

Cardioprotection – Next Steps

Robert M. Mentzer, Jr., MD

**Wayne State University School of Medicine
Detroit, Michigan**

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I/R Injury: A Clinical Problem

- Incidence of myocardial stunning requiring inotropic support ranges between 60% and 90%
- New myonecrosis after CABG ranges between 40% and 60%
- Incidence of Q-wave or non-Q-wave MI ranges between 12% and 19%
- Postop enzyme elevation is independent predictor of increased risk (40% to 50%) of intermediate and late death

Challenge

- To develop safe and effective agents or techniques to prevent I/R injury after cardiac surgery or AMI
- Problem persists despite decades of research
 - Preclinical testing in disease-free animals
 - Misleading Phase II trials
- Lack of enthusiasm by large Pharma and surgical community to sponsor large-scale trials that require enrollment >3,500 surgery or MI pts

Phase III Cardioprotection Trials

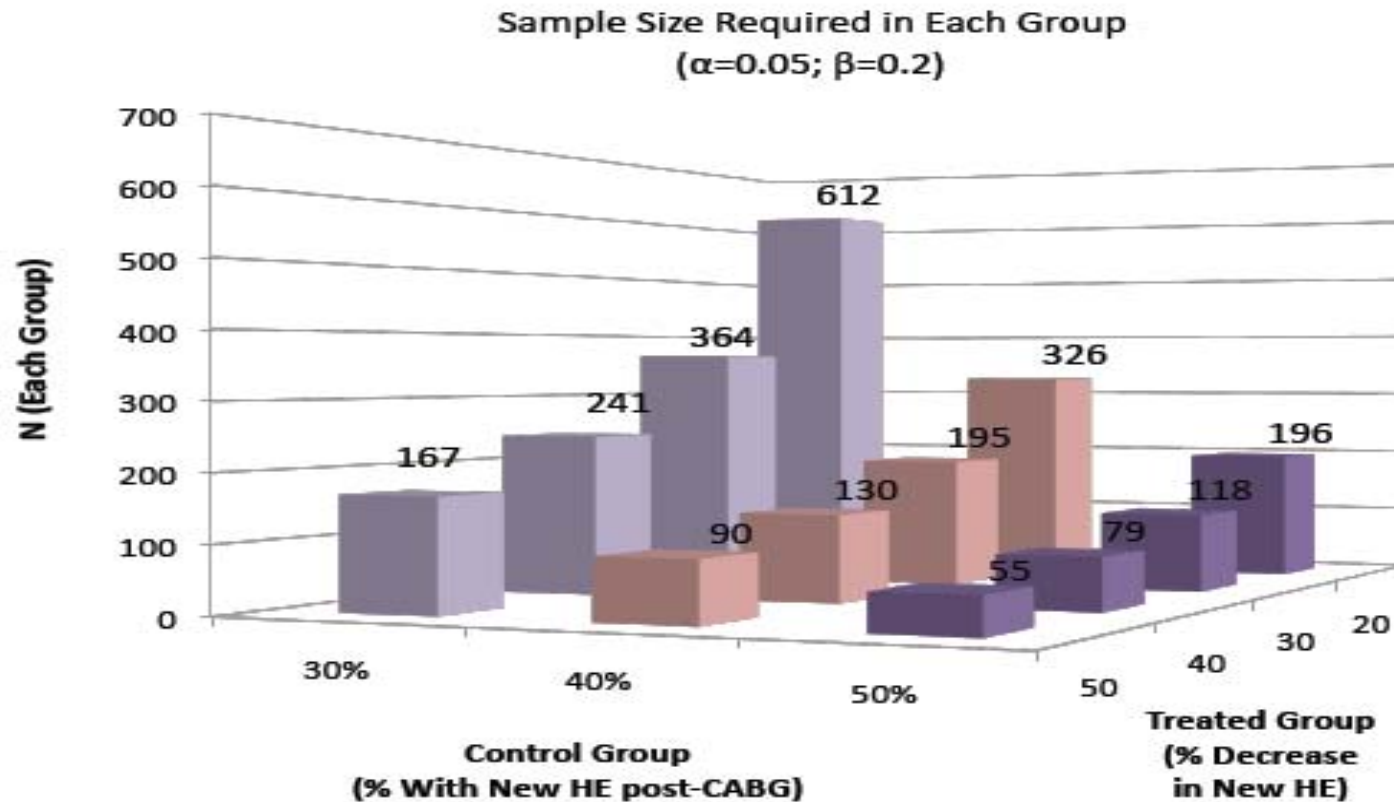
YEAR	TRIAL	FINDINGS
2004	PRIMO-CABG Pexelizumab (N=3,099)	No effect on nonfatal MI and Death in CABG pts
2008	EXPEDITION Cariporide (N=5,761)	25% RRR MI and death (p=.000002) Neurotoxicity 4.5%
2008	MEND-CABG II Pyridoxal-5'-Phosphate (N=3,023)	No effect on nonfatal MI and death
2009	RED-CABG Acadesine (N-7,500)	No effect on MI and death. Terminated for futility at 30% enrollment

Advantages of Myocardial Protection Trials in Cardiac Surgery vs AMI

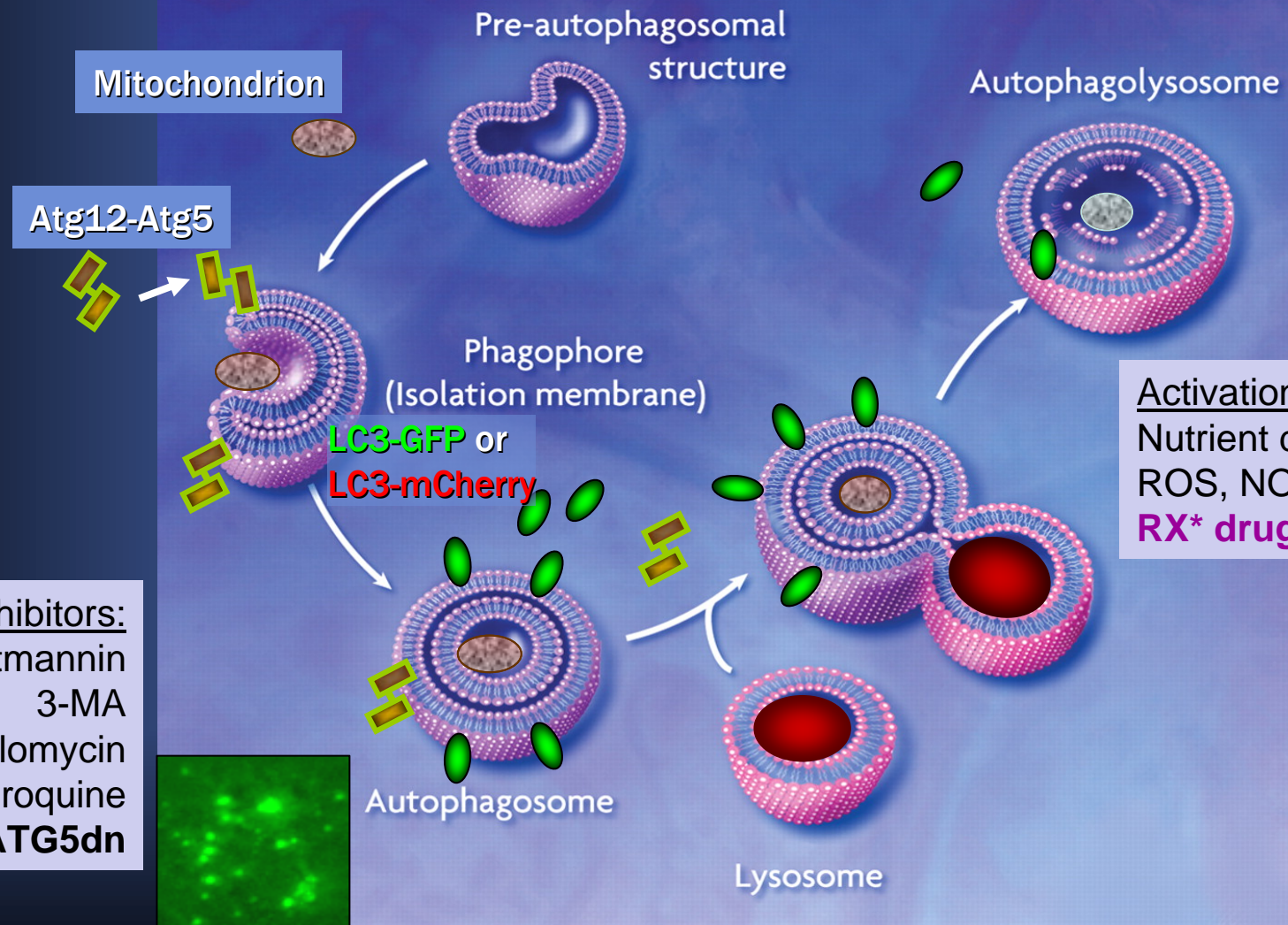
Category	CABG
Patient Characteristics	Heterogeneous aging, coexisting illnesses
Medications	Often multiple
Coronary Artery Anatomy	LM disease and multi-vessel disease
Onset of Ischemia (time)	Easy to determine
Time to Reperfusion	Easy to determine
Timing of Intervention	Before, during, or after ischemia
Myocardial Area at Risk (AAR)	Global – new and old infarct size; LV mass can be measured before and after surgery using DE-CMR

Endpoint: Prevention of MI or reduction in infarct size

Delayed-Enhancement Cardiac MRI (DE-CMR)



Autophagy : Cardioprotection Strategy



Candidate Drug

Chloramphenicol

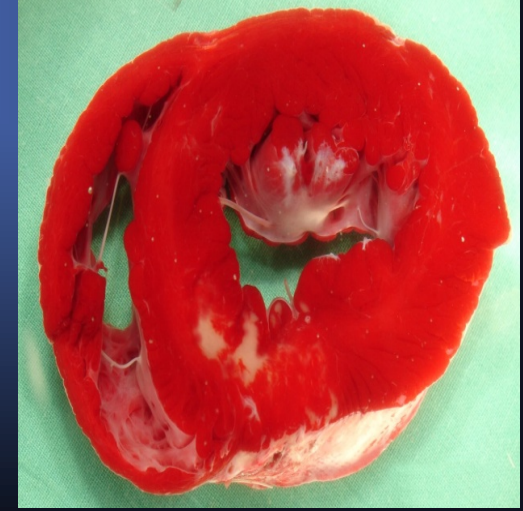
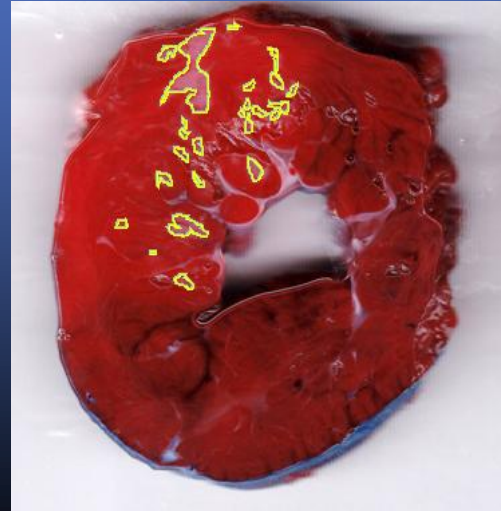
Adenosine

Ivabradine

Con



Tx



Clinical Research Gap

Absence of phase II trials that include robust measurements of prevalence, incidence, quantification of area at risk and infarct size as primary endpoints in humans