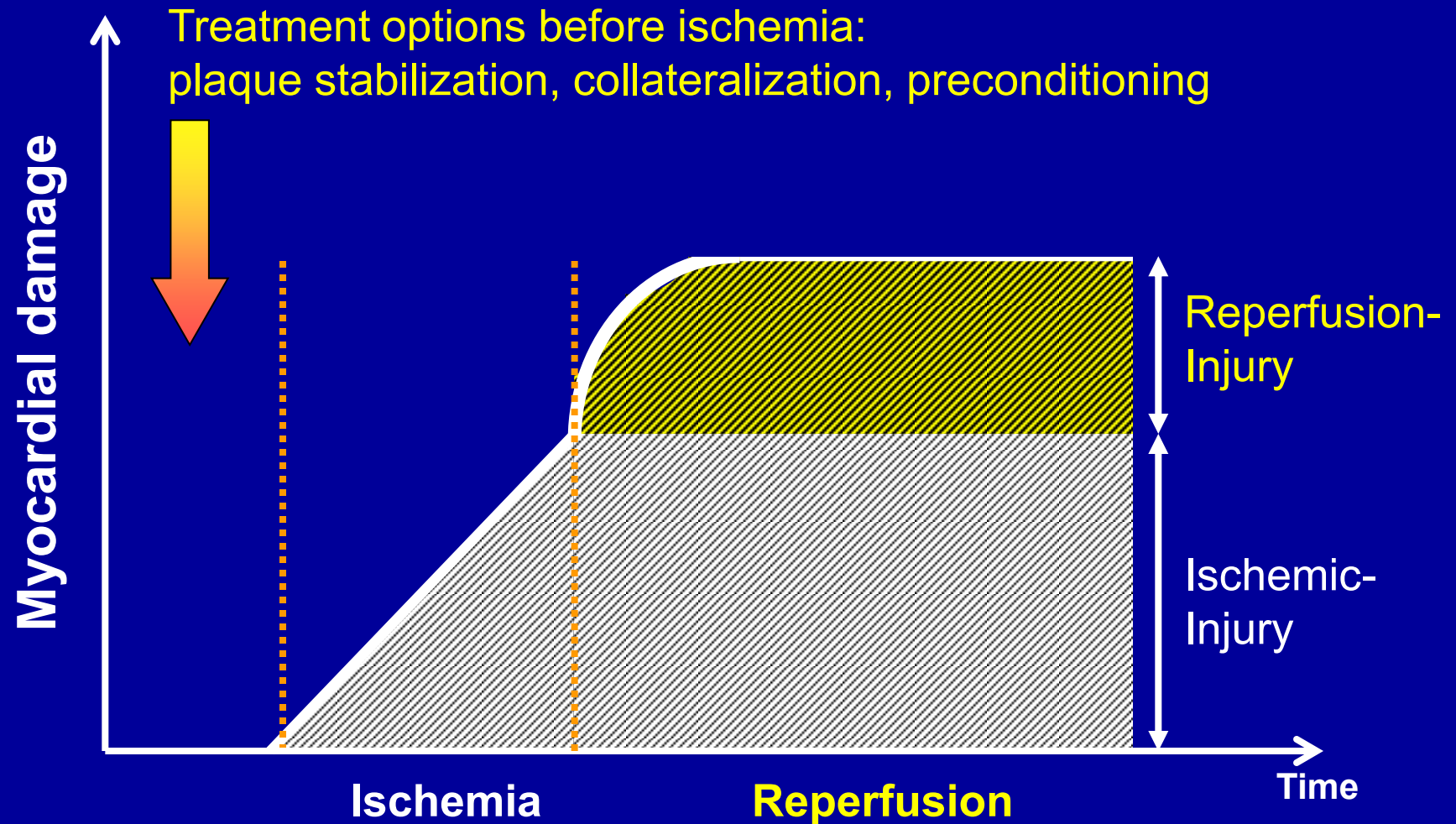


Ischemia-reperfusion injury



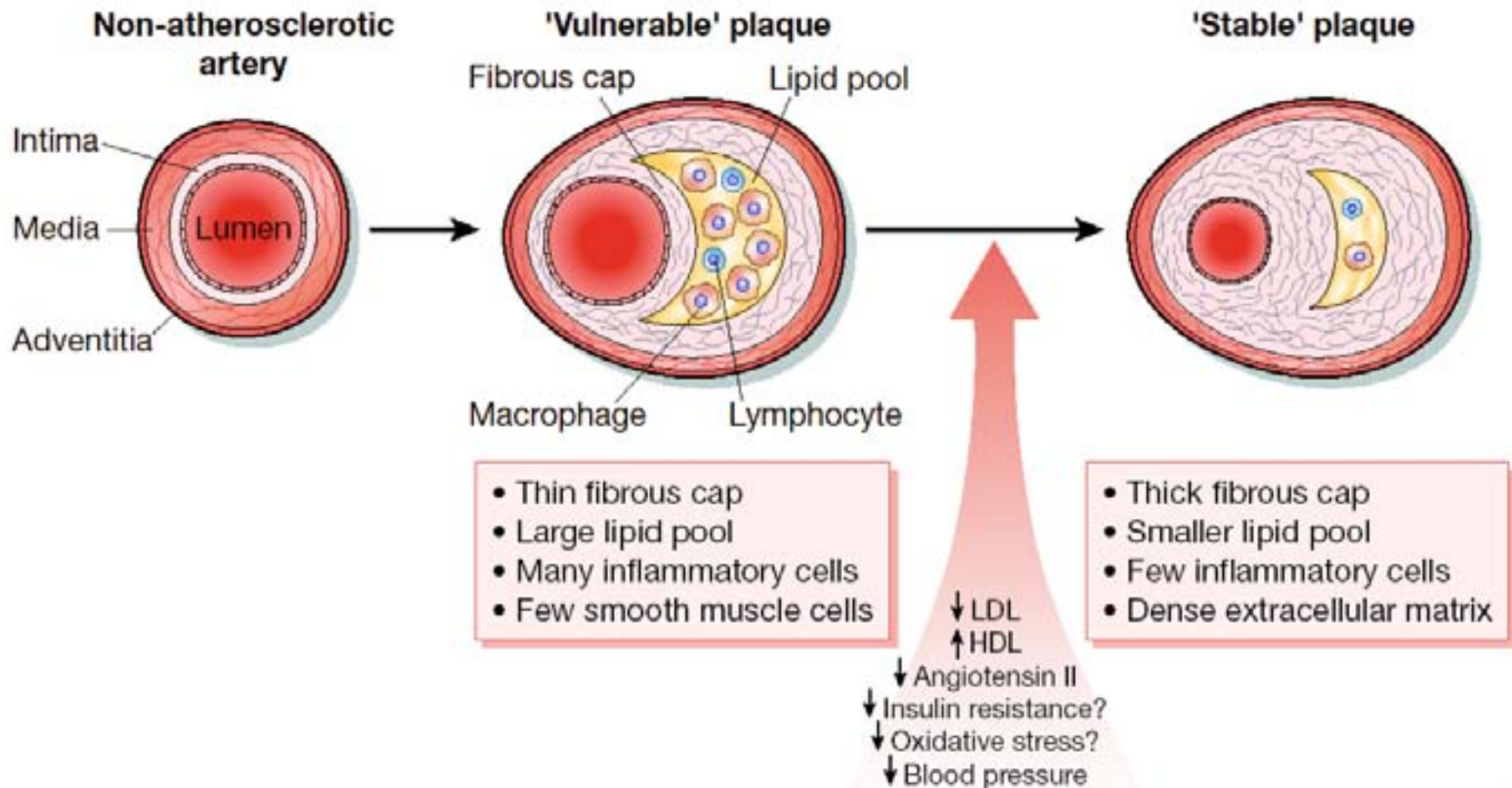


Ischemia-reperfusion injury





Development of an unstable plaque





Avoiding plaque rupture: statins (1976)

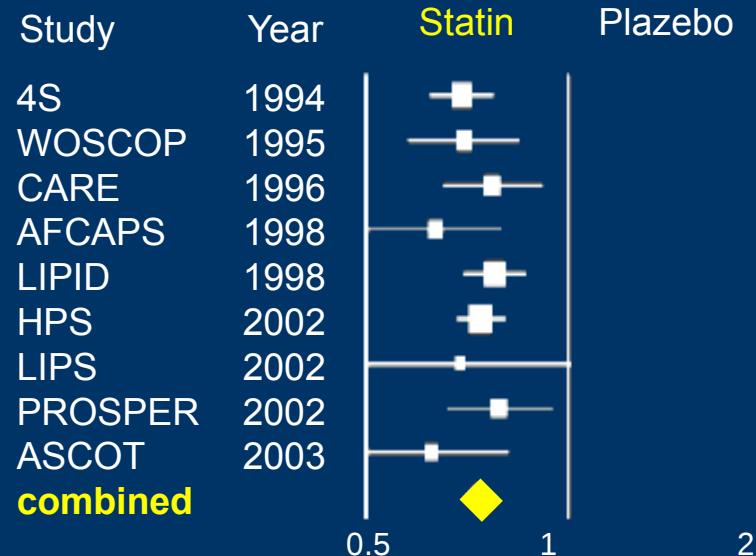


Akira Endo

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



Cheung et al., Br J Clin Pharmacol 57:640-651, 2004



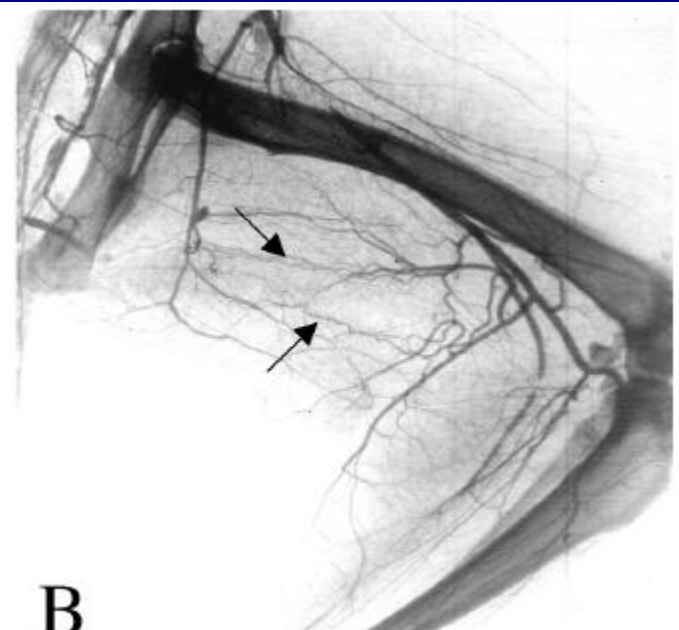
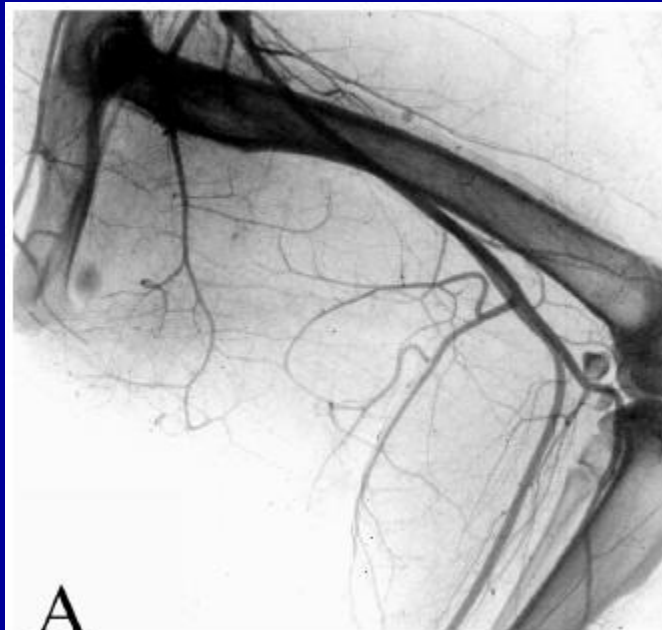
Collateral vessel growth



Postmortem angiograms of rabbit hindlimbs

control

7d occlusion of the femoral artery

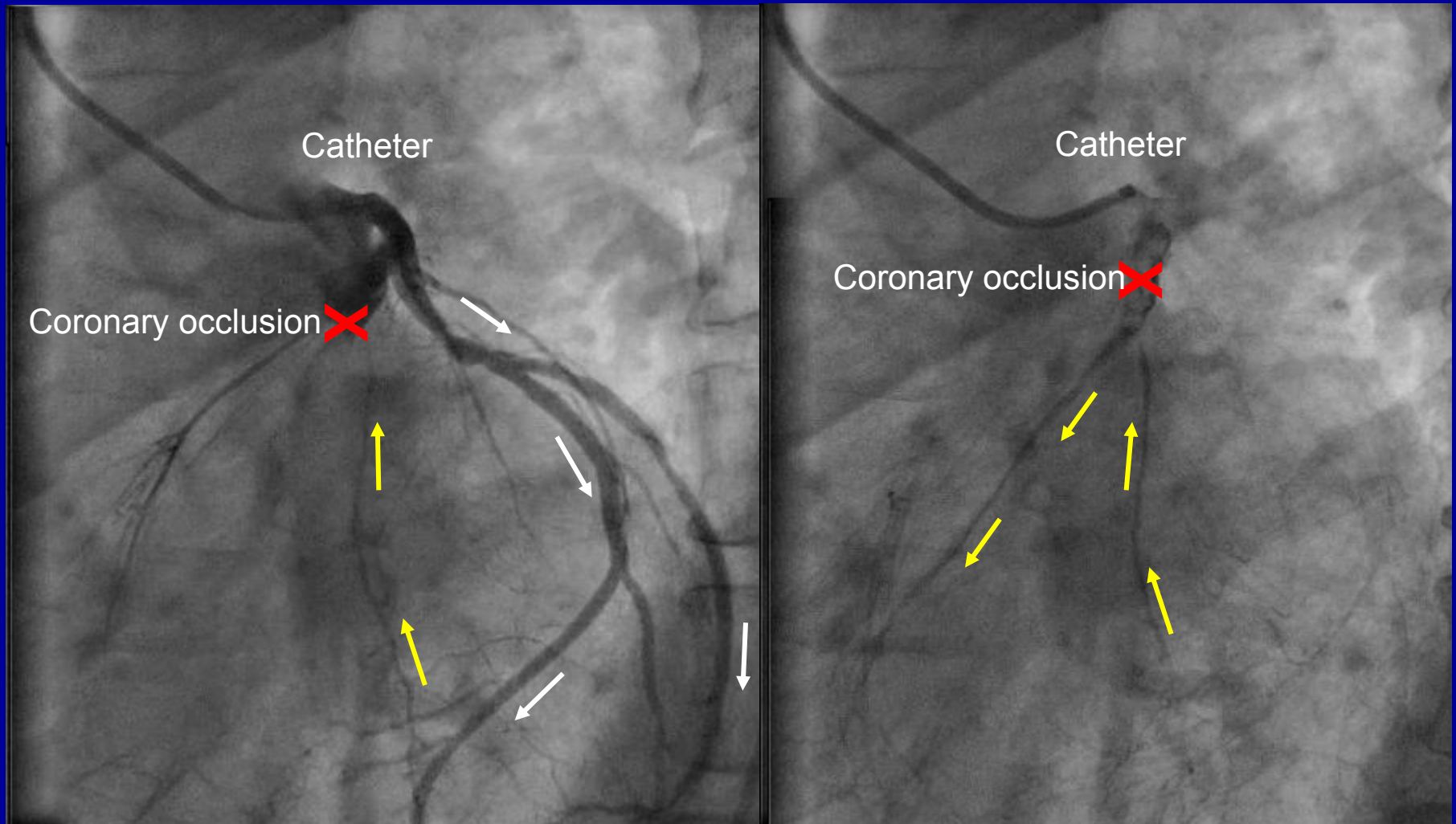


Patient



CHD

Collateral vessel growth

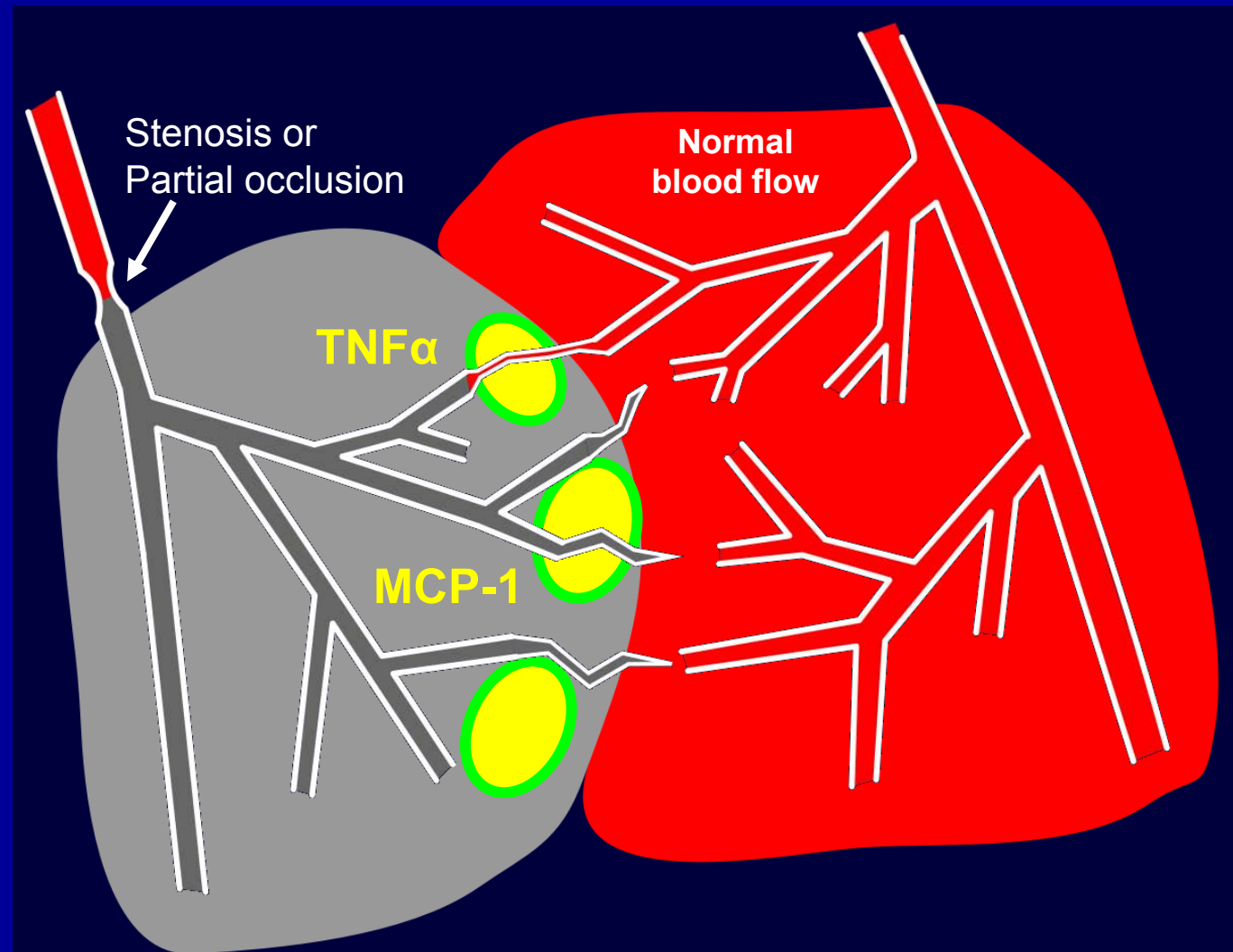
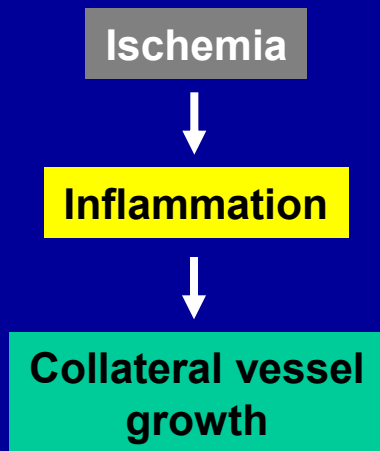


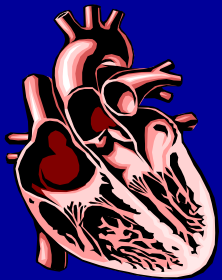
Patient



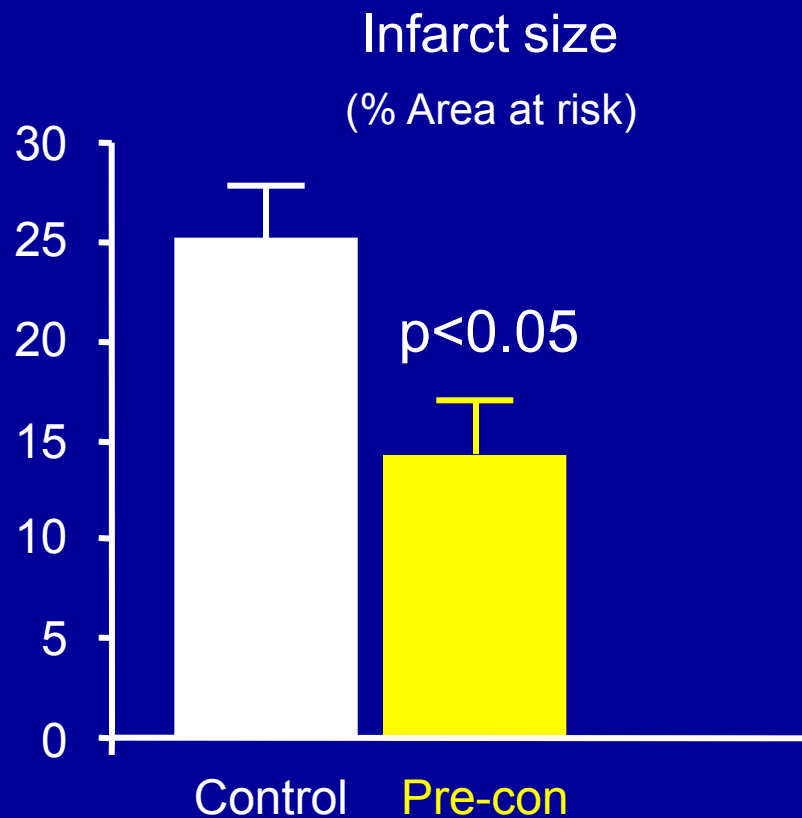
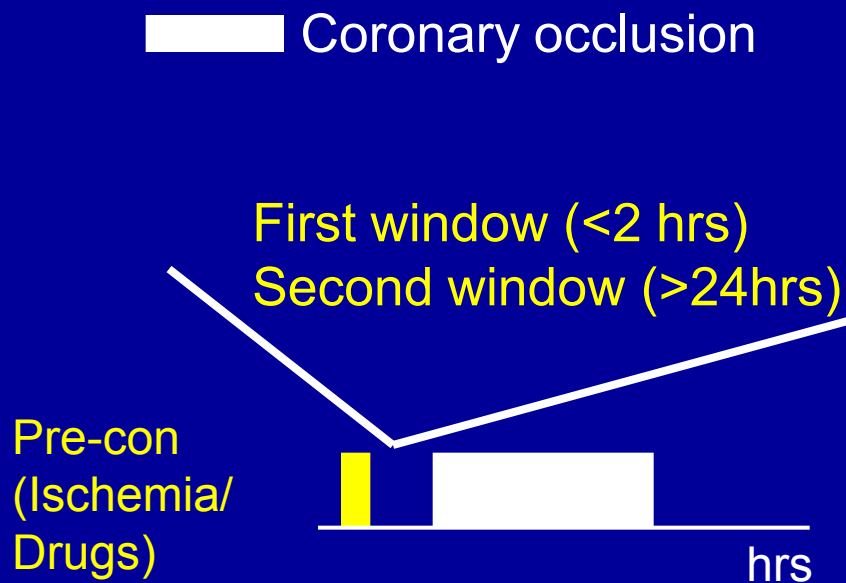
CHD

Collateral vessel growth

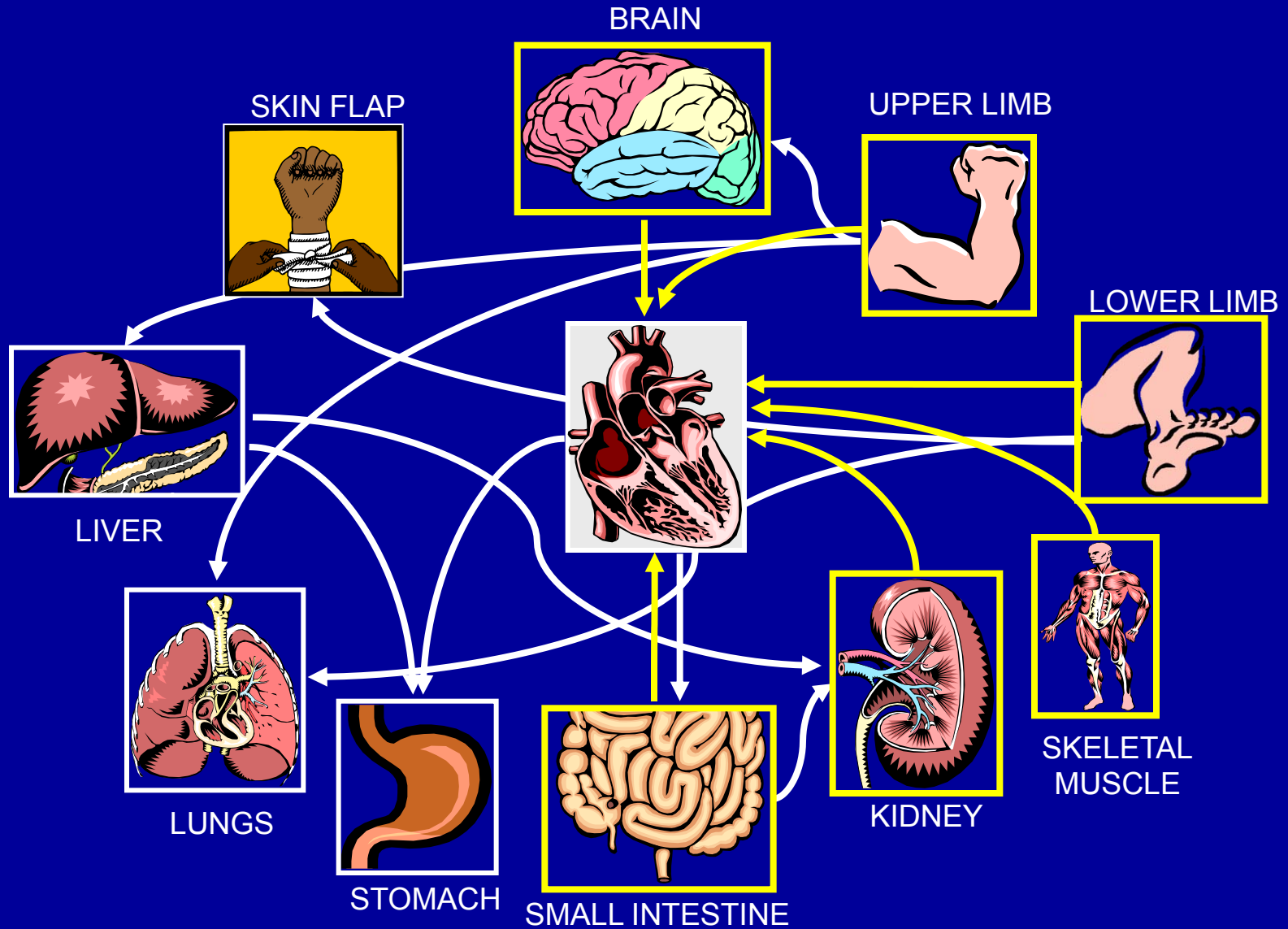




Endogenous cardioprotection: Ischemic Preconditioning



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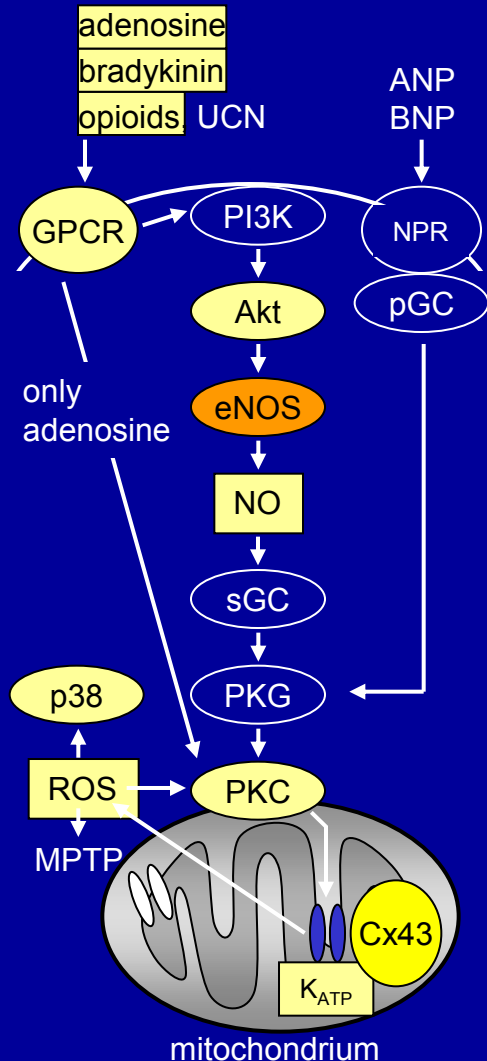
Interaction of Cardiovascular Risk Factors with Myocardial Ischemia/Reperfusion Injury, Preconditioning, and Postconditioning

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



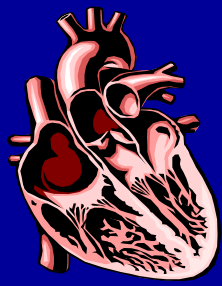
Heinzel et al., Circ Res 97:583-586, 2005

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

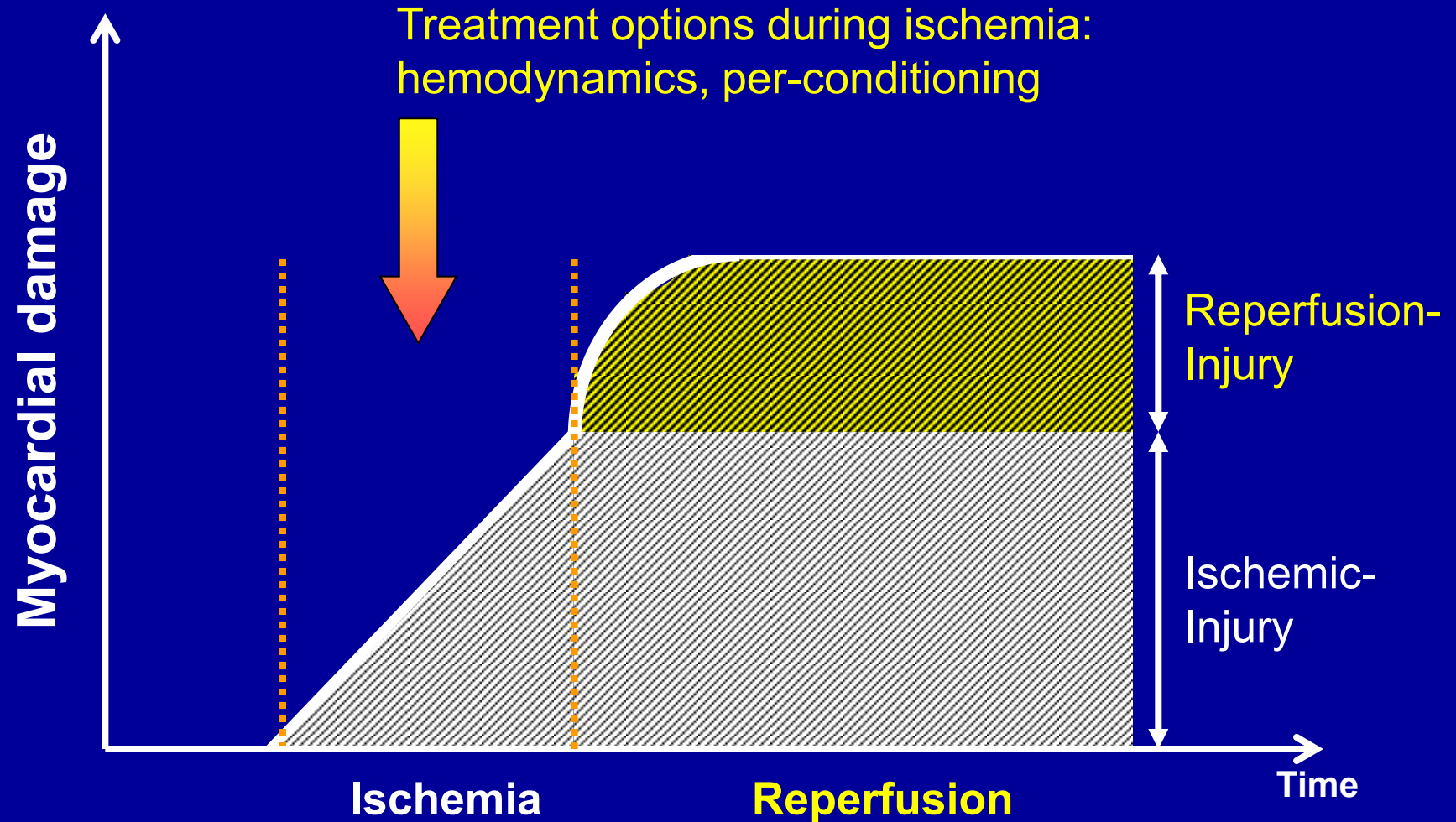
Rodriguez-Sinovas et al., Circ Res 99:93-101, 2006

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

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



Ischemia-reperfusion injury



Patient



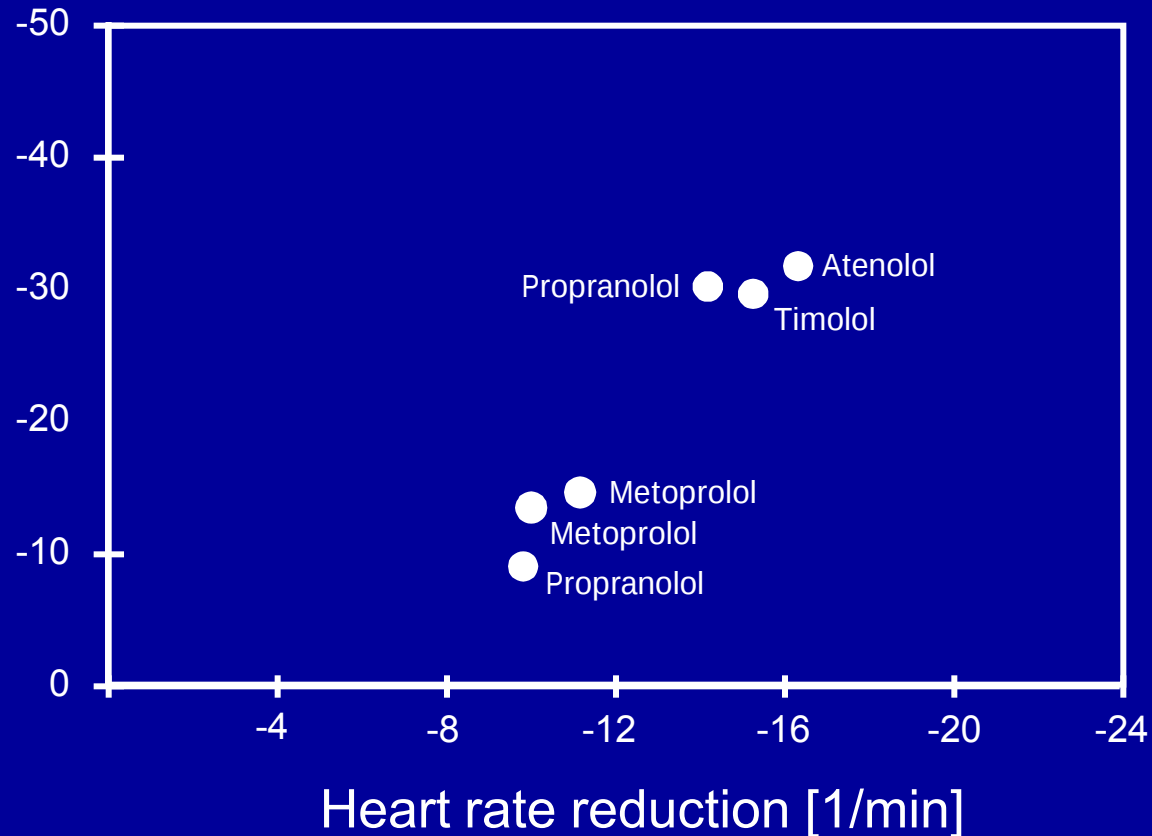
CHD

Ischemia-reperfusion injury: β -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 Bøtker, 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

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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

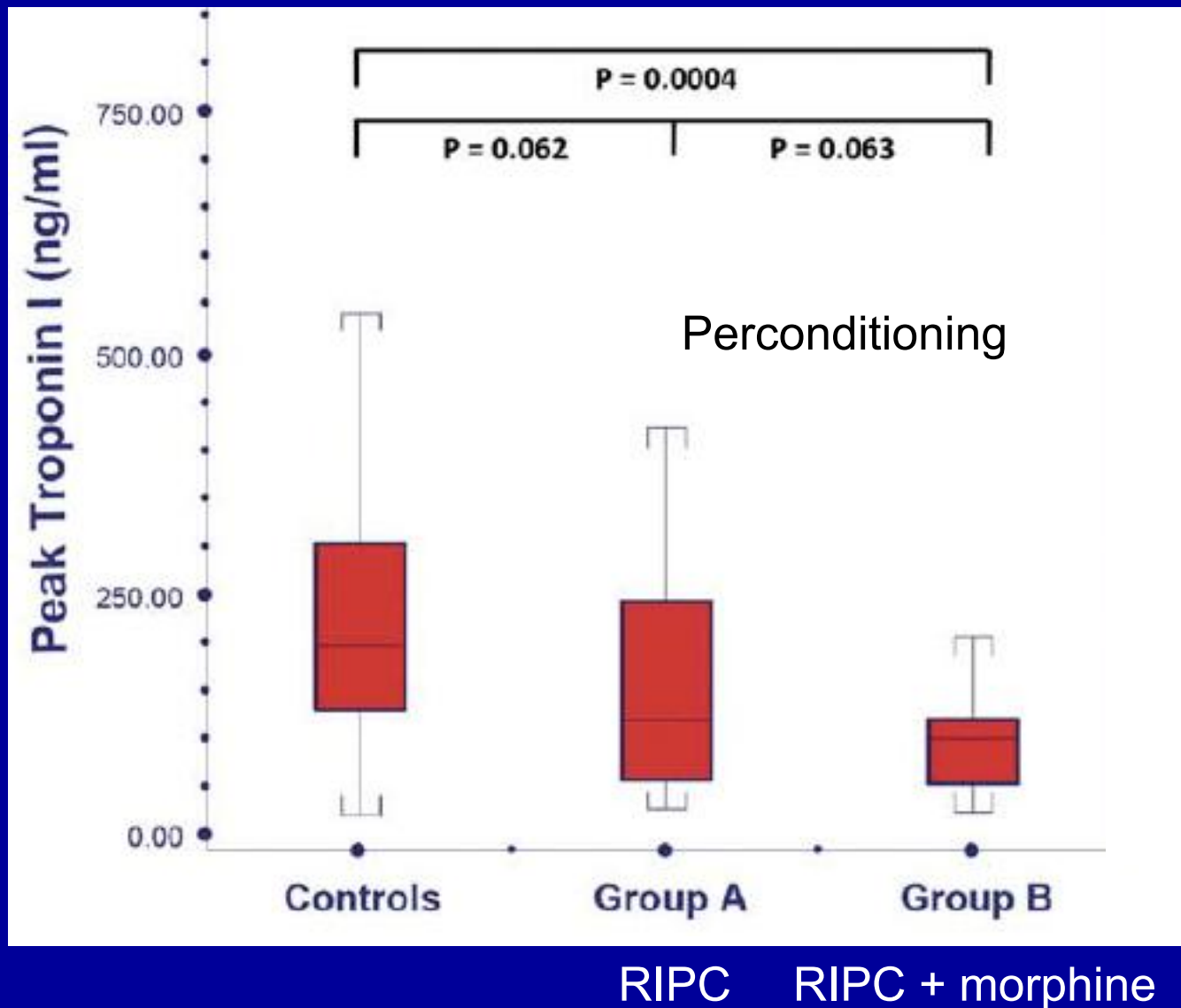
Ilias Rentoukas, MD,* Georgios Giannopoulos, MD,† Andreas Kaoukis, MD,†

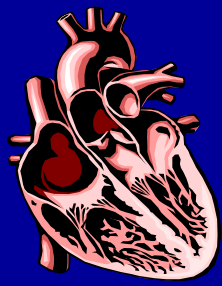
Patient



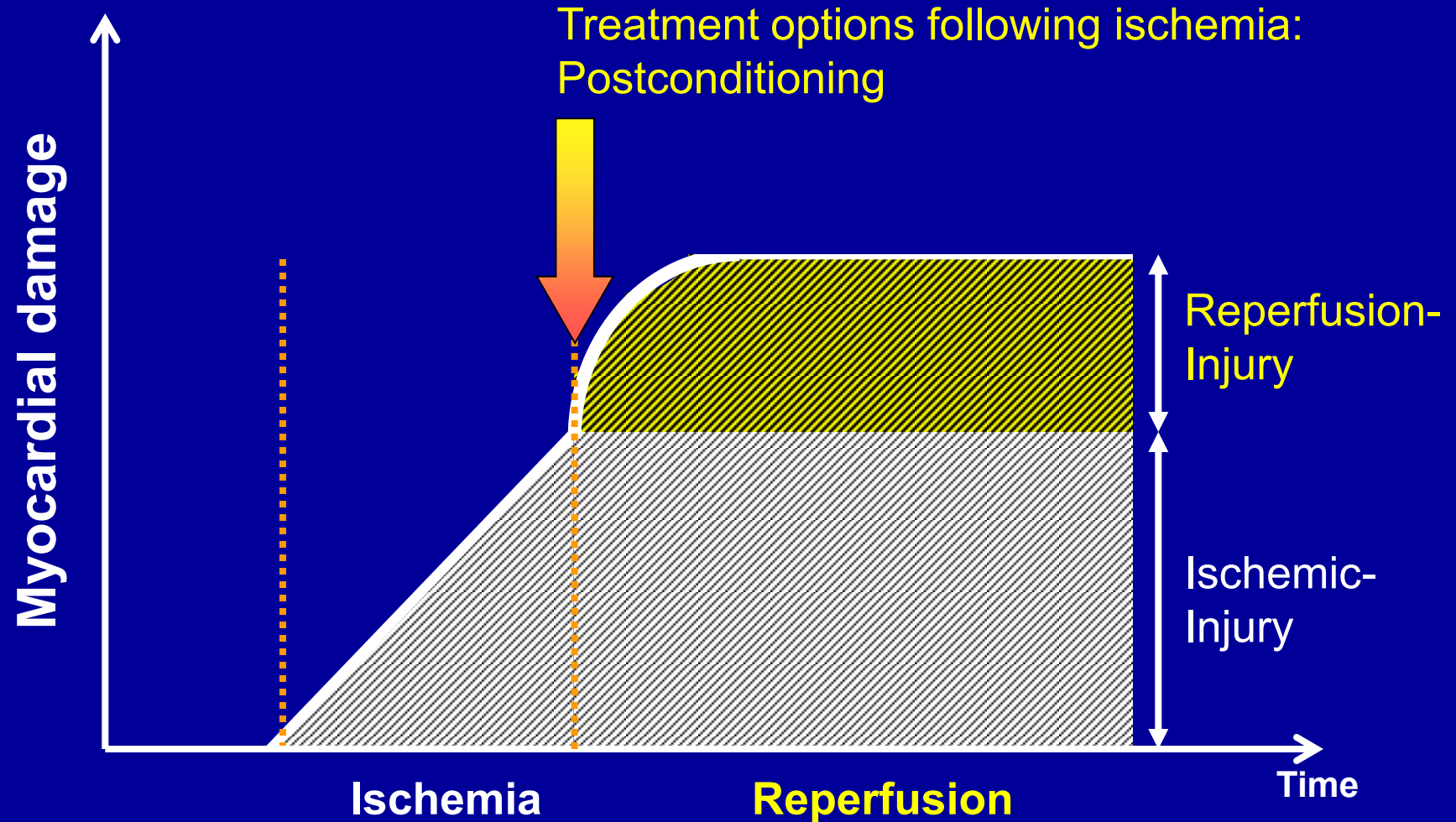
CHD

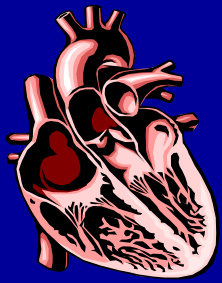
Endogenous cardioprotection: Perconditioning





Ischemia-reperfusion injury





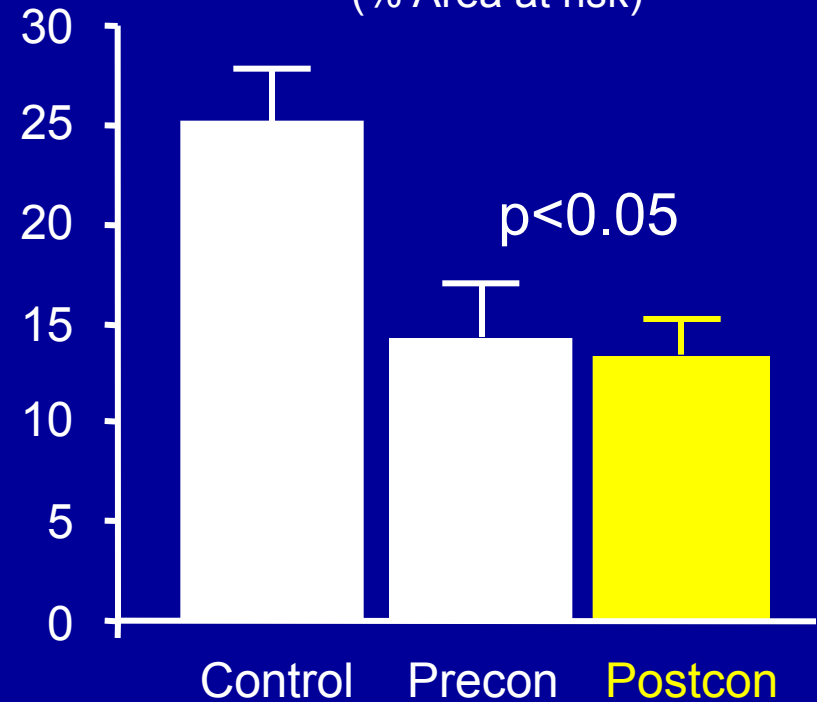
Endogenous cardioprotection: Pre- and Post-conditioning



Coronary occlusion



Infarct size
(% Area at risk)

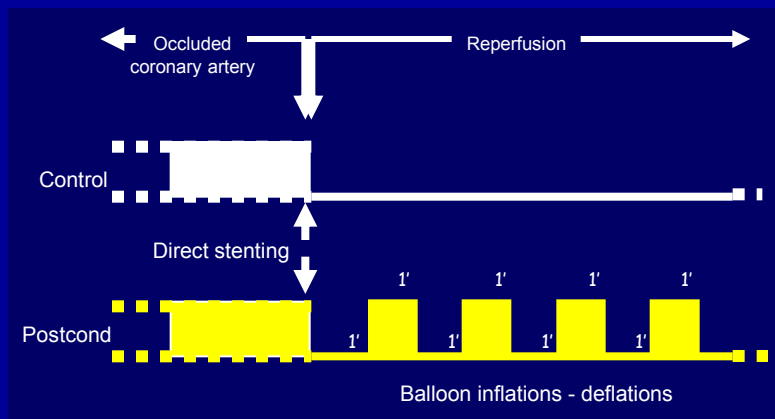
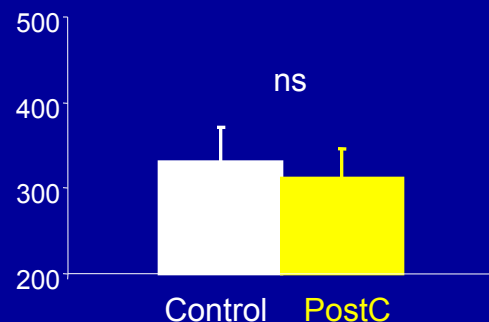




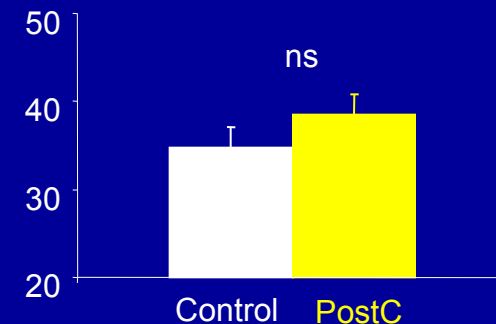
Endogenous cardioprotection: Ischemic Postconditioning



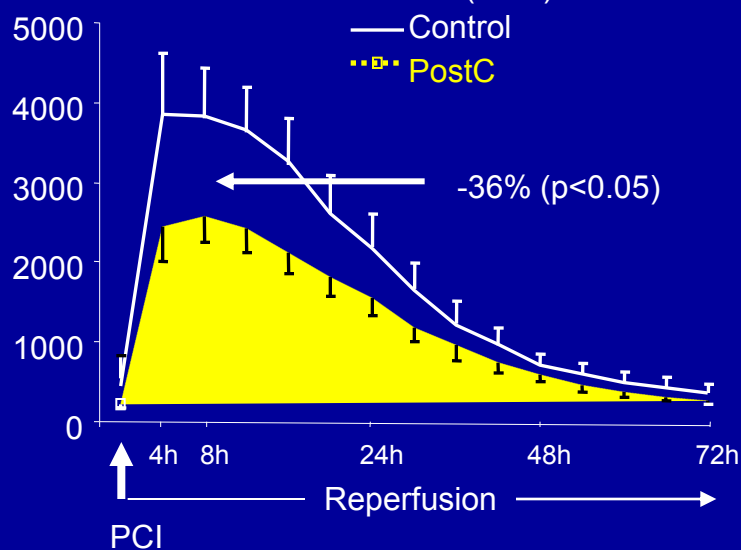
(min) Duration of Ischemia



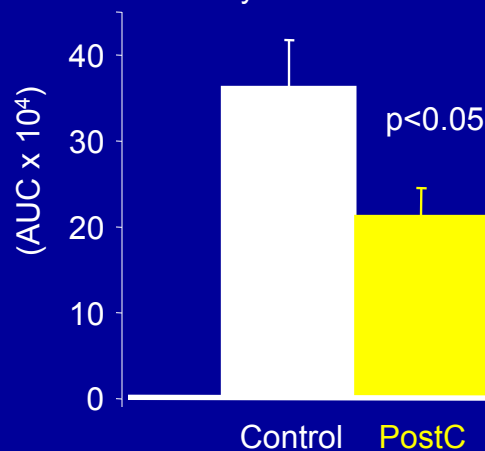
(%) Area at Risk



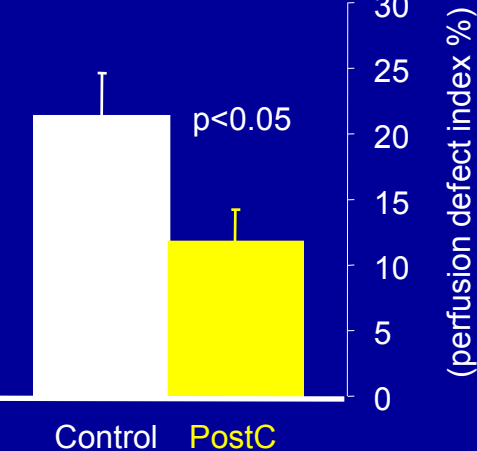
CK release (AUC)



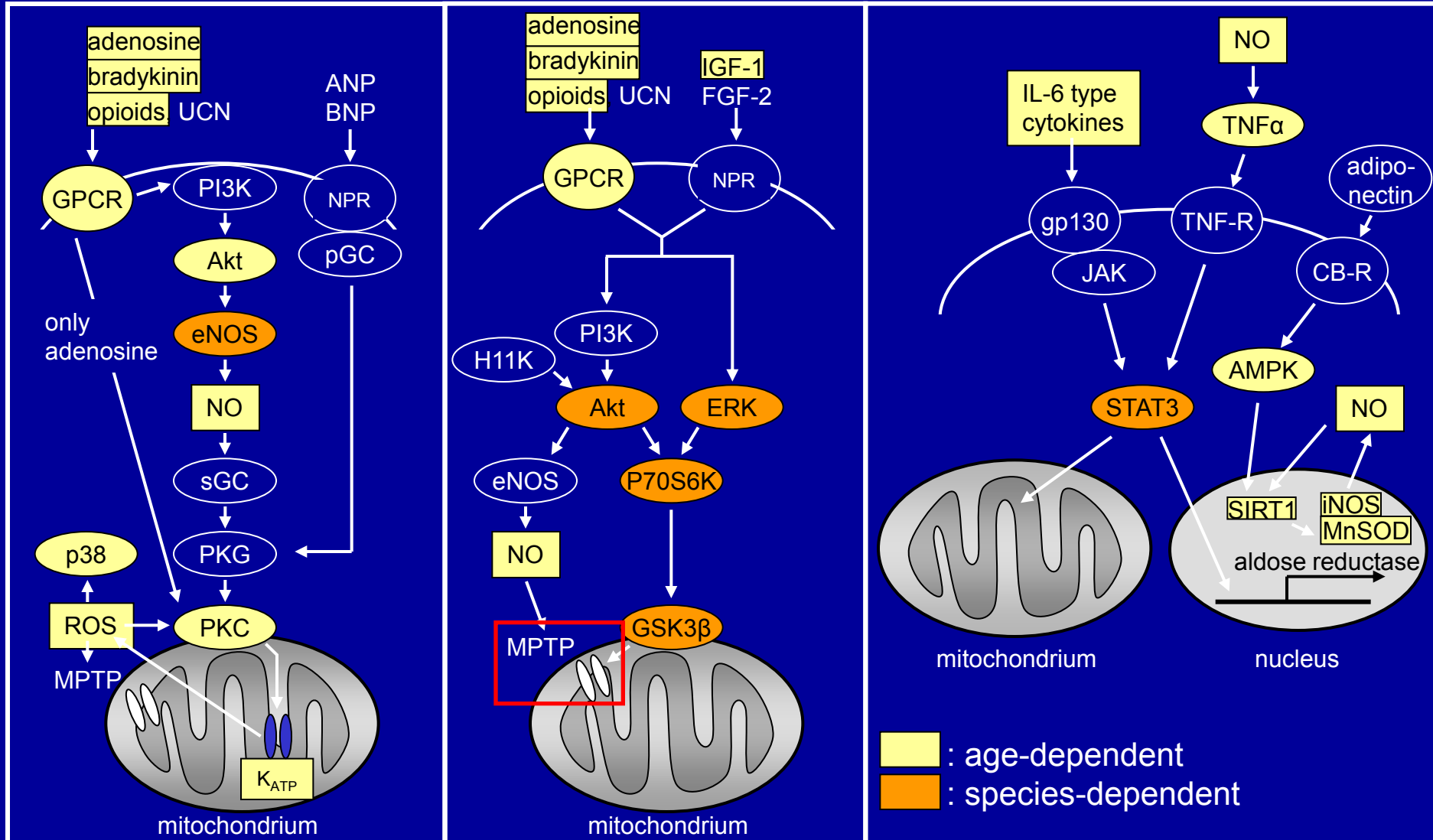
Day 1-3 CK release



SPECT at 6 months



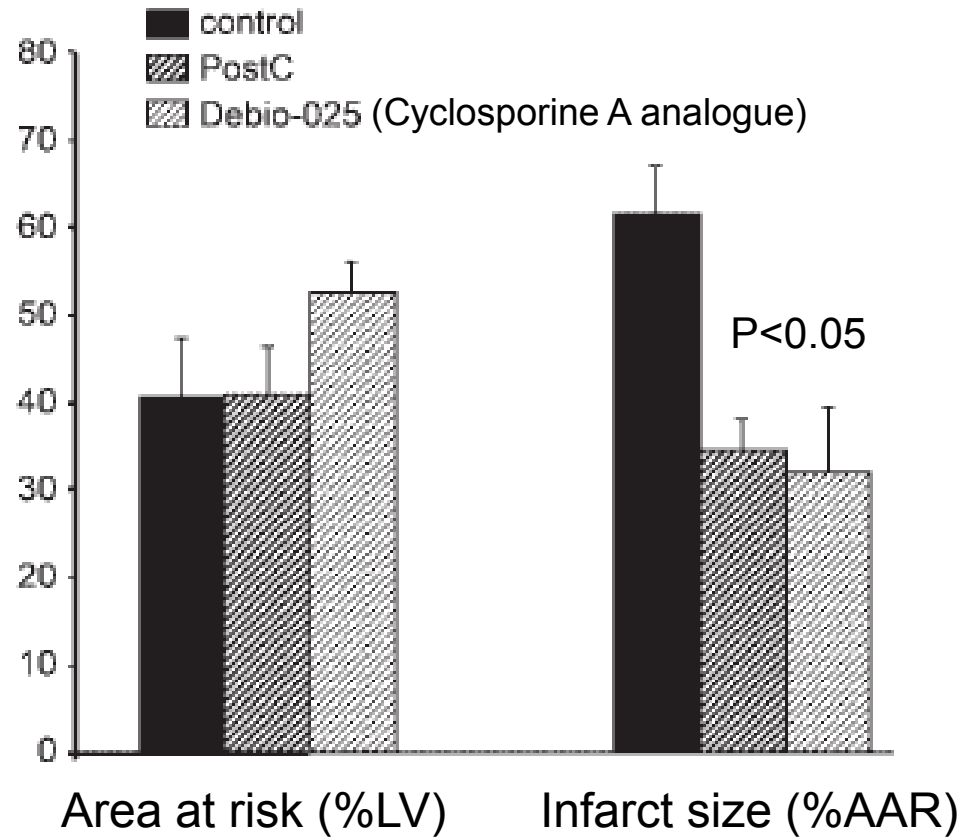
Pre- and Post-conditioning: Signal transduction





Mice

Ischemic Postconditioning: Signal transduction



Patient



CHD

Pharmacological Postconditioning



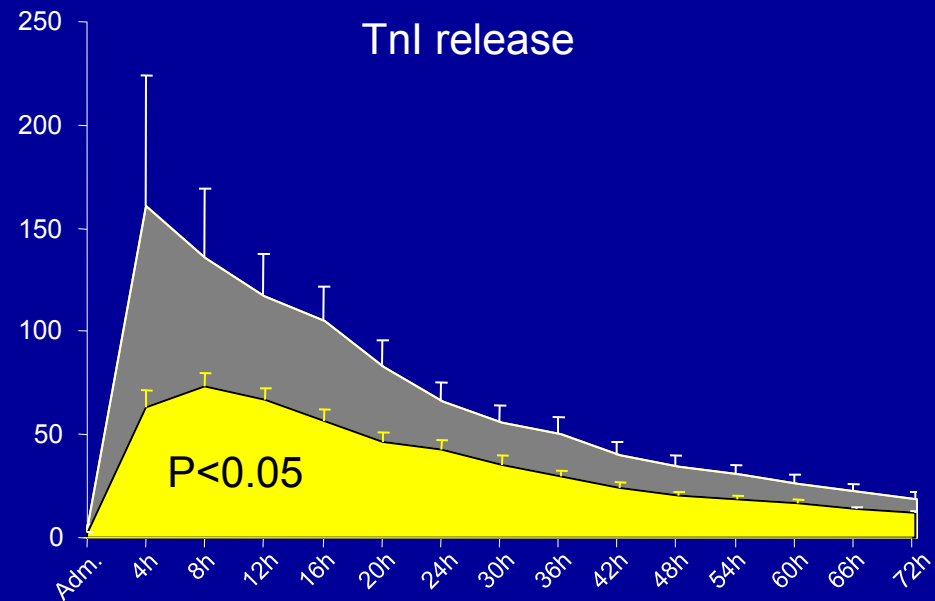
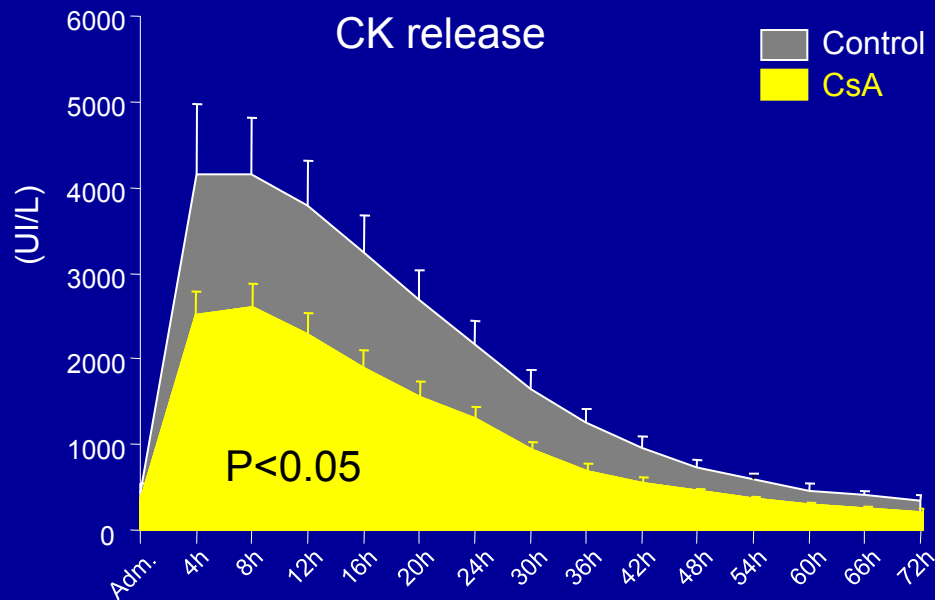
Cyclosporine A (or saline)
(2.5 mg/kg, IV bolus)

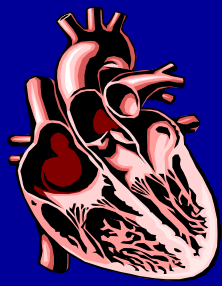
Coronary artery occlusion

Direct stenting

Day 1-3
CK / Tnl release

Infarct size





Ischemia-reperfusion injury

