Update of Ischemic CMP

# Medical Treatment to Prevent Heart Failure after Acute MI

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# 질병의 치료

- 일차예방 : 질병 예방,
  질병의 발생을 제거하는데 목적.

- 이차예방 : 질병 조기발견,
  질병기간 단축으로 유병율 감소에 목적.

- 삼차예방 : 합병증을 최소화,
  재활에 목적.

* 예방은 질병에 초점, 증진은 건강에 초점.

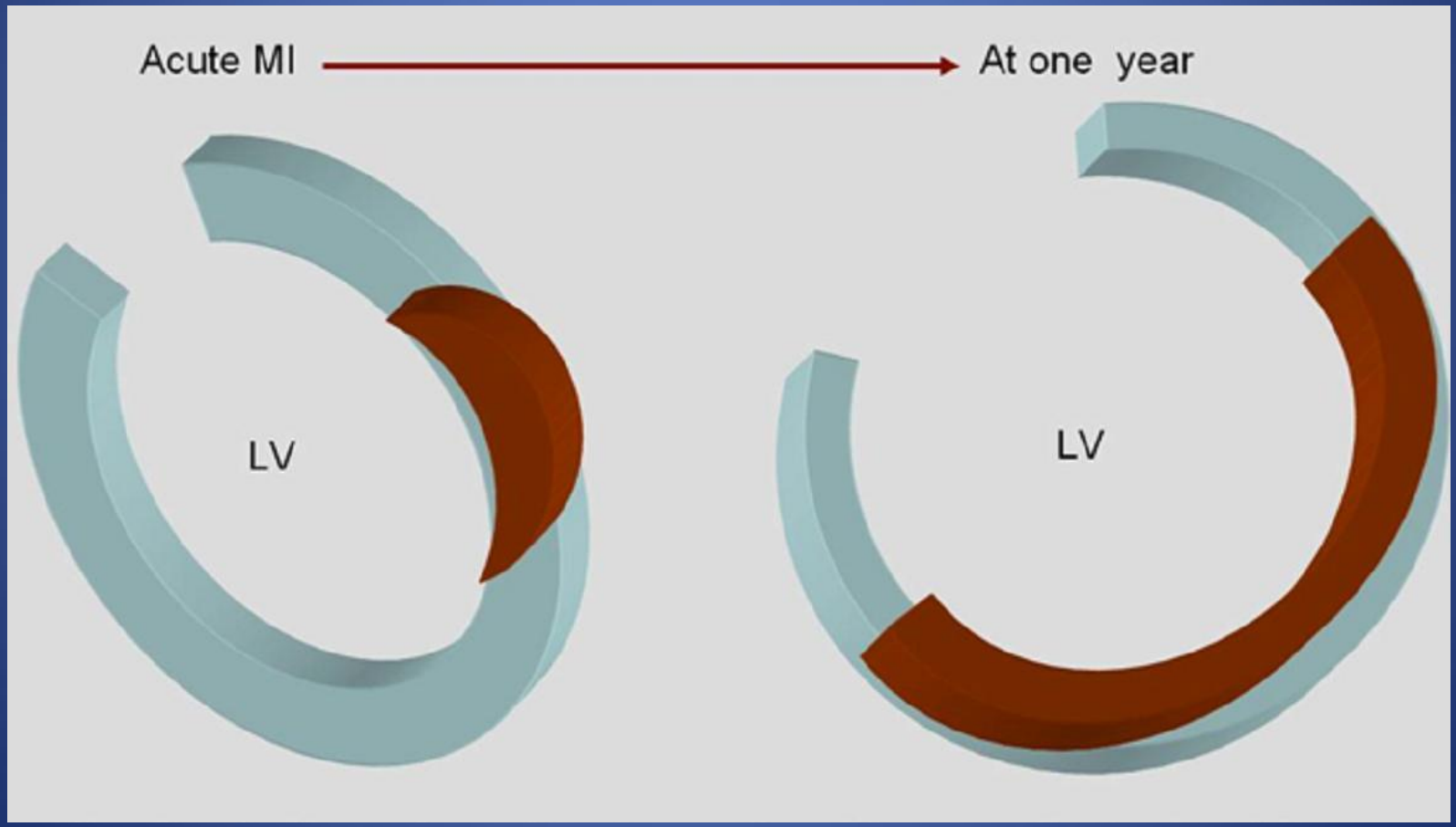
# Prevention of HF after AMI

**Risk factors** → prevention of AMI

**Acute MI** → decrease injury

**Ischemic CMP** → prevention of HF

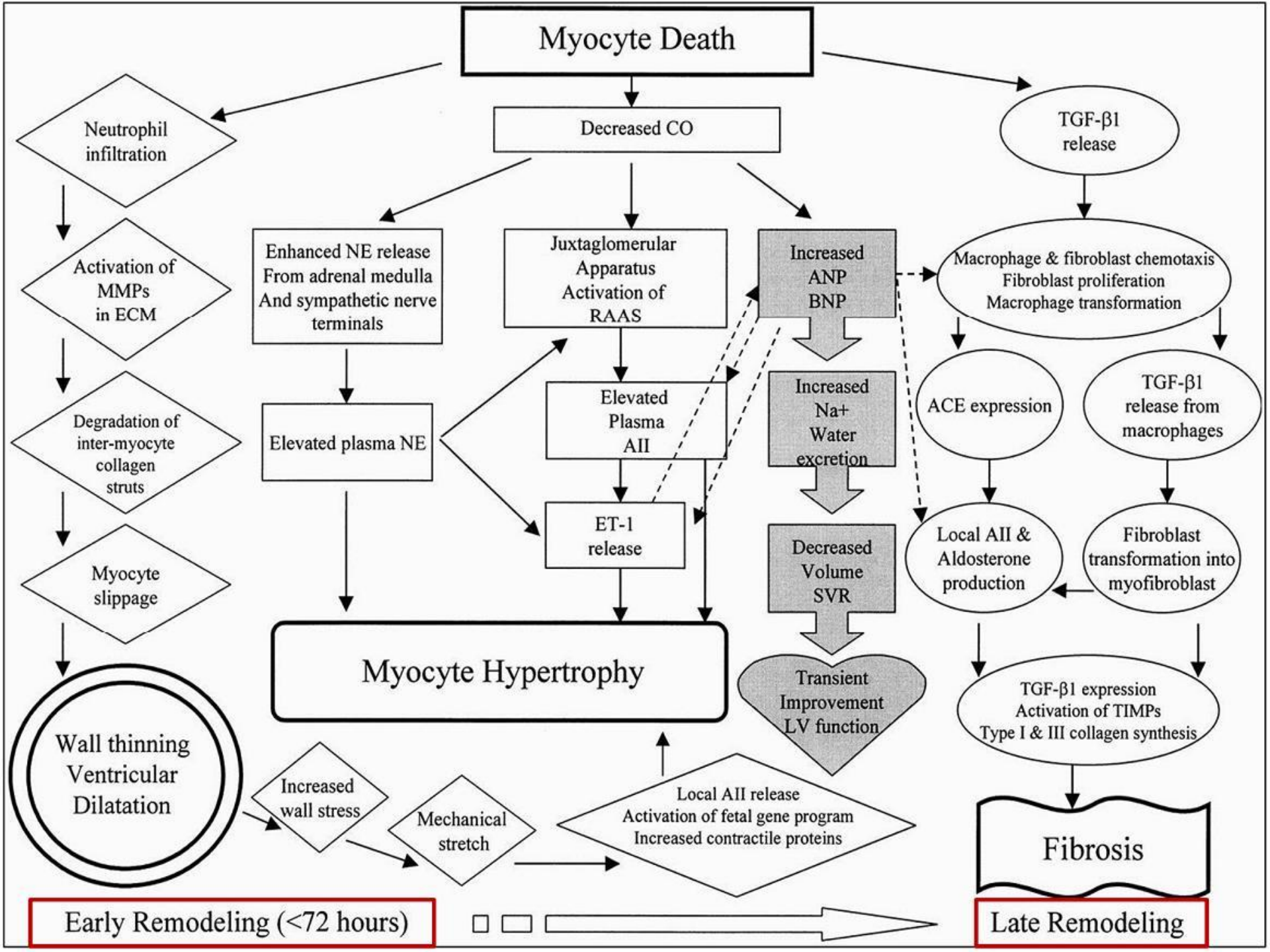
# HF after AMI
# Prevent LV Remodeling



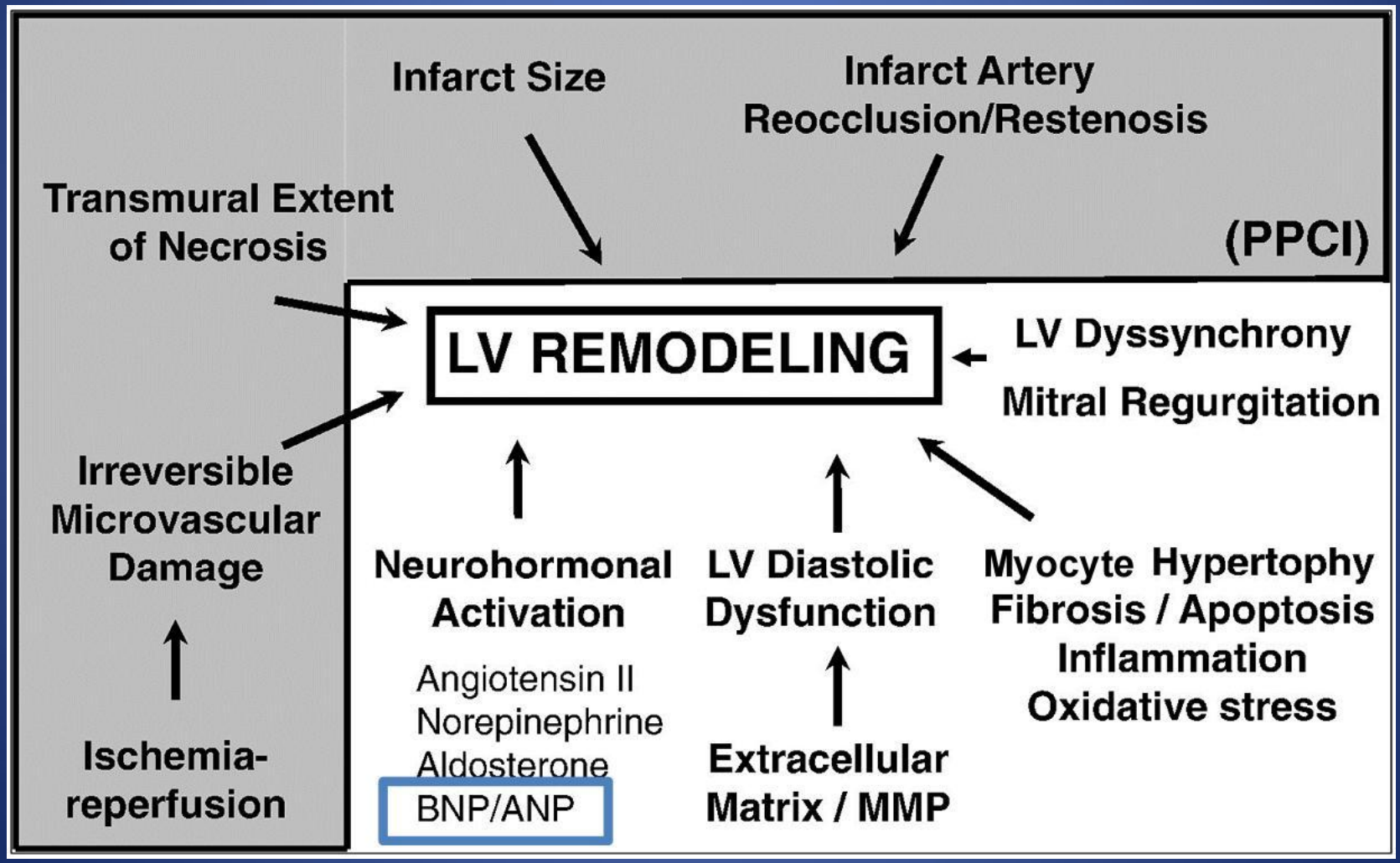
# LV Remodeling

- Def) Cellular, interstitial, molecular and genetic changes that manifest clinically as changes in size, shape and function of the LV after a cardiac injury such as a MI

- Physiological and adaptive during normal growth
- Pathological due to MI, CMP, HTN or VHD


Myocyte Death
Neutrophil infiltration
Decreased CO
TGF-β1 release
Activation of MMPs in ECM
Enhanced NE release From adrenal medulla And sympathetic nerve terminals
Juxtaglomerular Apparatus Activation of RAAS
Increased ANP BNP
Macrophage & fibroblast chemotaxis Fibroblast proliferation Macrophage transformation
Degradation of inter-myocyte collagen struts
Elevated plasma NE
Elevated Plasma AII
Increased Na+ Water excretion
ACE expression
TGF-β1 release from macrophages
ET-1 release
Local AII & Aldosterone production
Fibroblast transformation into myofibroblast
Myocyte slippage
Decreased Volume SVR
Myocyte Hypertrophy
Transient Improvement LV function
TGF-β1 expression Activation of TIMPs Type I & III collagen synthesis
Wall thinning Ventricular Dilatation
Increased wall stress
Mechanical stretch
Local AII release Activation of fetal gene program Increased contractile proteins
Fibrosis
Early Remodeling (<72 hours)
Late Remodeling

# Factors ac LV remodeling during(gray box) & after PPCI for AMI



# Management of LV Remodeling

I. Reperfusion

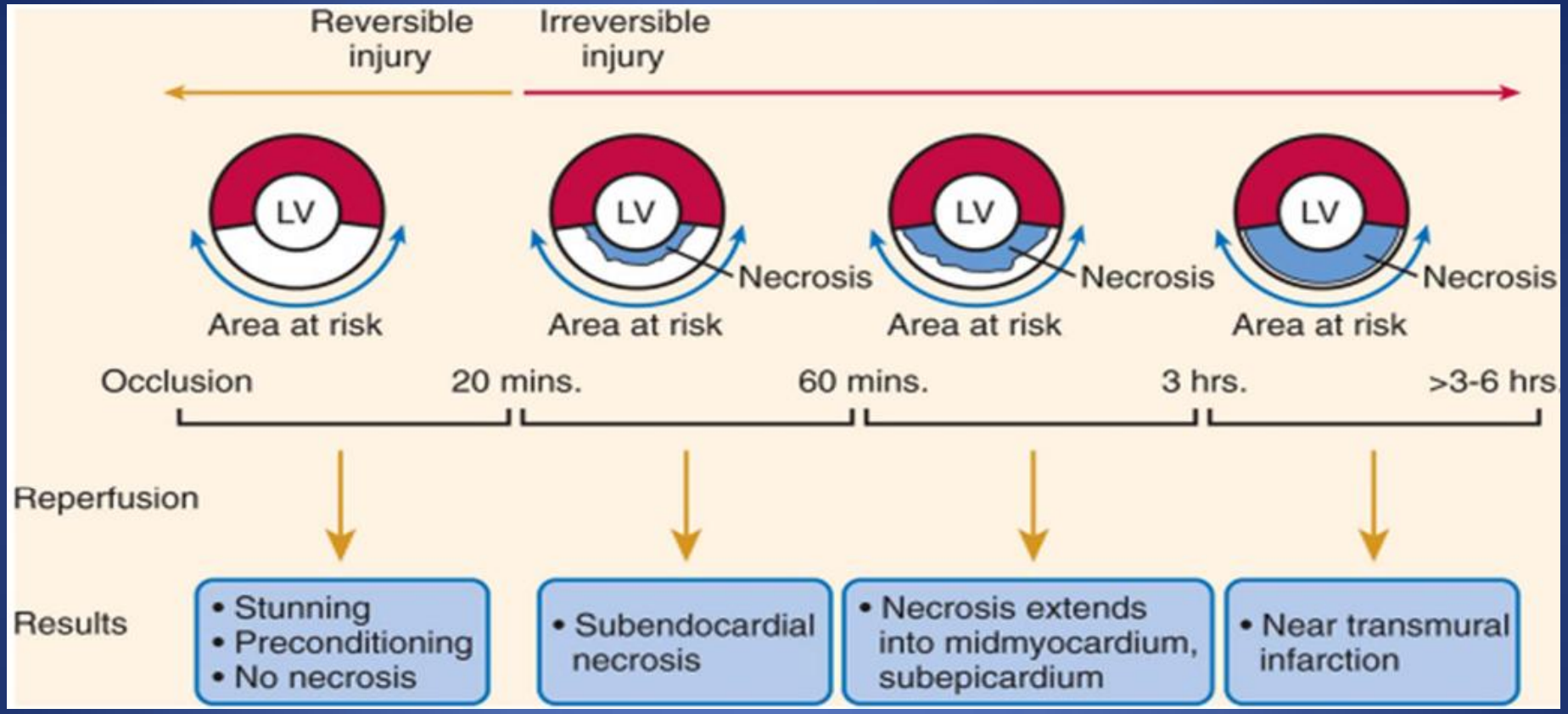
II. Ischemic pre- and post-conditioning

III. Pharmacological Therapy combined with reperfusion

IV. Pharmacological therapy in the chronic phase after AMI

# I. Reperfusion

- Early reperfusion is crucial in reducing infarct size, cardiac mortality and in-hospital events
- Reduce mechanical stress on non-infarcted myocardium
- Preventing LV remodeling
- Reperfusion injury


Reversible injury
Irreversible injury
LV
LV
LV
LV
Necrosis
Necrosis
Necrosis
Area at risk
Area at risk
Area at risk
Area at risk
Occlusion
20 mins.
60 mins.
3 hrs.
>3-6 hrs
Reperfusion
Results
• Stunning
• Preconditioning
• No necrosis
• Subendocardial necrosis
• Necrosis extends into midmyocardium, subepicardium
• Near transmural infarction

# Reperfusion injury

- Cellular and mitochondrial $Ca^{++}$ overload
- Oxidative stress (free radical)
- Endothelial dysfunction with
  reduced NO formation
- Apoptosis
- Platelet aggregation
- Immune activation

# II. Ischemic pre- and Post-conditioning

Murry et.al

Multiple anginal episodes that often precede myocardial infarction in man may delay cell death after coronary occlusion, and thereby allow for greater salvage of myocardium through reperfusion therapy.

*Circulation 74, No. 5, 1124-1136, 1986.*

Ischemic pre-conditioning

- Early (~1-2H), delayed (12H~3-4D)
- Protein kinase C
  - (adenosine A1, A3 receptor, 5'-Nucreotidase)
- ATP-sensitive K channels, NO

Post-conditioning

- Zhao et al.
- Repetitive occlusion and reperfusion early after PCI reduces oxidative stress, neutrophil activation and adhesion, calcium overload, apoptosis

| Preconditioning | | |
|---|---|---|
| Nakagawa et al[15] | 84 | Significantly better LV function in the patients with prodromal angina, particularly with new angina pectoris occurring ≤7 d after onset of infarction |
| Ishihara et al[16] | 350 | Better survival rate for 5 y in patients with prodromal angina in the 24 h before MI |
| Kloner et al[17] | 3002 | Better clinical outcomes in patients with preinfarct angina within 24 h but not in those with this duration >24 h |
| Solomon et al[18] | 283 | Better LV function and prevention of LV remodeling in patients with ischemic symptoms before MI but not in diabetic patients |
| Colonna et al[19] | 51 | A greater microvascular reflow extent, better coronary flow reserve, and better regional myocardial function in patients with preinfarct angina |

| Postconditioning | | |
|---|---|---|
| Staat et al[21] | 30 | Significant 36% reduction in infarct size and significantly higher blush grade in the postconditioning group |
| Ma et al[22] | 94 | Faster corrected TIMI frame count after PCI and better LV wall motion in the postconditioning group |

# III. Pharmacological Therapy Combined with reperfusion

1. Adenosine
2. Nicorandil
3. Nitric oxide
4. Atrial natriuretic peptide and BNP
5. HMG-CoA reductase inhibitor: Statin

# 1. Adenosine

Marzilli et al.

Beneficial effects of IC Adenosine as an adjunctive to primary angioplasty in AMI

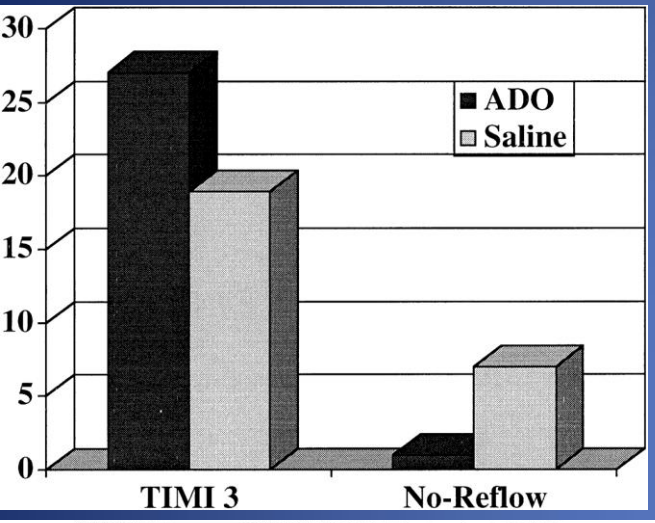
54 AMI Pts.

Primary PCI with Adnosine vs. saline

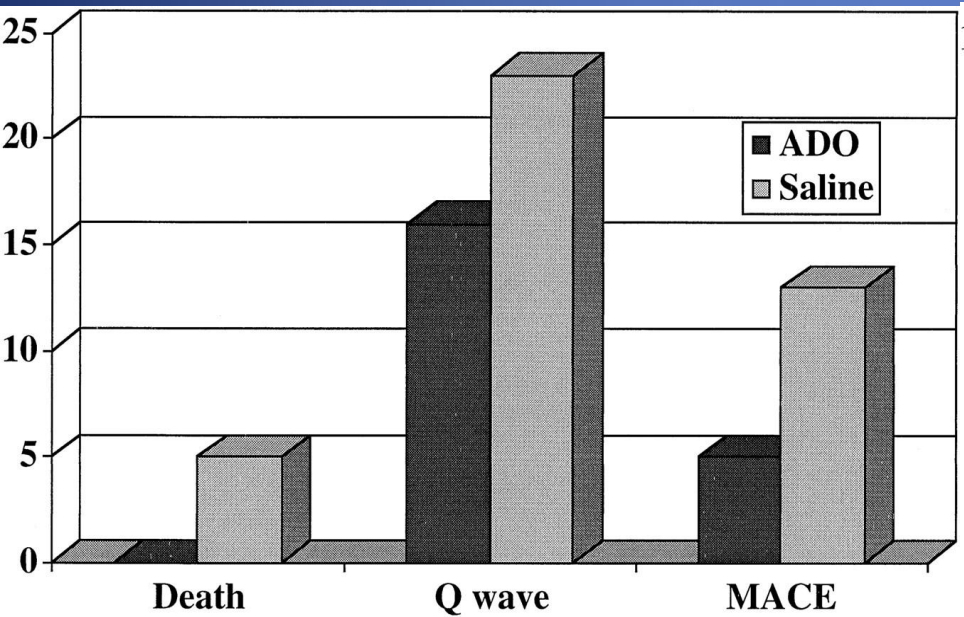
*Circulation, 2000;101:2154-9*

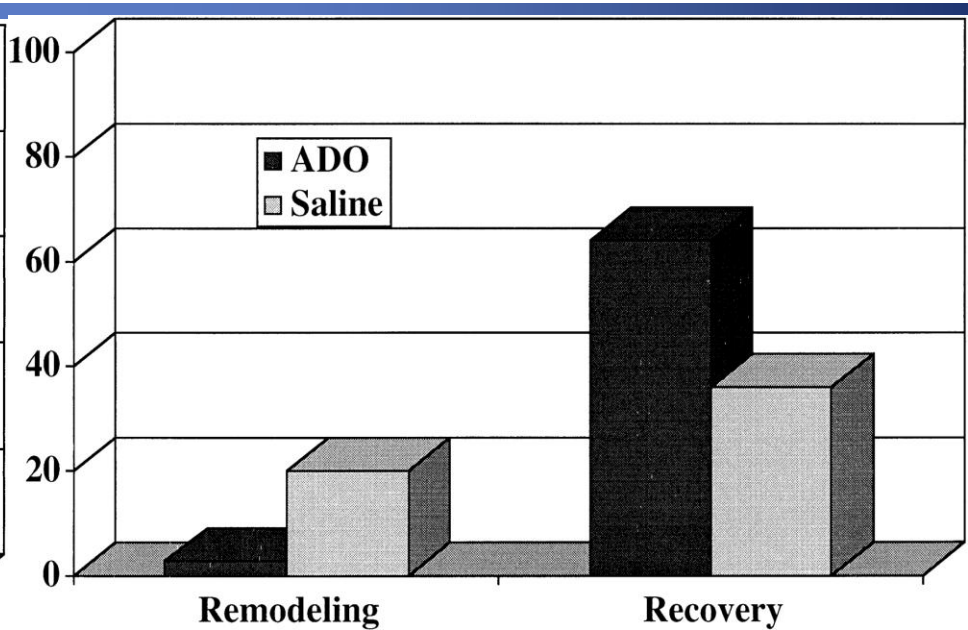
No-reflow: 1 vs. 7 (p=0.02)
Lower CK, Q-wave MI (p=0.04)
Improving dyssynergic segments:
65% vs. 36% (p=0.001)
Function worsening of dyssynergic seg.:
2% vs. 20% oup (P=0.0001)
Adverse cardiac events:
5 vs. 13 pts (P=0.03).

*Circulation, 2000;101:2154-9*




| | Adenosine (n=27) | Saline (n=27) | *P* |
|---|---|---|---|
| Recurrent angina and/or ischemia | 3 (11) | 2 (7) | NS |
| Nonfatal AMI | 0 (0) | 1 (4) | NS |
| Heart failure | 2 (7) | 5 (18) | NS |
| Cardiac death | 0 (0) | 5 (18) | 0.02 |
| Cumulative clinical end points | 5 (18) | 13 (48) | 0.03 |



# 2. Nicorandil

- K-ATP channel opener, NO donor
- 5'-nucleotide (mimicking ischemic preconditioning)
- Both early (K-ATP channel) and delayed preconditioning (cyclooxynase-2, Bcl-2)

## Ito et al.

IC nicorandil
preserve microvascular integrity, m. viability
better functional and clinical outcomes
in patients with an anterior AMI.

*J Am Coll Cardio 1999:33;654-60*

## Kitakaze et al.

IC nicorandil did not affect LVEF
Oral nicorandil during FU increased LVEF
between the chronic and acute phases

*Lancet 2007:370;1483-93*

# Ishii et al.

## Single IV Nicorandil Before Reperfusion in STEMI

| | Nicorandil (n=185) | Placebo (n=183) | Hazard Ratio (95% Confidence Interval) | *P* |
|---|---|---|---|---|
| Primary end point | 12 (6.5) | 30 (16.4) | 0.39 (0.20–0.76) | 0.0058 |
| Cardiovascular death | 6 (3.2) | 10 (5.5) | 0.59 (0.22–1.64) | |
| Unplanned hospital admission for CHF | 6 (3.2) | 20 (10.9) | 0.29 (0.11–0.71) | |
| All deaths and all-cause admission | 47 (25.4) | 66 (36.1) | 0.72 (0.49–1.04) | 0.08 |
| All deaths | 7 (3.8) | 12 (6.6) | 0.58 (0.23–1.47) | 0.26 |
| Target lesion revascularization | 30 (16.2) | 30 (16.4) | 1.02 (0.61–1.69) | 0.98 |
| Re-PCI | 24 (13.0) | 22 (12.0) | ... | |
| CABG | 6 (3.2) | 8 (4.4) | ... | |
| Re-PCI for new lesions | 5 (2.7) | 7 (3.8) | 0.72 (0.23–2.27) | 0.57 |

Values are n (%). CABG indicates coronary artery bypass graft.

# 3. Nitric Oxide

- Many experimental studies showed the effectiveness of NO such as delayed preconditioning-like action
- Limited data in humans

# Amit et al.

NTP, IC, just before primary PCI for STEMI
98 Pts, NTP (60 microg) vs. placebo.
IRA, distal to the occlusion

Selective IC fixed dose of NTP failed to
improve coronary flow, m. tissue reperfusion
but improved clinical outcomes at 6 months.

*Am Heart J 2006:152;887.e9-14*

# 4. Atrial Natriuretic Peptide, BNP

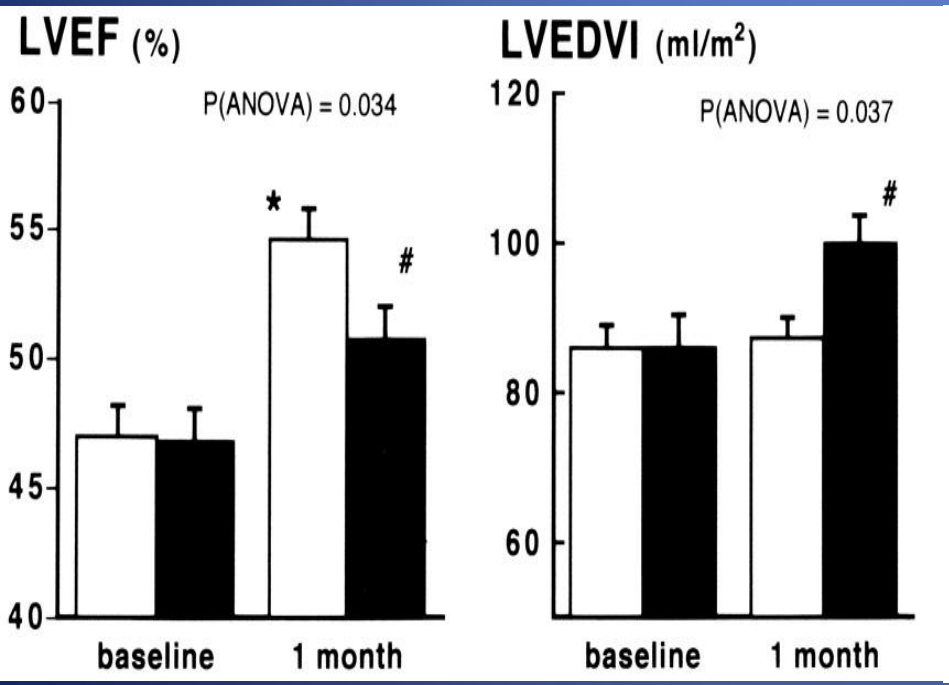
- Increase intracellular cGMP
- Cardioprotective effects;
  anti-apoptosis, -fibrosis, -hypertrophy
- Accelerate NO generation
- Suppress aldosterone, An-II, ET-1
- Inhibition reperfusion arrhythnmia,
- Preservation of ATP

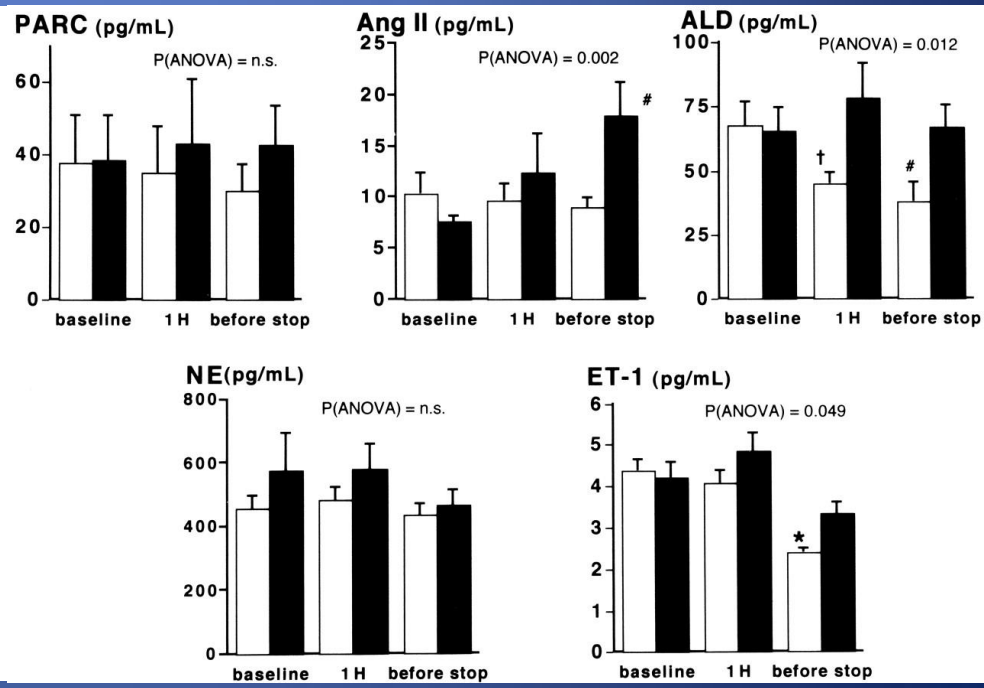
# Hayashi et al.

ANP

can prevent LV remodeling better than NTG

effectively suppresses aldosterone, Ang II, ET-1




*J Am Coll Cardiol 2001;37:1820-1826*

## Kitakaze et al.

ANP had
- lower infarct size,
- fewer reperfusion injuries, and
- better outcomes than controls.

We believe that ANP could be a
- safe and effective adjunctive treatment
- in patients with AMI who receive PCI

*Lancet 2007:370;1483-93*

# 5. Statin

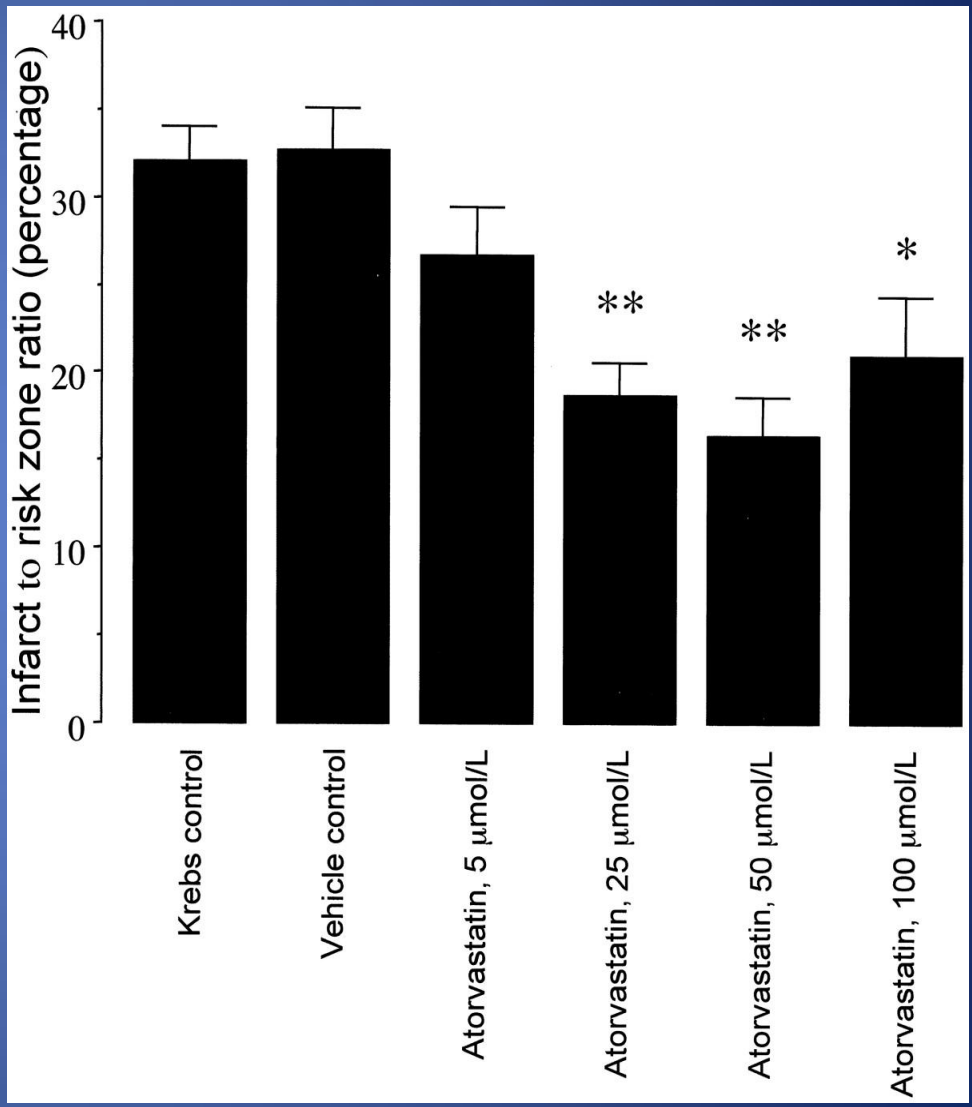
- ↓ Cardiomyocyte hypertrophy (animal)
- Prevent LV remodeling (animal)
- eNOS activity
- Down regulation of An-II type 1 receptor
- Attenuation of increased MMP-2

- Beneficial outcome: MUSASHI-AMI, HIJC
- Beneficial in earlier stage of HF?
  (CORONA, GISSI-HF)

## Bellet al.

Atorvastatin, administered at the onset of reperfusion, and independent of lipid lowering, protects the myocardium by up-regulating a pro-survival pathway

*J ACC, 2003; 41:508-515*



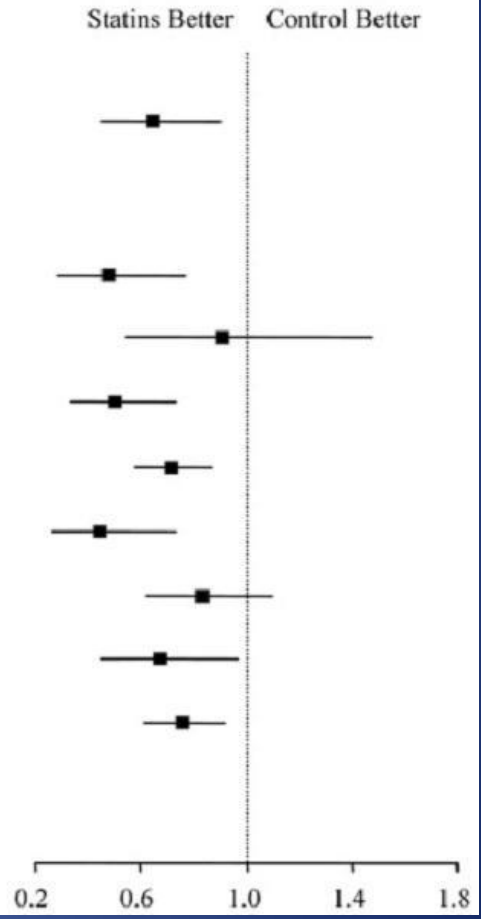
## Nagashima et al.

- 1999 – 2004, 4,075 AMI(1,404)
- Statin prescription or not
- Total mortality rate
- FU median 4.1 years(97.2%)
- Early statin, strongly correlated with lower risk of cardiovascular death, less recurrence of AMI, and less HF

*Am J Cardiol. 2007:99;1523-8*

# Nagashima et al.

| | Control (N=702) | | Statins (n=702) | | Hazard Ratio (95% Confidence Interval) |
|---|---|---|---|---|---|
| | No. (%) of Events | Rate per 1000 Patient-Years | No. (%) of Events | Rate per 1000 Patient-Years | |
| Primary Endpoint | | | | | |
| Total Death | 87 (12.4) | 32 | 52 (7.4) | 20 | 0.64 (0.45–0.90) |
| Secondary Endpoint | | | | | |
| Death from CVD | 52 (7.4) | 19 | 23 (3.3) | 9 | 0.47 (0.29–0.76) |
| Death from non-CVD | 35 (5.0) | 13 | 29 (4.1) | 11 | 0.90 (0.55–1.48) |
| Death from CHD or Nonfatal MI | 77 (11.0) | 28 | 37 (5.3) | 14 | 0.49 (0.33–0.73) |
| Major Adverse Cardiac Event | 221 (31.5) | 80 | 157 (22.4) | 60 | 0.71 (0.58–0.87) |
| Fatal MI or Nonfatal MI | 49 (22.2) | 18 | 21 (3.0) | 8 | 0.44 (0.26–0.73) |
| Hospitalization for Ischemia | 106 (15.1) | 39 | 86 (12.3) | 33 | 0.83 (0.62–1.10) |
| Hospitalization for Heart Failure | 67 (9.5) | 24 | 44 (6.3) | 17 | 0.66 (0.45–0.97) |
| PCI or CABG | 220 (31.3) | 80 | 173 (24.6) | 66 | 0.75 (0.62–0.92) |




*Am J Cardiol. 2007:99;1523-8*

# Nagashima et al.

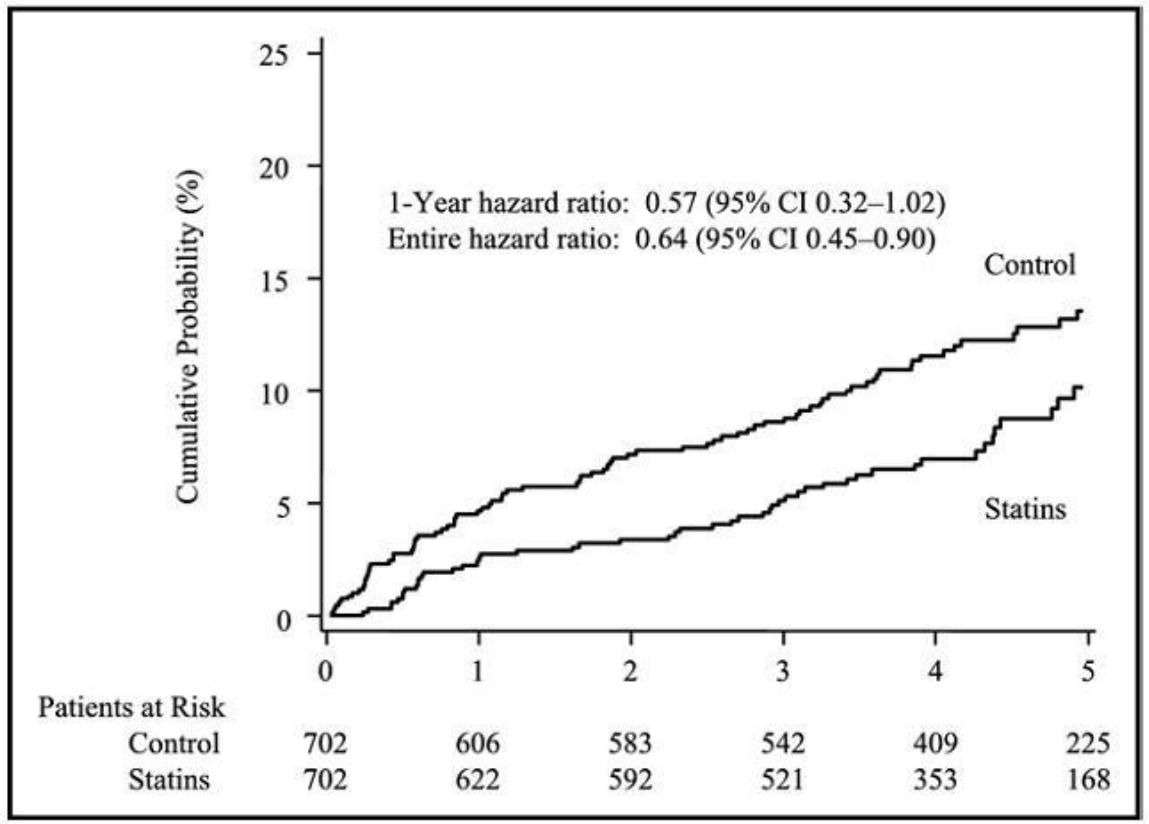



Figure 2. Kaplan-Meier estimates of the incidence of the primary end point. Kaplan-Meier 1-, 3-, and 5-year cumulative survival rates were 95.4%, 91.4%, and 86.6%, respectively, in the control groups, and 97.3%, 94.9%, and 90.0%, respectively, in the statin group. CI = confidence interval.

*Am J Cardiol. 2007:99;1523-8*

# IV. Pharmacological Therapy in the chronic phase after AMI

- 3 Factors ac Chronic LV remodeling after AMI;
  modification of infarct size,
  infarct healing,
  ventricular wall (mechanical) stress

- Activation of RAA system, increased NE, inflammatory cytokines

# Pharmacological Therapy in the chronic phase after AMI

1. RAA system blockade
   ACE-inhibitors
   Angiotensin II Receptor Blockers
   Spironolactone
   Renin inhibitors
2. Nicorandil
3. Beta-blockers
4. HMG-CoA reductase inhibitor: Statin

# 1. RAS Blockade

- Hemodynamic effects
  Reduce arterial and LVED pr.
  –> reduce LV wall stress
- Improving LV diastolic fc. :Bradykinin
- ↓ fibrosis in non-infarcted myocardium
- ↓ Proliferation of fibroblast
- ↓ TGF-Beta1

# 1-1. ACE inhibitors

>120,000 post MI patients

| Trial | Drug | No of Pt. | Mortality↓ |
|---|---|---|---|
| SOLVD (1992) | Enalapril | 4228 | 8% (p=0.30) |
| SAVE (1992) | Captopril | 2231 | 19% |
| CONSENSUS (1993) | Enalapril | 6090 | NS |
| AIRE (1993) | Ramipril | 2006 | 27% |
| ISIS 4 (1994) | Captopril | 58050 | 7% |
| CCS-1 (1995) | Captopril | 14962 | NS |
| TRACE (1995) | Trandolapril | 2606 | 22% |
| GISSI 3 (1996) | Lisinopril | 19394 | 12% |
| PREAMI (2009) | Perindopril | 1252 | NS |

# SAVE Trial

In patients with asymptomatic LV dysfunction after MI,

Long-term captopril was improved survival, reduced morbidity and mortality due to major cardiovascular events

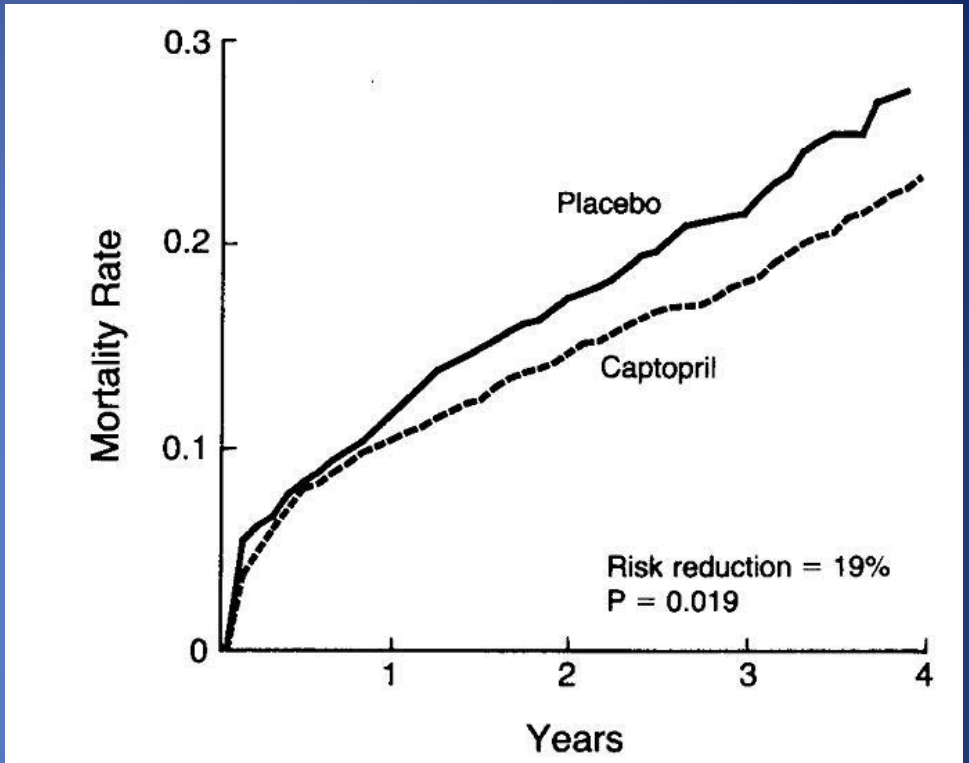
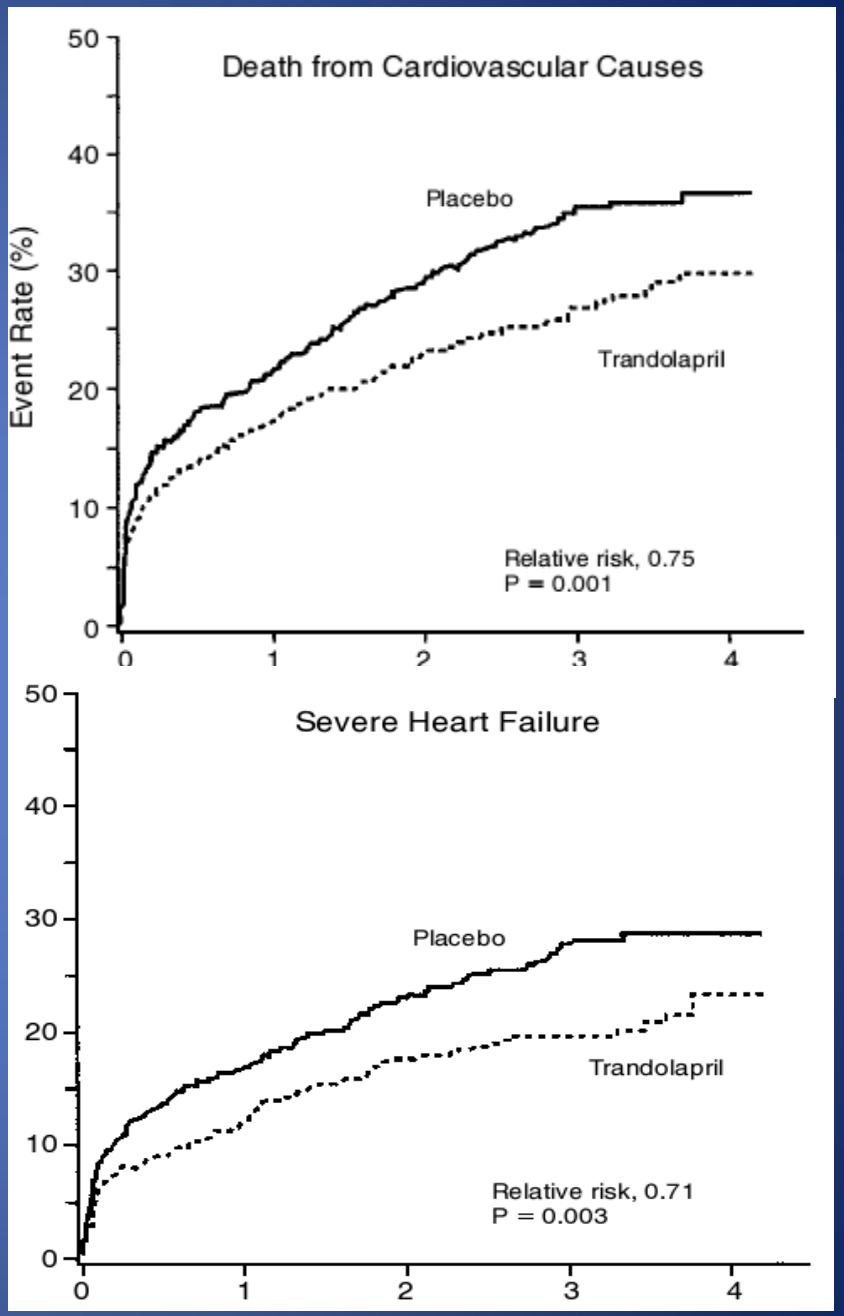



Figure 1. Cumulative Mortality from All Causes in the Study Groups.

*NEJM 1992:327:669-77.*

## TRACE Trial

Long-term trandolapril in pts with reduced LV soon after MI significantly reduced the risk of overall mortality, mortality from cardiovascular causes, sudden death, and develop. of severe HF




*NEJM, 1995:333:1670-6*

# 1-2. AR-Blockers

- block Ang-II receptor more completely
- failed to superiority than ACEI

| Trial | Drug | No of Pt. | Mortality ↓ |
|---|---|---|---|
| OPTIMAAL (2002)* | Losartan | 5477 | NS |
| VALIANT (2003)* | Valsartan | 14703 | NS |
| Val-HeFT (2002) | Valsartan | 5010 | NA |

# OPTIMAAL Trial

Losartan vs. captopril

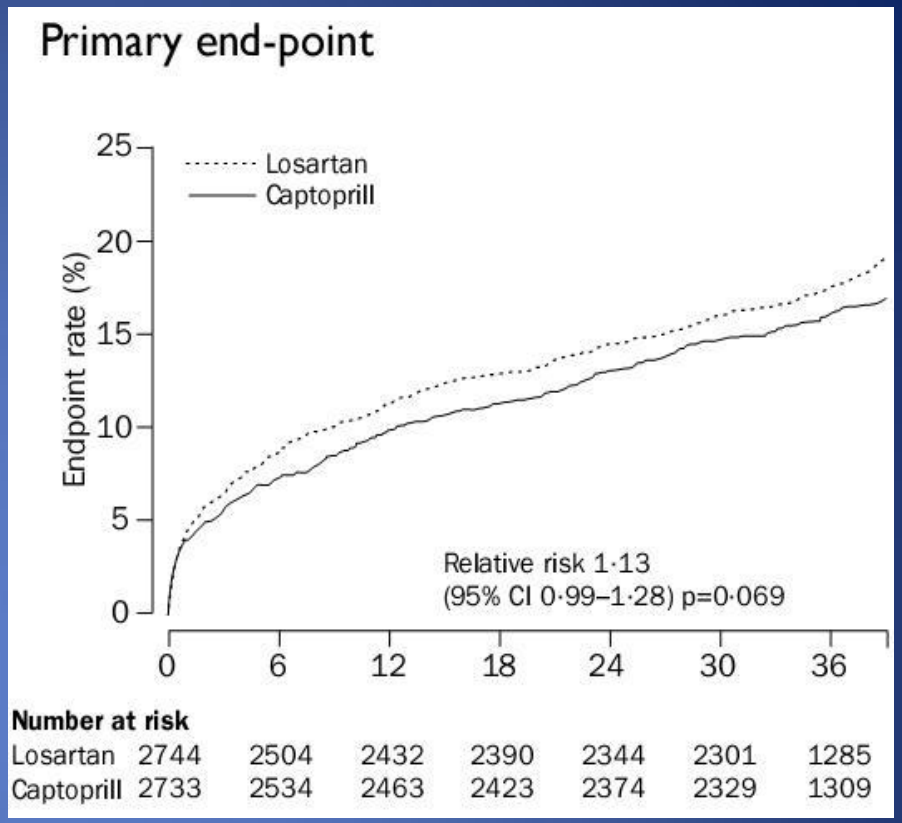
Non-significant
difference in total
mortality

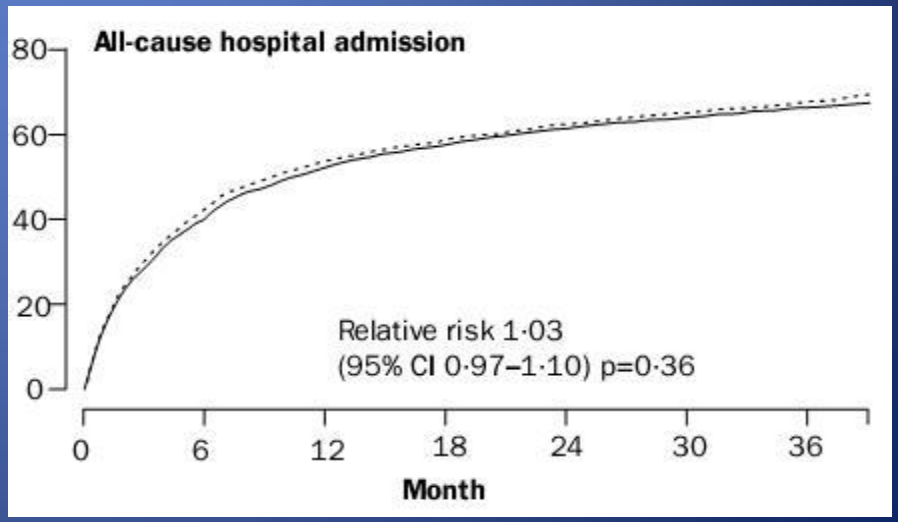
ACE inhibitors should
first-choice
in pts after AMI

Losartan,
not recommended
in this population

However,
better tolerated

*Lancet,2002:360:752-60*



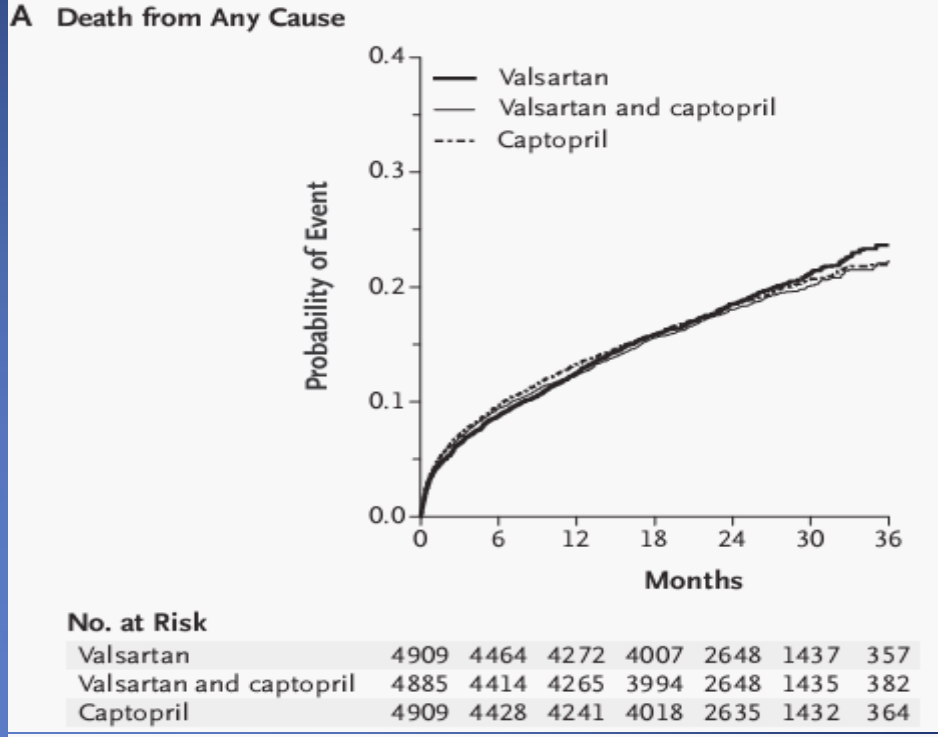
# VALIANT Trial

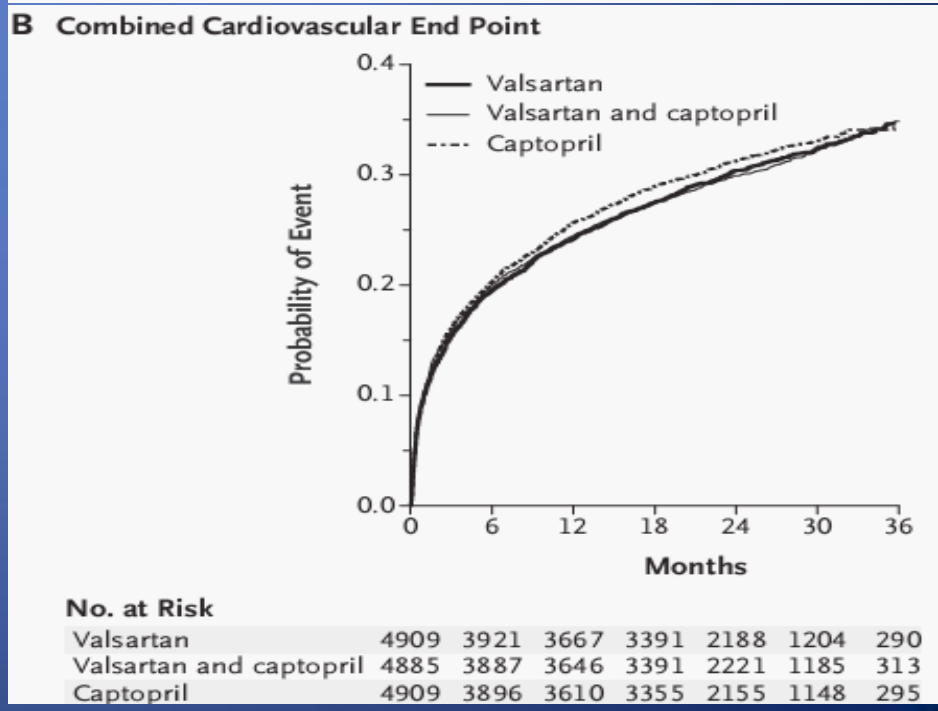
Valsartan vs. captopril

As effective as captopril in pts, high risk for cardiovascular events after MI

Combining valsartan with captopril increased rate of adverse events without improving survival

*NEJM. 2004 Jan 8;350(2):203*



# 1-3. Renin inhibitors

- First rate-limiting step of RAA system
- Decrease LVEDP and systolic afterload in experimental models with LV failure after MI
- Limited clinical data

# 2. Nicorandil

Kasama et al.

- 40 pts with their first AMI
- IV nicorandil during PCI
  (20 ,oral nicorandil and 20 placebo)
- Long-term nicorandil therapy can be more beneficial for cardiac sympathetic nerve activity and LV remodeling than short-term therapy in AMI

*J Nucl Med. 2007:48;1676-82*

# Kasama et al.

| Parameter | Group A | | | Group B | | |
|---|---|---|---|---|---|---|
| | 3 wk | 6 m | δ | 3 wk | 6 m | δ |
| Left ventriculography | | | | | | |
| LVEDV (mL) | 82 ± 54 | 70 ± 44* | −12 ± 16 | 87 ± 60 | 78 ± 52 | −9 ± 17 |
| LVESV (mL) | 40 ± 31 | 29 ± 22* | −10 ± 12 | 44 ± 37 | 36 ± 23* | −8 ± 15 |
| LVEF (%) | 51 ± 9 | 59 ± 12* | 9 ± 10 | 50 ± 13 | 54 ± 11 | 5 ± 11 |
| Plasma PIIINP (U/mL) | 0.67 ± 0.15 | 0.66 ± 0.15 | −0.01 ± 0.05 | 0.69 ± 0.19 | 0.75 ± 0.20 | 0.06 ± 0.08† |

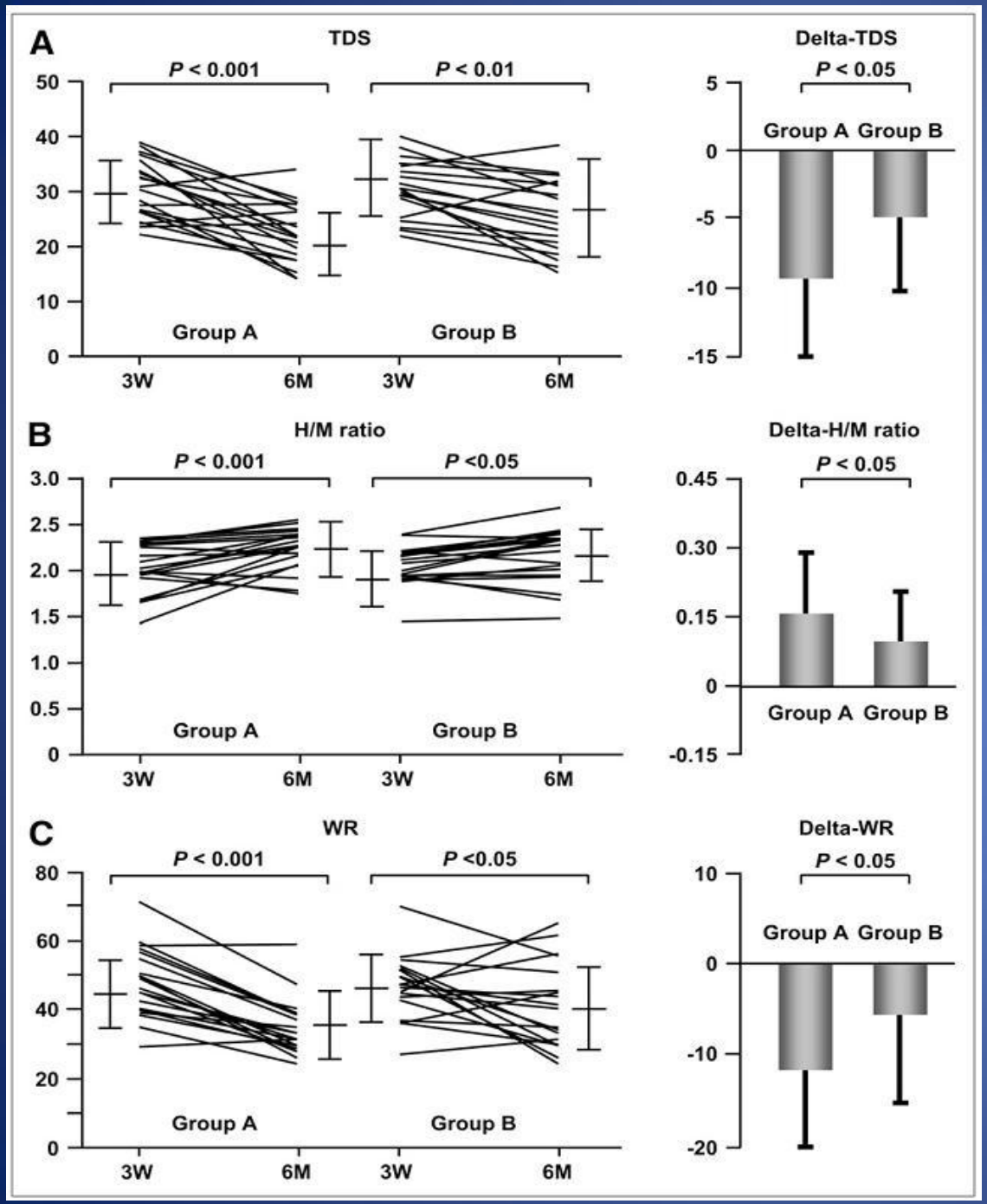
*$P < 0.05$ vs. baseline.

†$P < 0.05$ vs. group A.

LVEDV = LV end-diastolic volume; LVESV = LV end-systolic volume; LVEF = LV ejection fraction; PIIINP = procollagen type III amino-terminal peptide.

Values are mean ± SD.

*J Nucl Med. 2007:48;1676-82*




# Kasama et al.

TDS,
Total defect score
H/M ratio,
Ht.-to-mediastinum count ratio
WR,
washout rate

*J Nucl Med. 2007:48;1676-82*

# 3. Beta-blockers

| Trial | Drug | No of Pt. | Mortality ↓ |
|---|---|---|---|
| Norwegian multicenter study (1981) | Timolol | 1884 | 39% |
| BHAT (1982) | Propranolol | 3837 | 27% |
| Gotheborg Metoprolol study (1983) | Metoprolol | 1395 | 36% |
| CAPRICON (2004) | Cervedilol | 1959 | 23% |

## CAPRICORN study

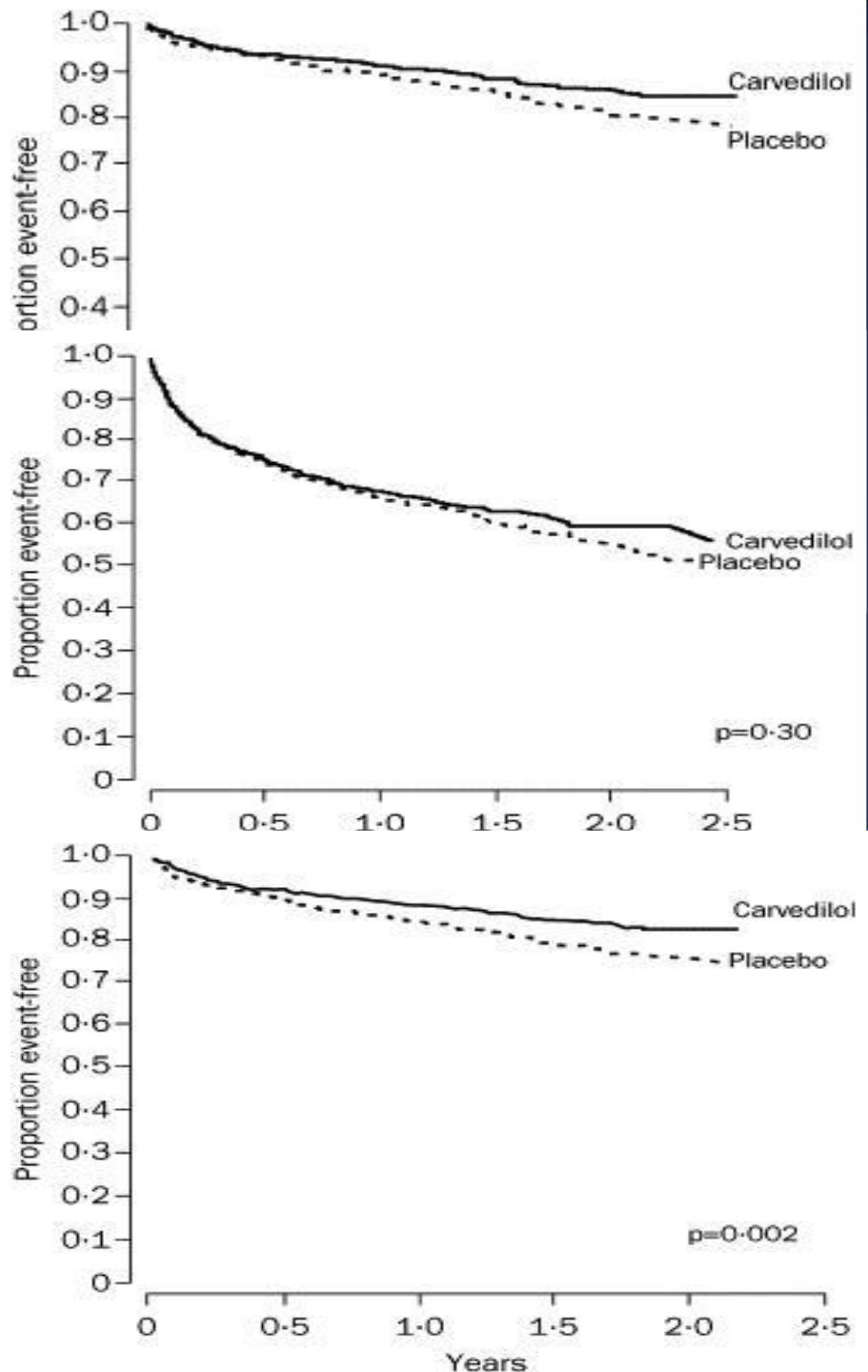
AMI complicated LV systolic dysfc.

Long-term carvedilol reduced
- all-cause and CV mortality
- non-fatal MI

These beneficial effects, additional to those of evidence-based treatments for AMI including ACE inhibitors.

*The Lancet, 2001: 357; 1385-90*

# CAPRICORN study




*The Lancet, 2001: 357; 1385-90*

# 4. Statin

- ↓ Cardiomyocyte hypertrophy (animal)
- Prevent LV remodeling (animal)
- eNOS activity
- Down regulation of An-II type 1 receptor
- Attenuation of increased MMP-2

- Beneficial outcome: MUSASHI-AMI, HIJC
- Beneficial in earlier stage of HF?
  (CORONA, GISSI-HF)

## Nakaya et al

Pravastatin vs. non-pravastatin

35 pts. After AMI, MMP-2, TIMP-2, LVG

Conclusion,

Serum MMP-2

- varied in time-dependent manner after AMI
- correlated with late changes in LVEDVI
- significantly lower in pravastatin group

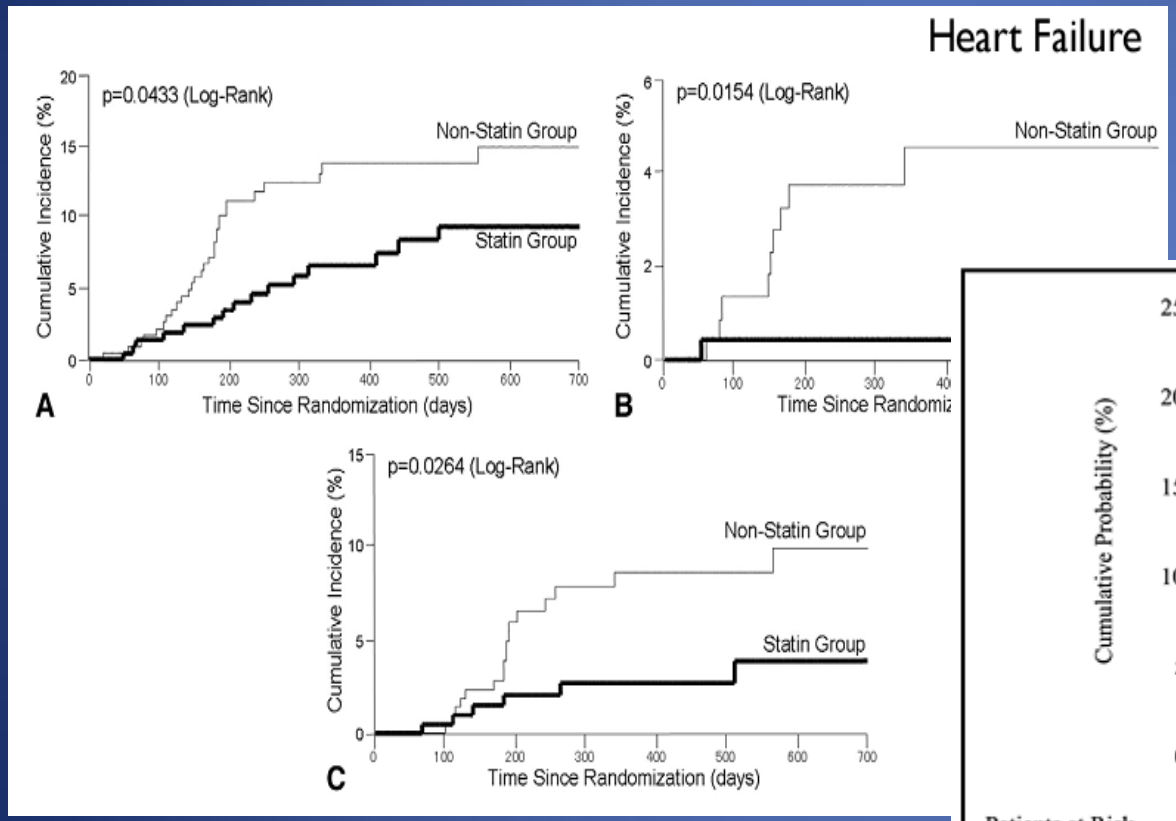
ΔLVEDVI was significantly smaller in Tx.

Use of statins in AMI patients may provide beneficial effects in terms of preventing HF over and above its lipid-lowering effects.

*International Journal of Cardiology, 2005:105;67-70*

# MUSASHI-AMI trial

# HIJC program



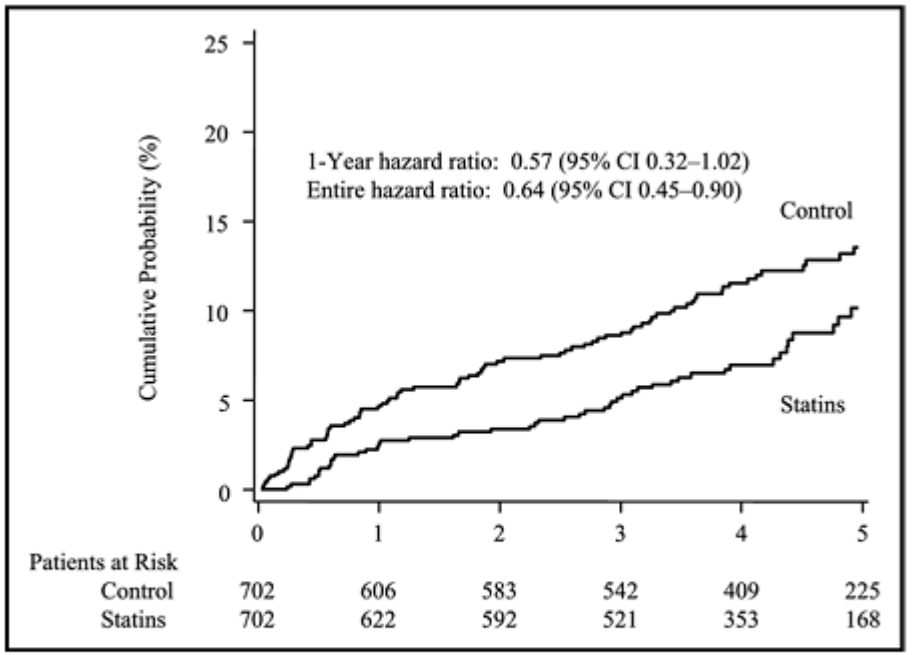




Figure 2. Kaplan-Meier estimates of the incidence of the primary end point. Kaplan-Meier 1-, 3-, and 5-year cumulative survival rates were 95.4%, 91.4%, and 86.6%, respectively, in the control groups, and 97.3%, 94.9%, and 90.0%, respectively, in the statin group. CI = confidence interval.

# 5. Others

- Anti-oxidant treatment
- Anti-inflammatory treatment
- Selective MMP inhibition
- Stem cell therapy

# Anti-oxidant treatment

- NAD(P)H oxidase
- Myeloperoxidase
- Xanthine oxidase – xanthine oxidase inhibition (Oxypurinol):

  improve LVEF, only in high uric acid level?

# Anti-inflammatory treatment

- Steroid, NSAIDs; ↑ thinning of infarct zone
- COX-2 inhibitor (Celecoxib): ↑ mortality
- IL-1 receptor antagonists (anakinra)
- Toll-like receptors (to be explored)

# Selective MMP inhibition

- PREMIER:
  selective MMP inhibition trial,
  oral MMP inhibitor (PG-116800),
  253 MI patients,
  No significant effects on LV remodeling,
  outcome
- Prolonged inhibition; adverse effect?

# Stem cell therapy

- Effective for LVEF
- Prevent LV remodeling ?

# Summary and Conclusions

- LV Remodeling;

  Maladaptive Compensatory Mechanism

  Cellular, interstitial, molecular and genetic changes that manifest clinically as changes in size, shape and function of the LV after a cardiac injury such as a MI

# Prevent HF (remodeling) after AMI

## Efficacy proven

- Early revascularization
- RAS blockade
  - ACE-inhibitor
  - ARB
  - Aldosterone antagonist
- Beta blockade

## Potential Novel Tx

- Statins
- NO signal modulation
- Anti-oxidant
- Anti-inflammatory Tx
- MMP inhibitors
- Cell transfer/angiogenesis
- PDE 5A inhibitor
- Ryanodine receptor stabilizer