β-Adrenergic Signaling in Heart Failure

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최 동 주

ß-Adrenergic Blockers in HF

British Heart Journal, 1975, 37, 1022–1036.

Effect of chronic beta-adrenergic receptor blockade in congestive cardiomyopathy

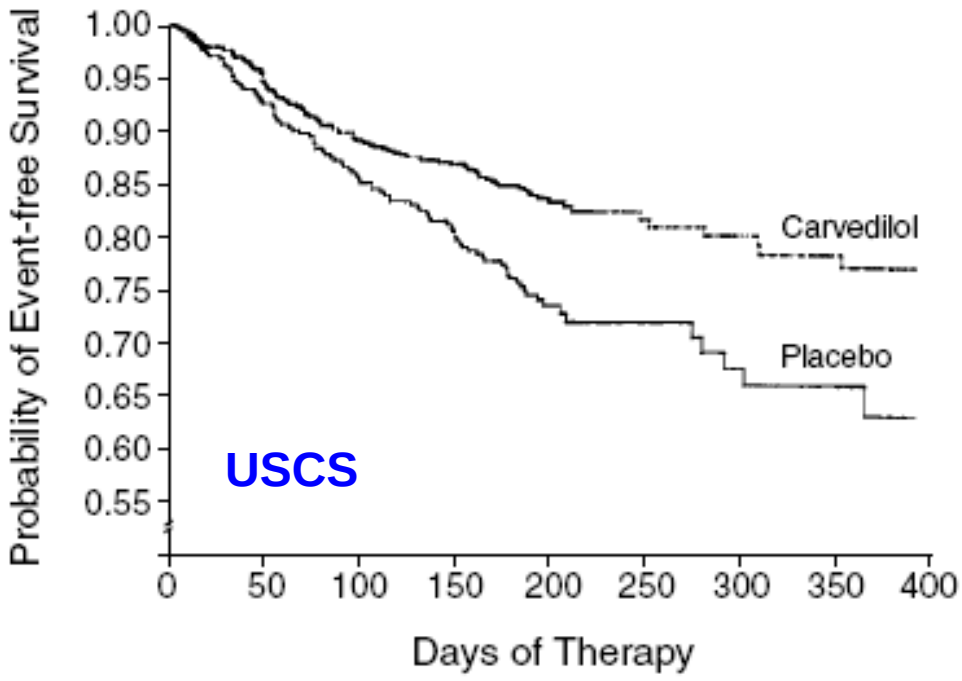
F. Waagstein, Å. Hjalmarson, E. Varnauskas, and I. Wallentin

From the Department of Medicine I, Division of Cardiology and Department of Clinical Physiology, Sahlgren's Hospital, University of Göteborg, Sweden

Adrenergic beta-blocking agents were given to 7 patients with advanced congestive cardiomyopathy who had tachycardia at rest (98 ± 13 beats/min). The patients were on beta-adrenergic receptor blockade for 2 to 12 months (average 5.4 months). One patient was given alprenolol 50 mg twice daily and the other patients were given practolol 50 to 400 mg twice daily. Virus infection had occurred in 6 of the patients before the onset of symptoms of cardiac disease. All patients were in a steady state or were progressively deteriorating at the start of beta-adrenergic receptor blockade. Conventional treatment with digitalis and diuretics was unaltered or reduced during treatment with beta-blocking agents. An improvement was seen in their clinical condition shortly after administration of the drugs. Continued treatment resulted in an increase in physical working capacity and a reduction of heart size.

Noninvasive investigations including phonocardiogram, carotid pulse curve, apex cardiogram, and echocardiogram showed improved ventricular function in all cases. The present study indicates that adrenergic beta-blocking agents can improve heart function in at least some patients with congestive cardiomyopathy. Furthermore, it is suggested that increased catecholamine activity may be an important factor for the development of this disease, as has been shown in animal experiments.

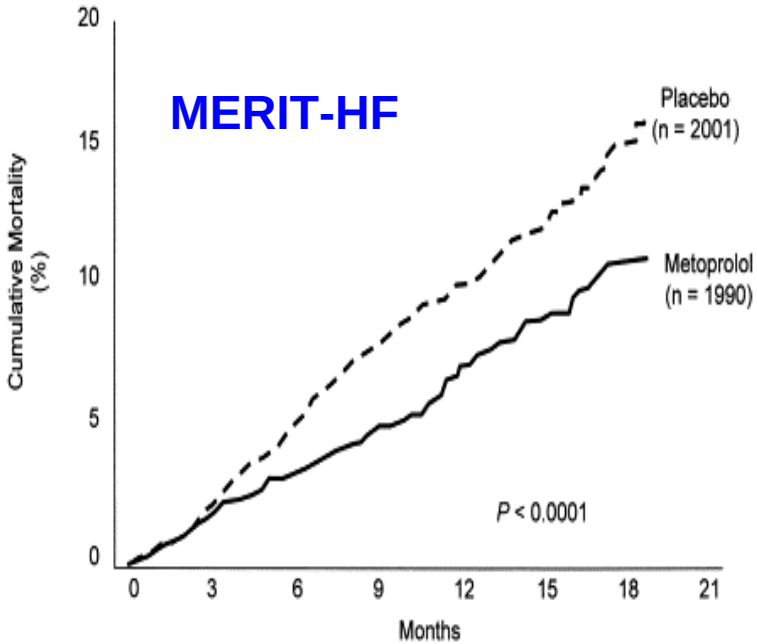
Carvedilol

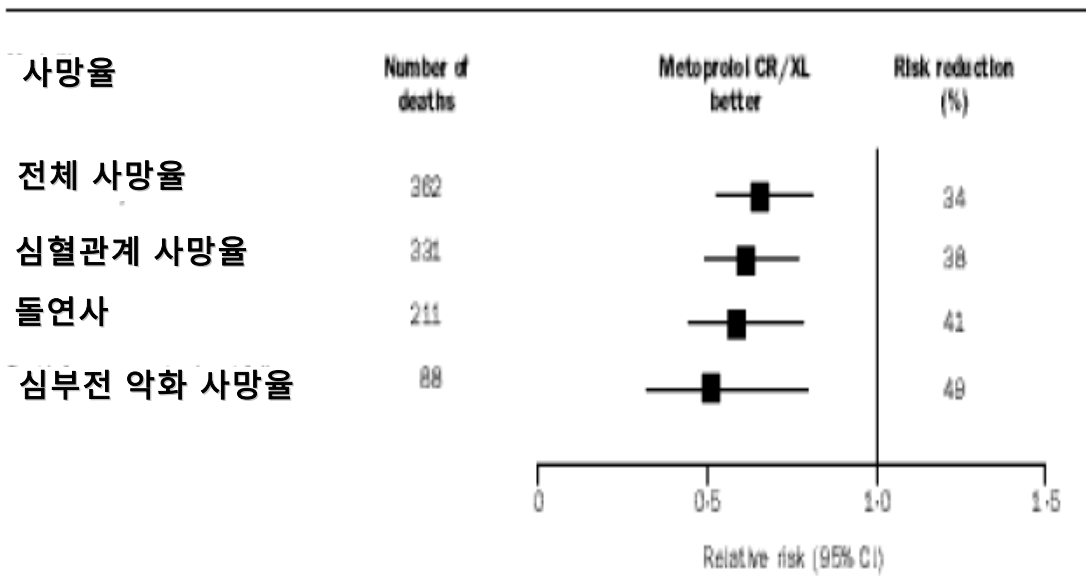


Paitents	*Sample*	*Beta-blocker*	*Dosage*
Chronic HF, EF<35%	**1094**	**Carvedilol**	**45mg/d**

65% risk reduction in mortality
Reduction in sudden death, hospitalization

Metoprolol

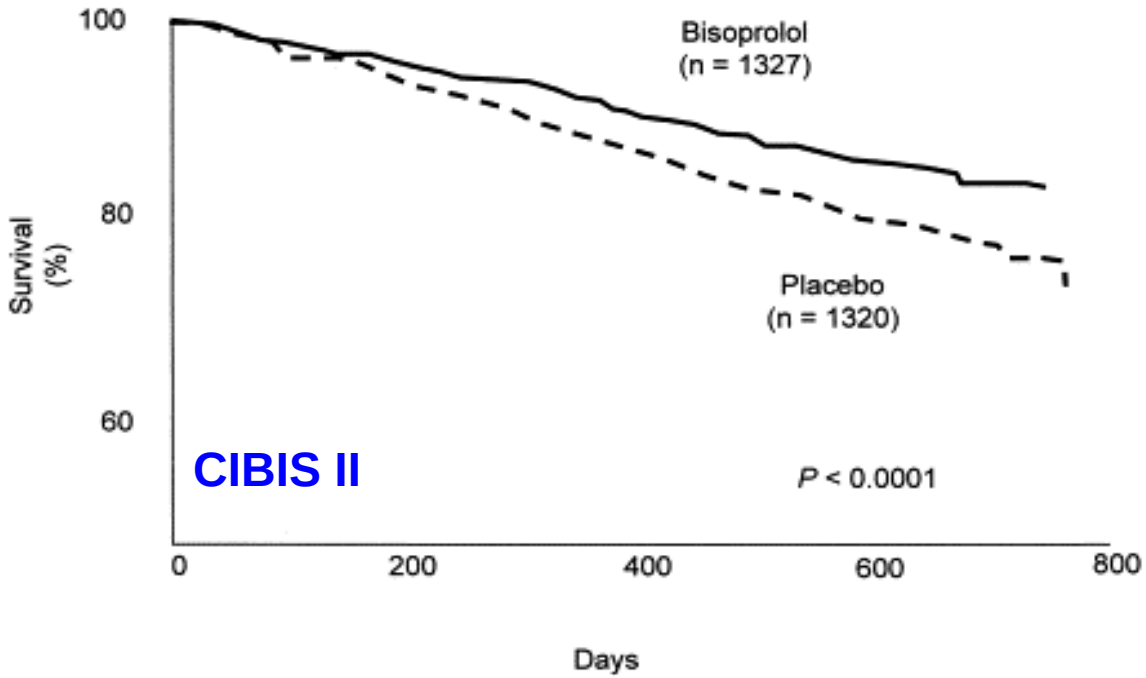




Paitents	*Sampl*	*Beta-blocker*	*Dosage*
DCMP, EF<40%	**3991**	**Metoprolol**	**159mg/d**
NYHA FC II-III		**CR/XL**	

34% risk reduction of mortality
Reduction in sudden death, hospitalization

Bisoprolol



Paitents	*Sample*	*Beta-blocker*	*Dosage*
DCMP, EF<35% NYHA FC III	**2647**	**Bisiprolol**	**7.5mg/d**

34% risk reduction in mortality
Reduction in sudden death, hospitalization

ß-Adrenergic Blockers

Clinical trials in HF

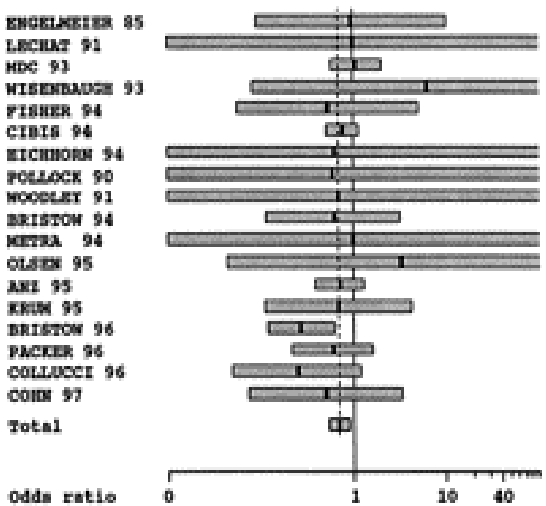
	DRUG	NYHA	EFFECT	starting dose	target dose
MDC	**Metoprolol**	-	-	**5 bid**	**50 bid**
MERIT-HF	**Metoprolol**	II-IV	35%	**12.5-25**	**200**
BEST	**Bucindolol**	III-IV	10%	**3**	**100-200**
CIBIS-II	**Bisoprolol**	III-IV	33%	**1.25**	**10**
Carvedilol US	**Carvedilol**	II-III	66%	**6.25 bid**	**25-50 bid**
MOCHA	**Carvedilol**	-	-	-	-
COPERNICUS	**Carvedilol**	IV	35%	**3.125 bid**	**25 bid**
COMET	**Carvedilol**	II-IV		**3.125 bid**	**25 bid**

ß-Adrenergic Blockers

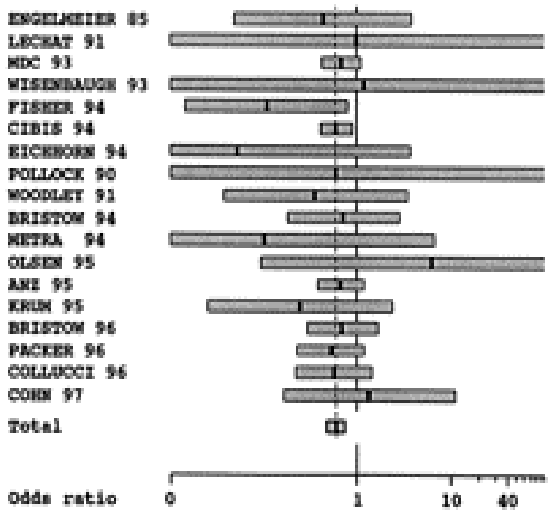
Clinical trials in HF

Reduction of Risk

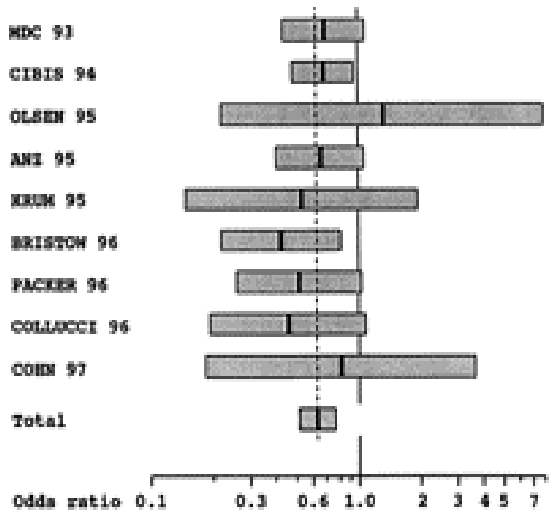
Mortality: 36%



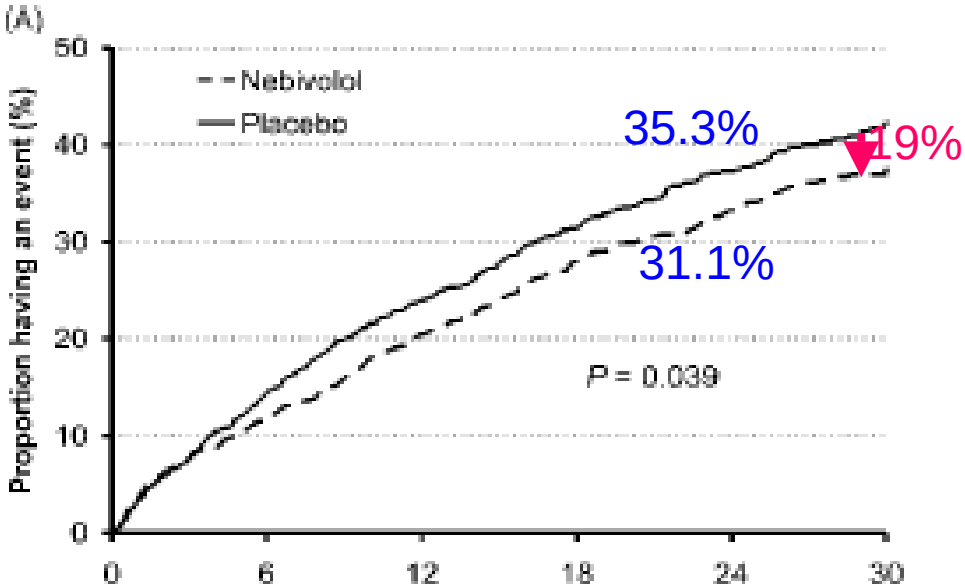
Hospitalizatio: 41%



Overall: 37%

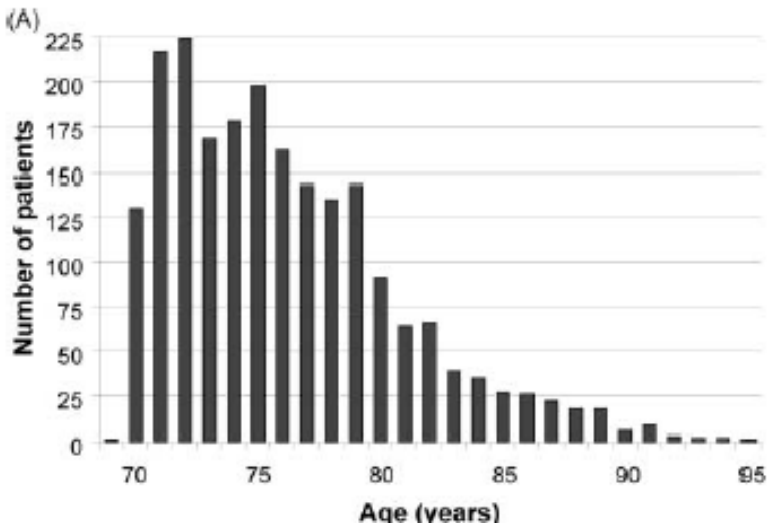


Nebivolol



SENIOR

Number at risk						
Nebivolol	1067	933	757	517	318	185
Placebo	1061	900	721	487	303	182



Paitents	*Sample*	*Beta-blocker*	*Dosage*
Age>70, EF<35% or H	**2128**	**Nebivolol**	**7.7mg/d**

19% risk reduction in primary end point

ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure)

Developed in Collaboration with the International Society for Heart and Lung Transplantation
Endorsed by the Heart Failure Society of America

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European Heart Journal
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EUROPEAN SOCIETY OF CARDIOLOGY®

ESC Guidelines

Guidelines for the diagnosis and treatment of Chronic Heart Failure: full text (update 2005)

The Task Force for the diagnosis and treatment of CHF of the European Society of Cardiology

Authors/Task Force Members: Karl Swedberg, Chairperson,* Göteborg (Sweden) *Writing Committee:* John Cleland, Hull (UK), Henry Dargie, Glasgow (UK), Helmut Drexler, Hannover (Germany), Ferenc Follath, Zurich (Switzerland), Michel Komajda, Paris (France), Luigi Tavazzi, Pavia (Italy), Otto A. Smiseth, Oslo (Norway).

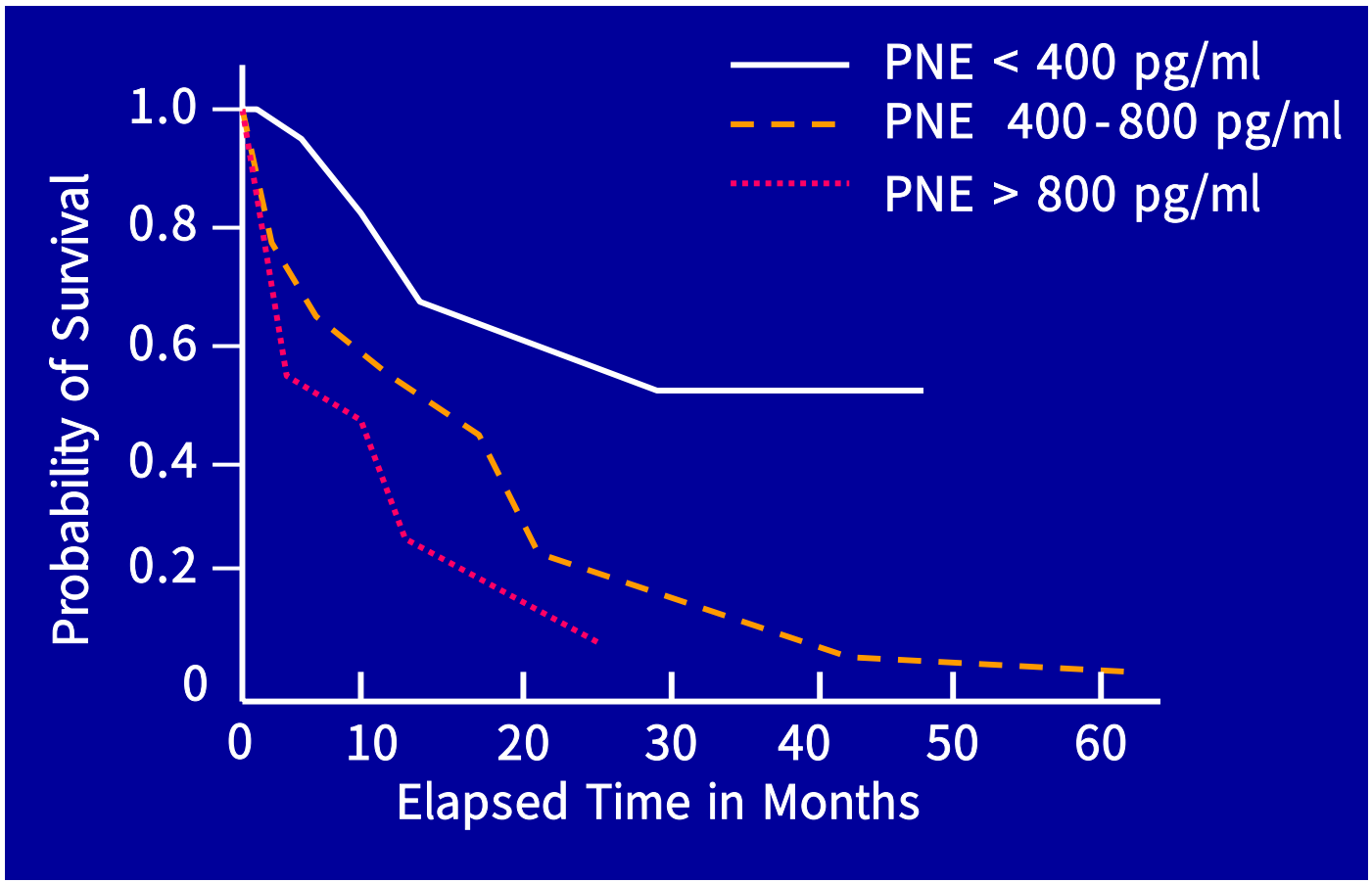
Recommended ß-Blockers in HF

1. **Bisoprolol**
2. **Metoprolol succinate CR**
3. **Carvedilol**
4. **Nebivolol**

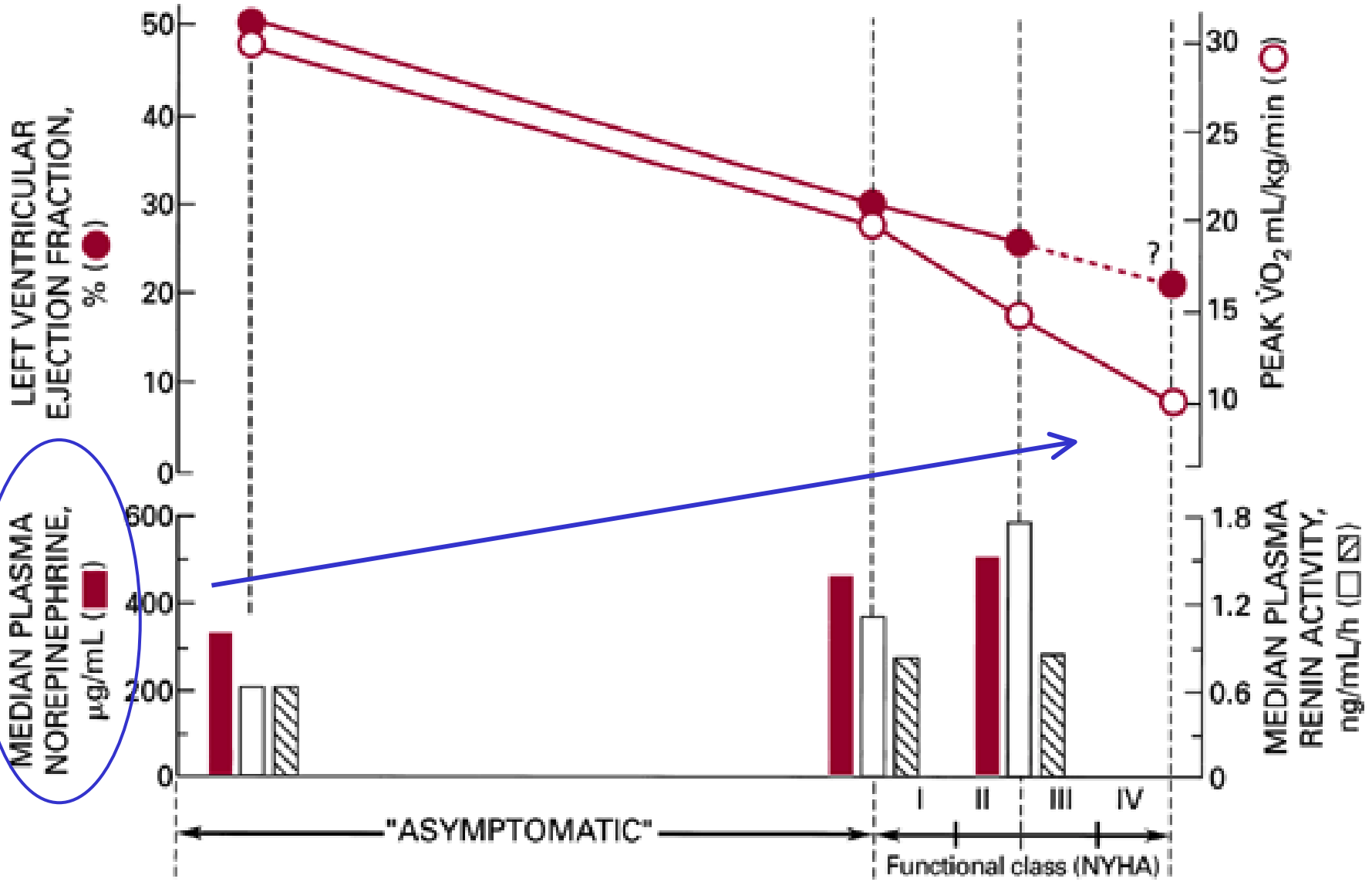
ß-Adrenergic Blockers는

왜 심부전 치료에 효과적인가?

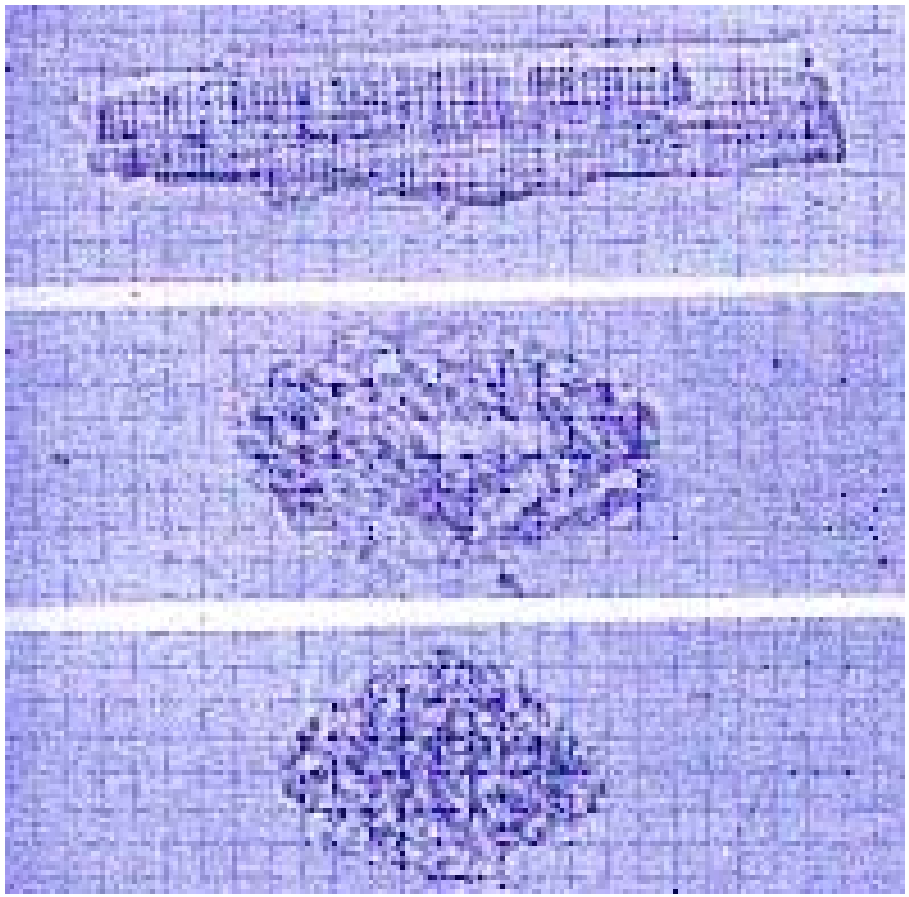
Sympathoadrenal system in HF



Sympathoadrenal system in HF



Sympathoadrenal system in HF

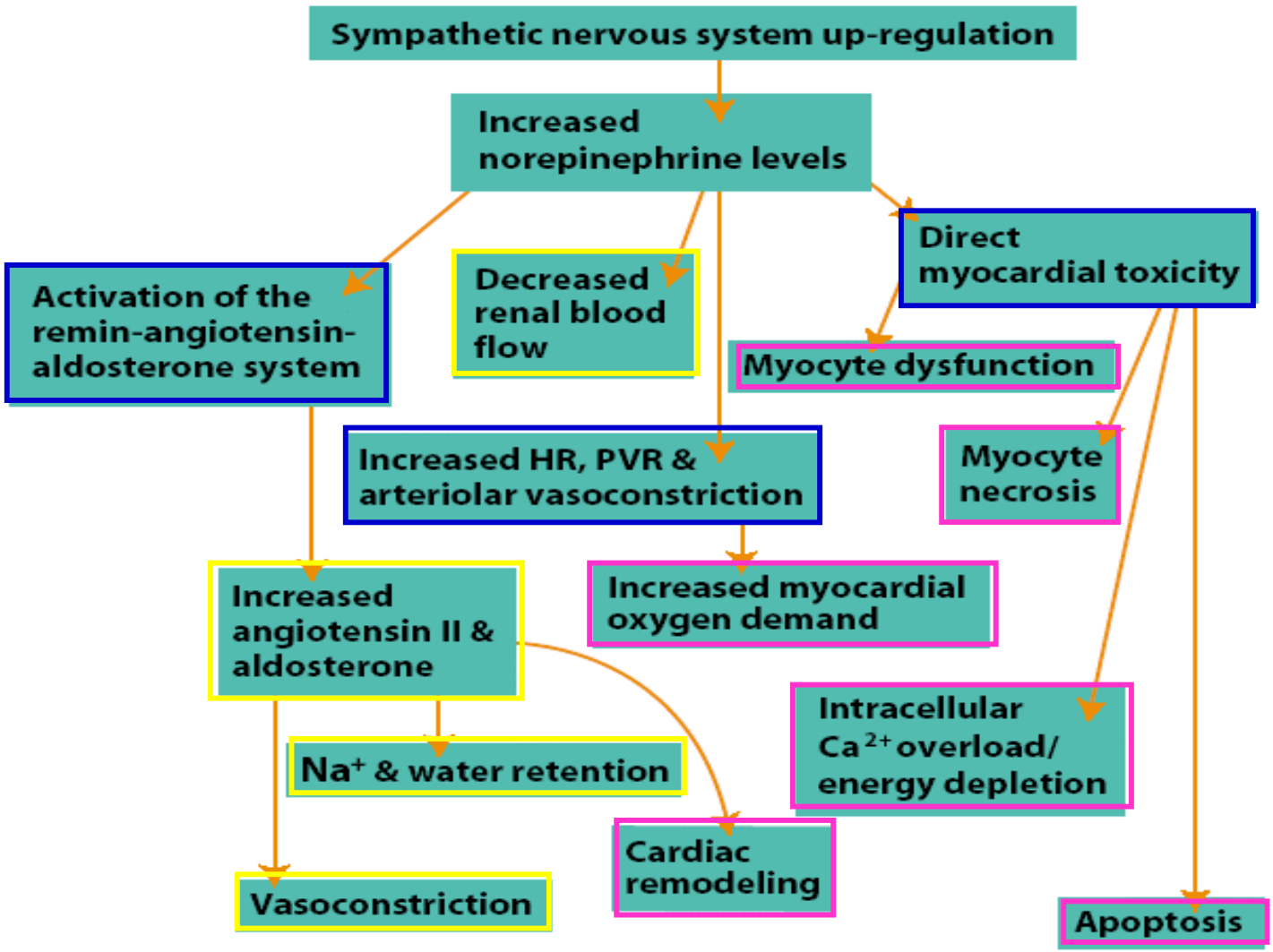


Add NE into myocyte

Apoptosis ⇐ β1
Direct toxisity ⇐ β1, (β2)

Cell Death

Sympathoadrenal system in HF



Sympathoadrenal system in HF

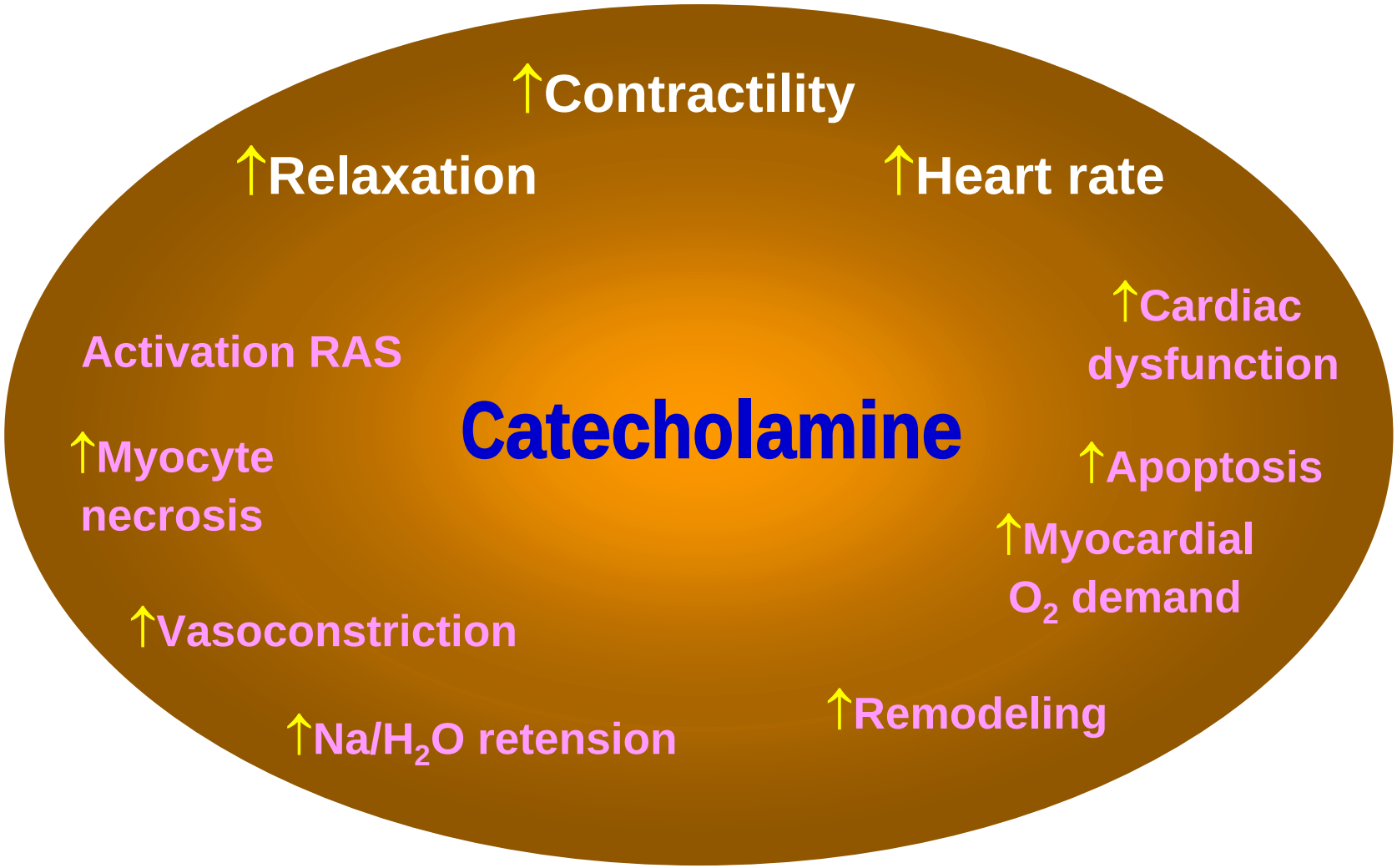
심근세포 수축반응

칼슘에 대한 수축반응:	변화없음
카테콜라민에대한 수축반응:	현저히 감소

교감신경계 구성요소의 변화

혈중 norepinephrin:	현저히 증가
심근 norepinephrin:	현저히 감소
β1–수용체의 수:	현저히 감소
β2–수용체의 수:	변화 없음
Gi 활성도:	증가
Gs 활성도:	변화없음
βARK 활성도:	현저히 증가

Pathophysiologic Effects of ß- Agonist



Mechanisms of ß-blockers in HF

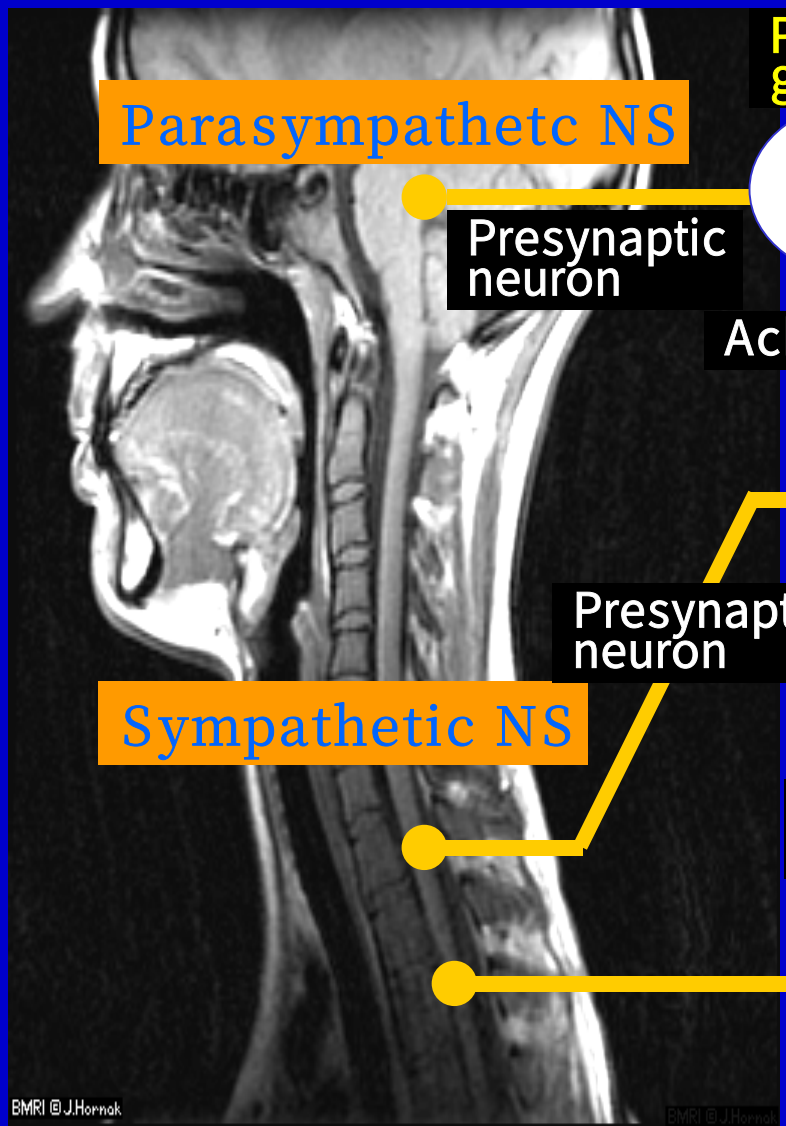
- Improve systolic function
- Improve energetics
- Reverse the remodeling

by

1. ↓Heart rate → ↓Oxygen consumption
2. ↓Systolic and diastolic wall stress
3. Shift utilization of FFA to glucose
4. Anti-arrythmogenic
5. Changed in gene expression

ß-Adrenergic system의 특징은?

ß-Adrenergic Receptor



Parasympathetc NS

Parasympathetic ganglion

Presynaptic neuron

Ach

Nicotinic R

Ach

Muscarinic Receptor in
Heart
Blood vessel
Glands
Visceral organ
Smooth m.

Sympathetic ganglion

NE

α-, β-Adrenergic Receptor in
Heart
Blood vessel
Glands
Visceral organ
Smooth m.

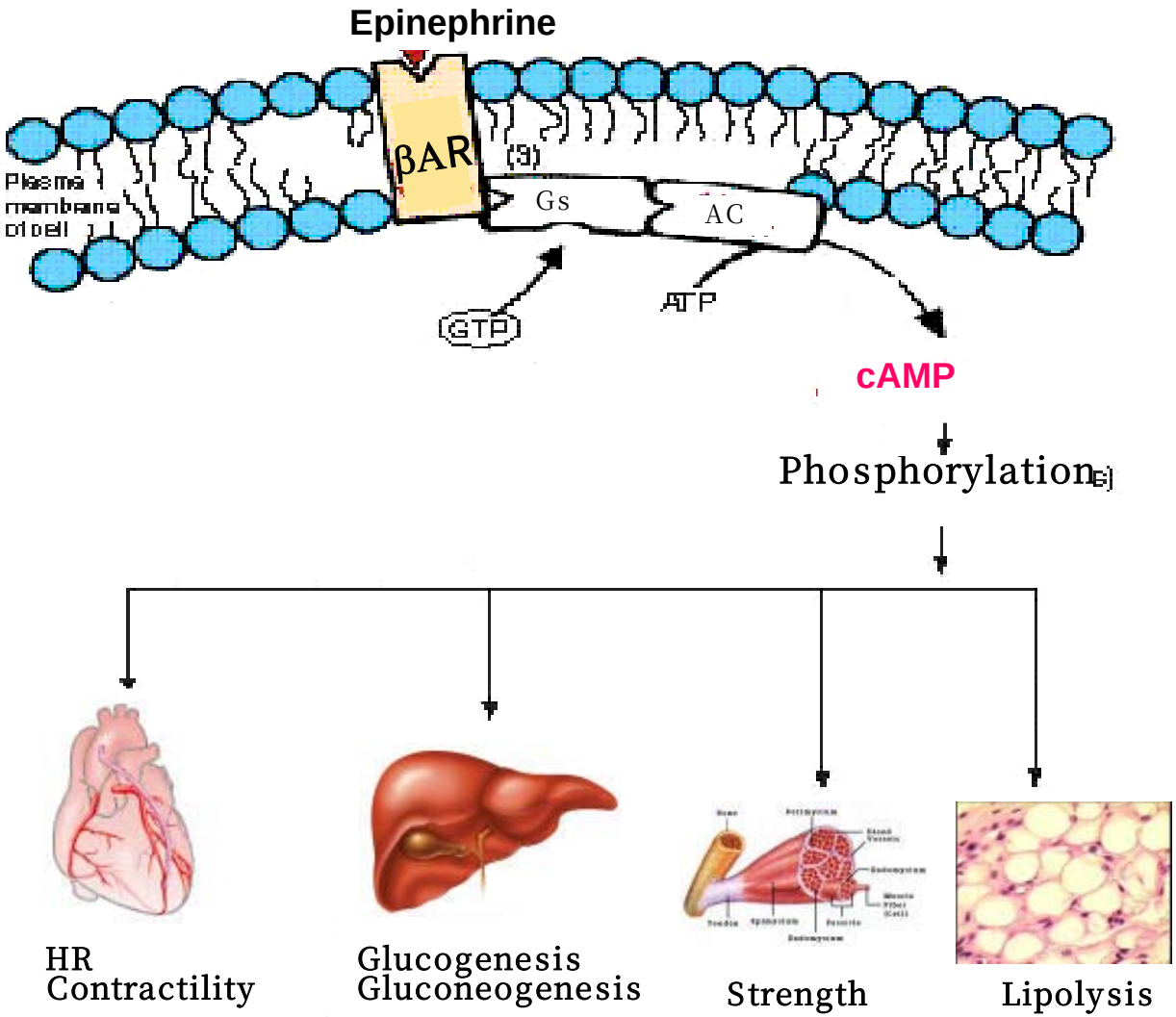
Presynaptic neuron

Sympathetic NS

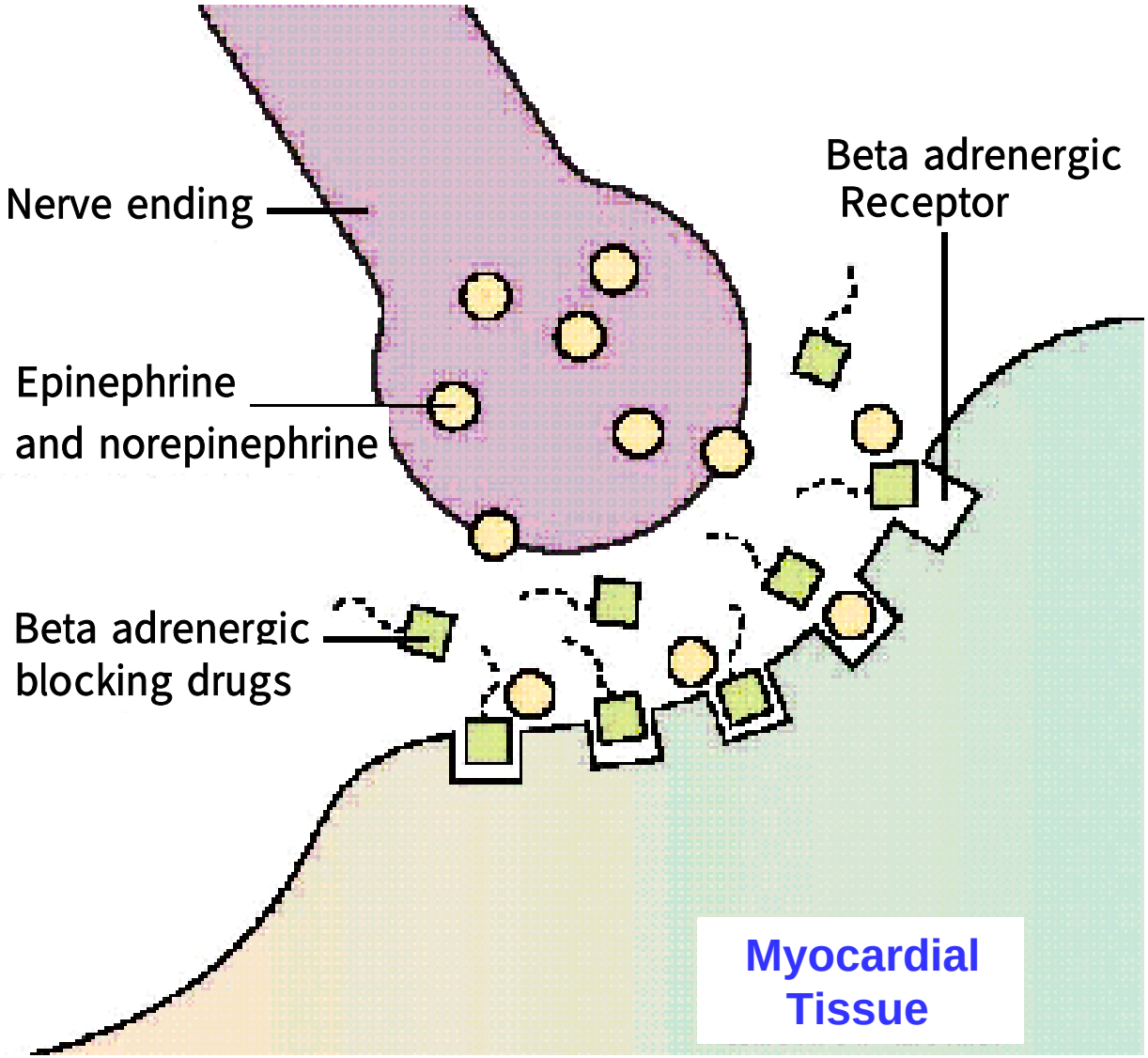
Adrenal medulla (nicotinic R)

Epinephrine /Norepinephrine *(into circulation)*

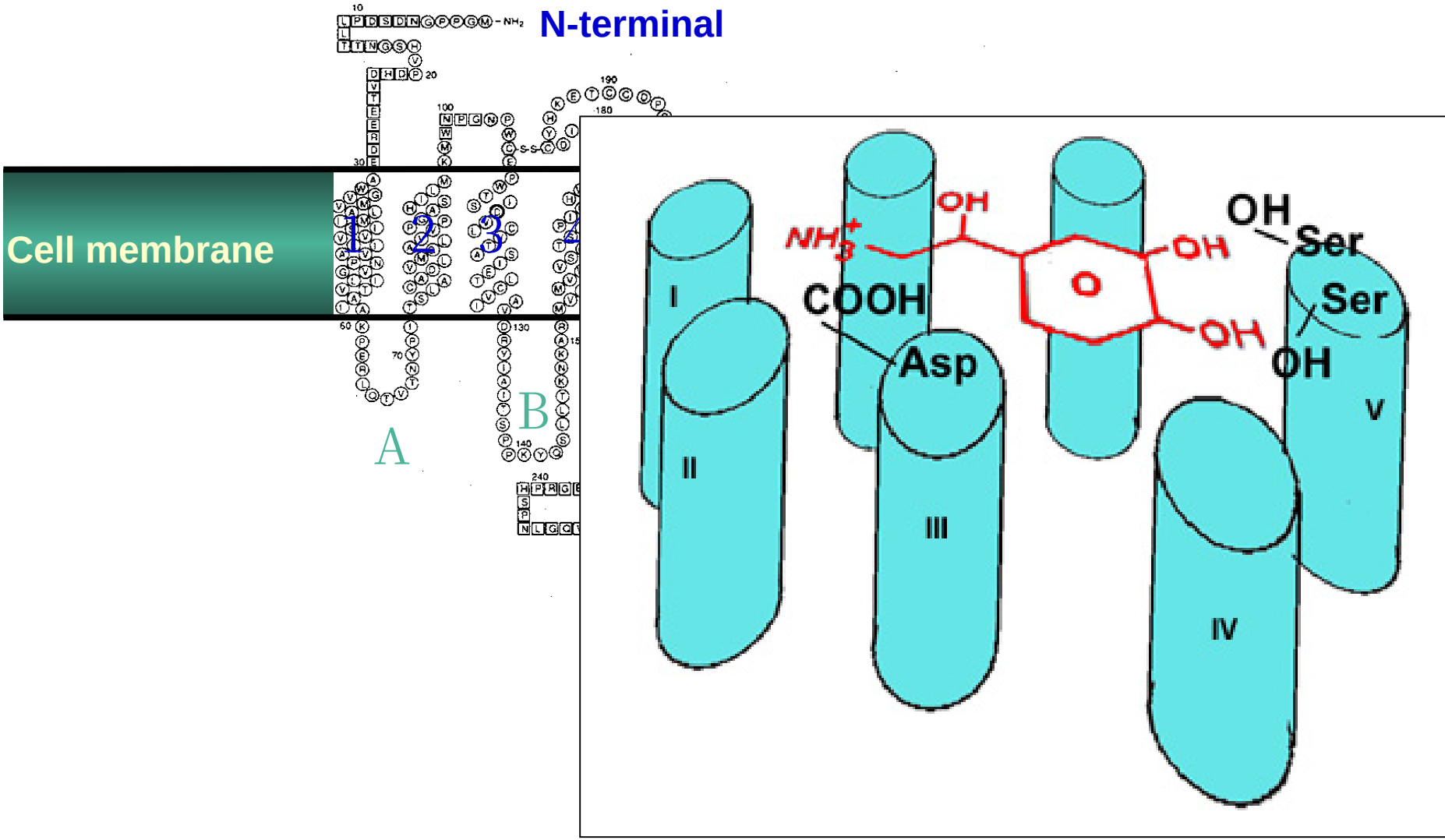
ß-Adrenergic Receptor



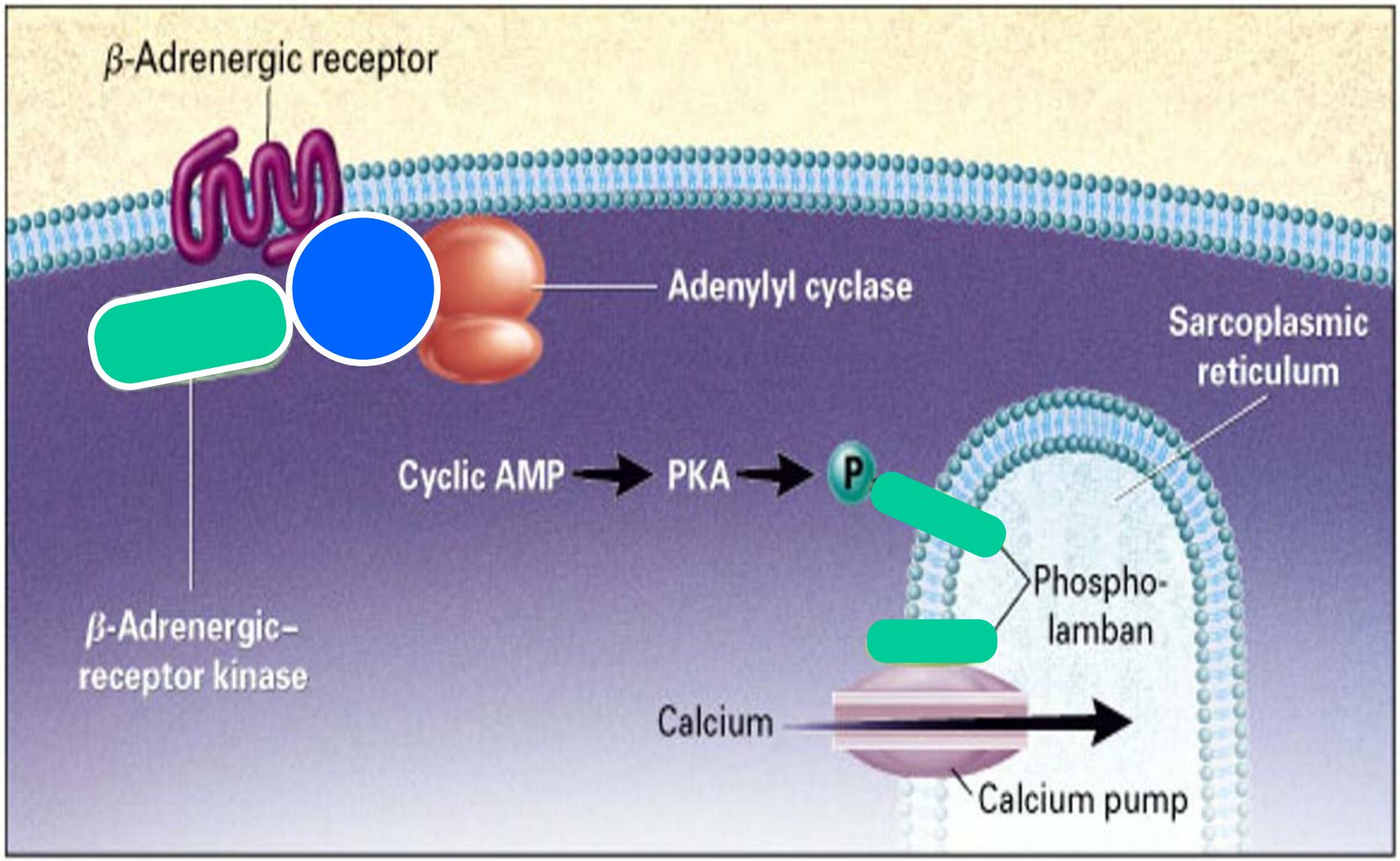
ß-Adrenergic Receptor



ß-Adrenergic Receptor

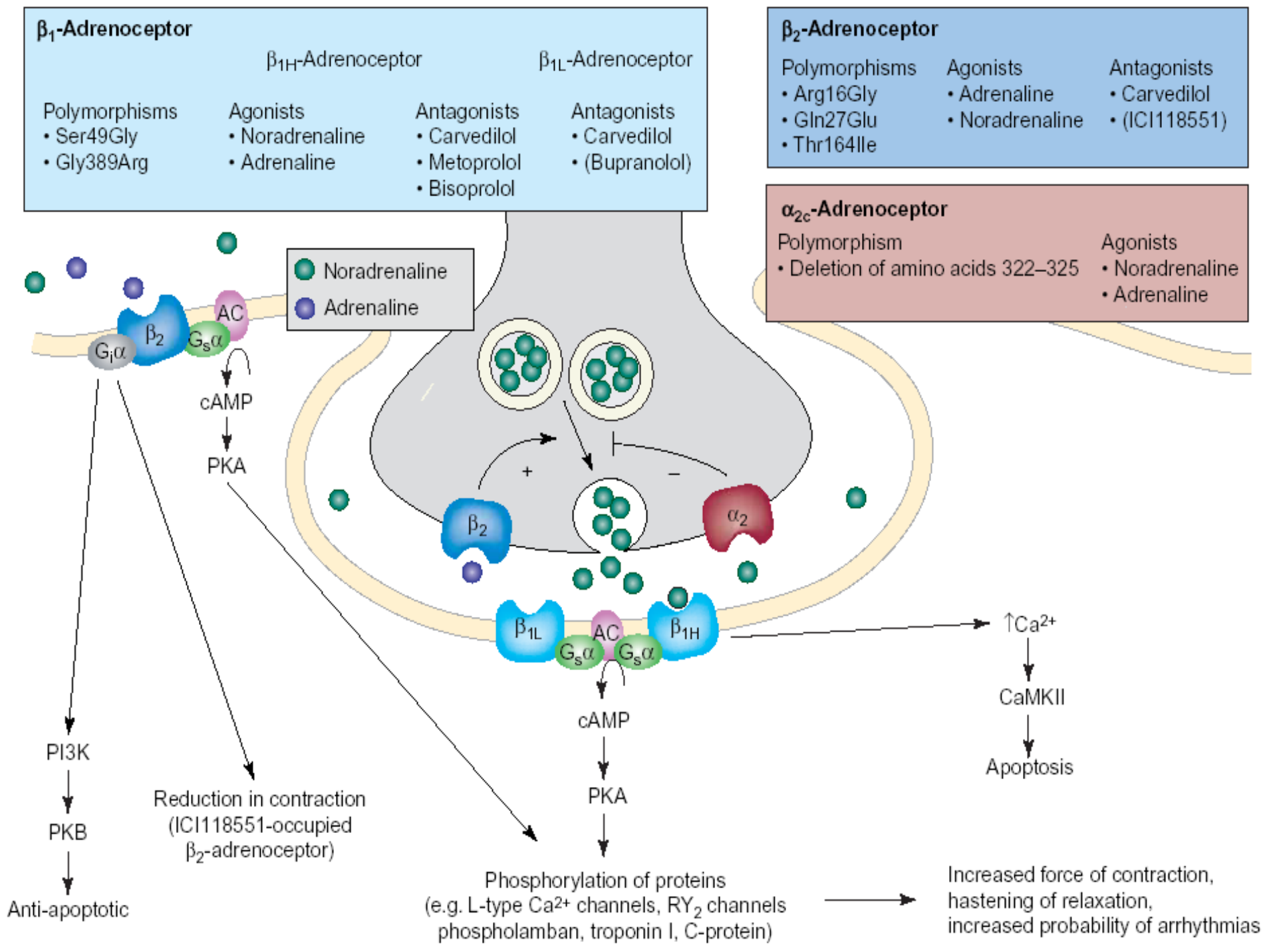


ß-Adrenergic Receptor Signal



Which β-blocker is better?

Which subtype, β1 or β2 ?
Inverse agonism ?


β1-Adrenoceptor
β1H-Adrenoceptor
β1L-Adrenoceptor
Polymorphisms
• Ser49Gly
• Gly389Arg
Agonists
• Noradrenaline
• Adrenaline
Antagonists
• Carvedilol
• Metoprolol
• Bisoprolol
Antagonists
• Carvedilol
• (Bupranolol)
β2-Adrenoceptor
Polymorphisms
• Arg16Gly
• Gln27Glu
• Thr164Ile
Agonists
• Adrenaline
• Noradrenaline
Antagonists
• Carvedilol
• (ICI118551)
α2c-Adrenoceptor
Polymorphism
• Deletion of amino acids 322–325
Agonists
• Noradrenaline
• Adrenaline
Noradrenaline
Adrenaline
β2
Gsα
Giα
AC
cAMP
PKA
+
–
α2
β1L
β1H
↑Ca2+
CaMKII
Apoptosis
PI3K
PKB
Anti-apoptotic
Reduction in contraction
(ICI118551-occupied
β2-adrenoceptor)
Phosphorylation of proteins
(e.g. L-type Ca2+ channels, RY2 channels
phospholamban, troponin I, C-protein)
Increased force of contraction,
hastening of relaxation,
increased probability of arrhythmias

ß-Adrenergic Receptor Blocker

	GENERATION/CLASS	K(β1)	β1/β2	β1 /α1
Propranolol	1st/nonsel	4.1	2.1	-
Metoprolol	2st/β1-sel	45	74	-
Bisoprolol	2st/β1-sel	121	119	-
Carvedilol	3rd/β-vasod	4	7.3	2.4
Nebivolol	3rd/β-vasod	5.8	1700	66
Bucindolol	3rd/β-vasod	3.6	1.4	-

ß1-Adrenergic Receptor Subtype

- β1 subtype: Myocardial contractility
- β2 subtype: Vascular SMC relaxation
- In human heart: both of β1- and β2-AR (ratio of **β1:β2 = 70:30**)
- β3 subtype: mainly expressed in **adipose tissue**, some in cardiac myocyte)

ß-Adrenergic Receptor Subtype

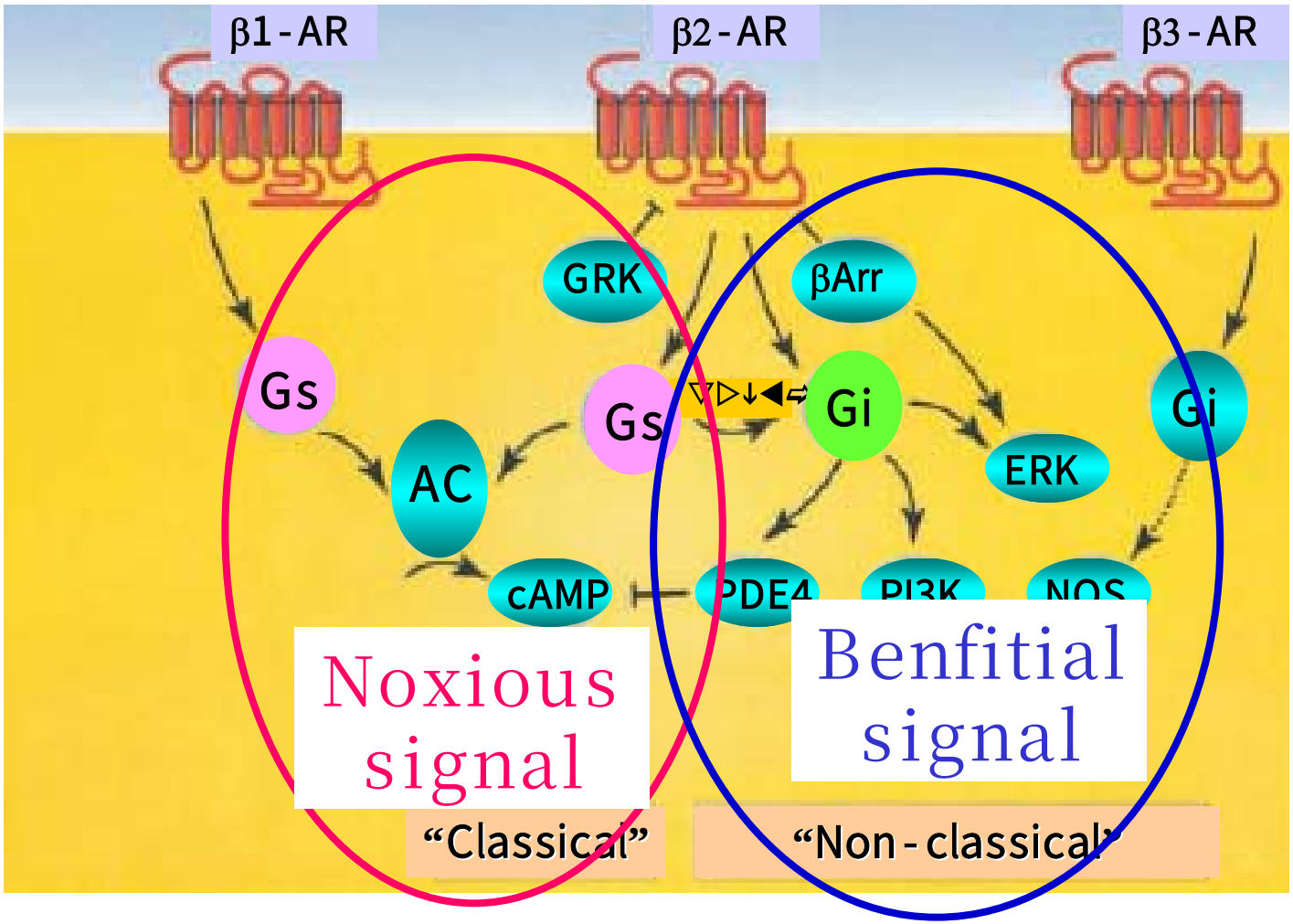
Toxic effect on myocardium

- **In Heart Failure**
  - **β1 receptor number: decreased**
  - **β2 receptor number: NOT changed**
- **In animal study**
  - **β1 receptor over-expressed animal**

    → develop HF
  - **β2 receptor over-expressed animal**

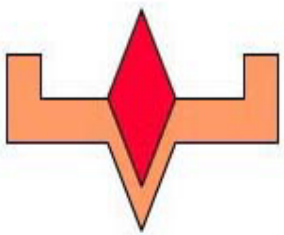
    → enhanced contractility

Subtype - ß1 vs ß2



Inverse agonism

Full Agonist



Large stimulus to cellular signaling machinery

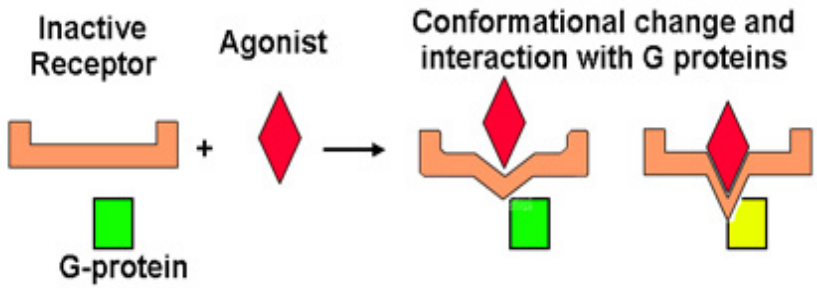
LARGE EFFECT

Partial Agonist

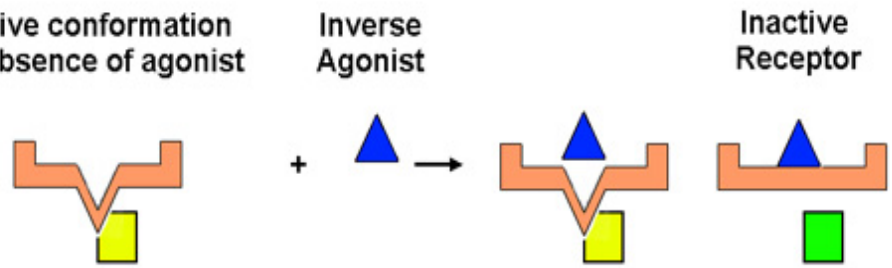
Small stimulus to cellular signaling machinery

small effect

Typical Agonist Promoted Receptor Activation



Constitutively Active Receptor and an Inverse Agonist



Inverse Agonism

Full agonist

>> Partial agonist

>> Neutral antagonist

>> Partial inverse agonist

>> Full inverse agonist

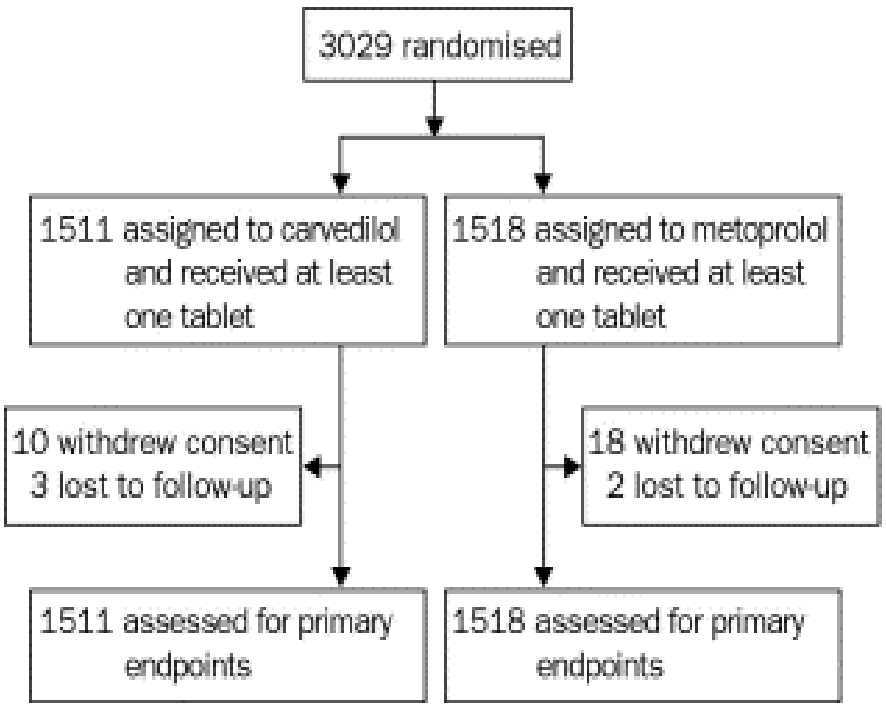
Ligand Affinity

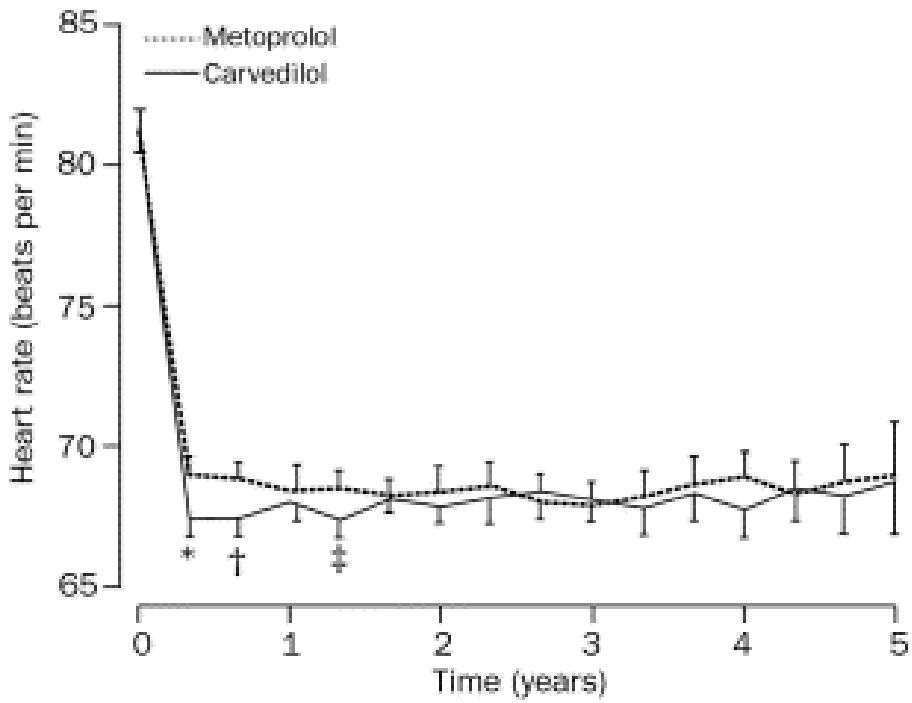
	Selectivity	Inverse agonism	Clinical data
Antagonist			
Carvedilol	**non-selective/α1**	neutral	Good
Bisoprolol	**β1-selective**	partial inverse agonist	Good
Metoprolol	**β1-selective**	partial inverse agonist	Good
Nebivolol	**β1-selective**	neutral	Good
Bucindolol	**non-selective/α1**	weak partial agonist	Neutral
Xamoterol	**β1-selective**	strong partial agonist	Bad

Which combination?

Which beta-blocker is better?

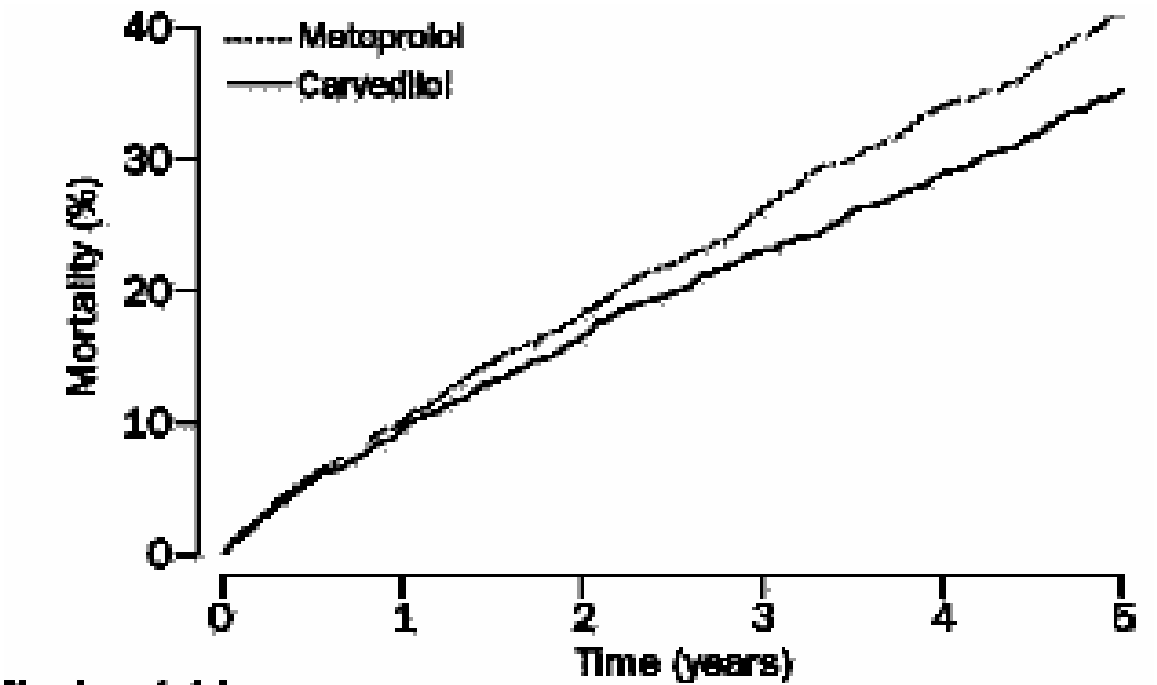
Carvedilol 50mg/d vs. Metoprolol 100mg/d
NYHA II-IV, EF<35%





Lancet. 2003 Jul 5;362(9377):7-13

Which beta-blocker is better?



Number at risk

Carvedilol	1511	1366	1259	1155	1002	383
Metoprolol	1518	1359	1234	1105	933	352

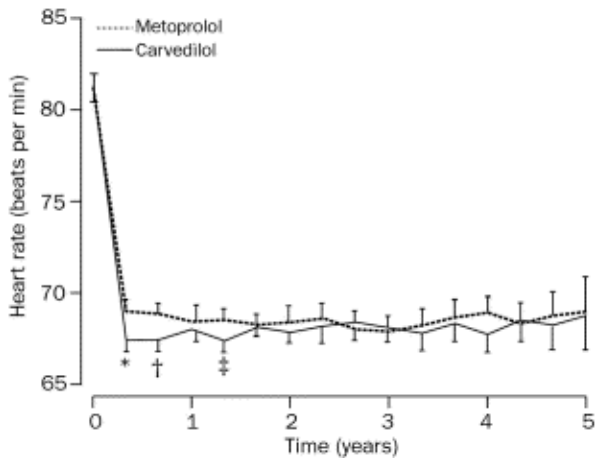
All-cause mortality

Carvedilol: 34%

Metoprolol: 40%

⇓

Carvedilol better (?)



Lancet. 2003 Jul 5;362(9377):7-13

Is it true?

- Not use the dose or formulation of metoprolol CR/XL that was shown to prolong life (ie, MERIT-HF)

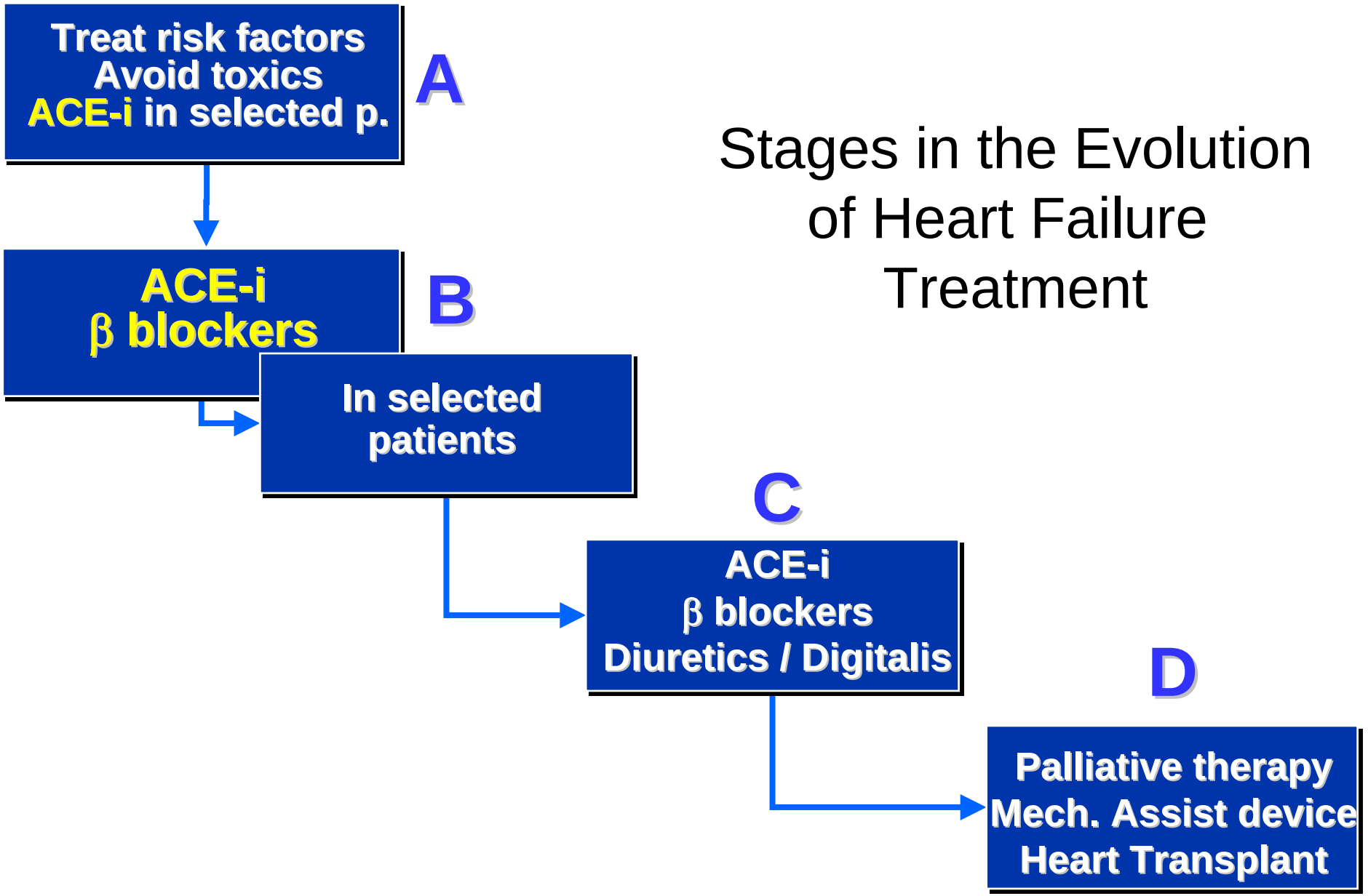
  -***Expert Opin Pharmacother. 2004;5:205-8***

- Dosing regimen of metoprolol in the COMET is similar to the dose of carvedilol

  -***Card Fail. 2003 Dec;9(6):429-43***

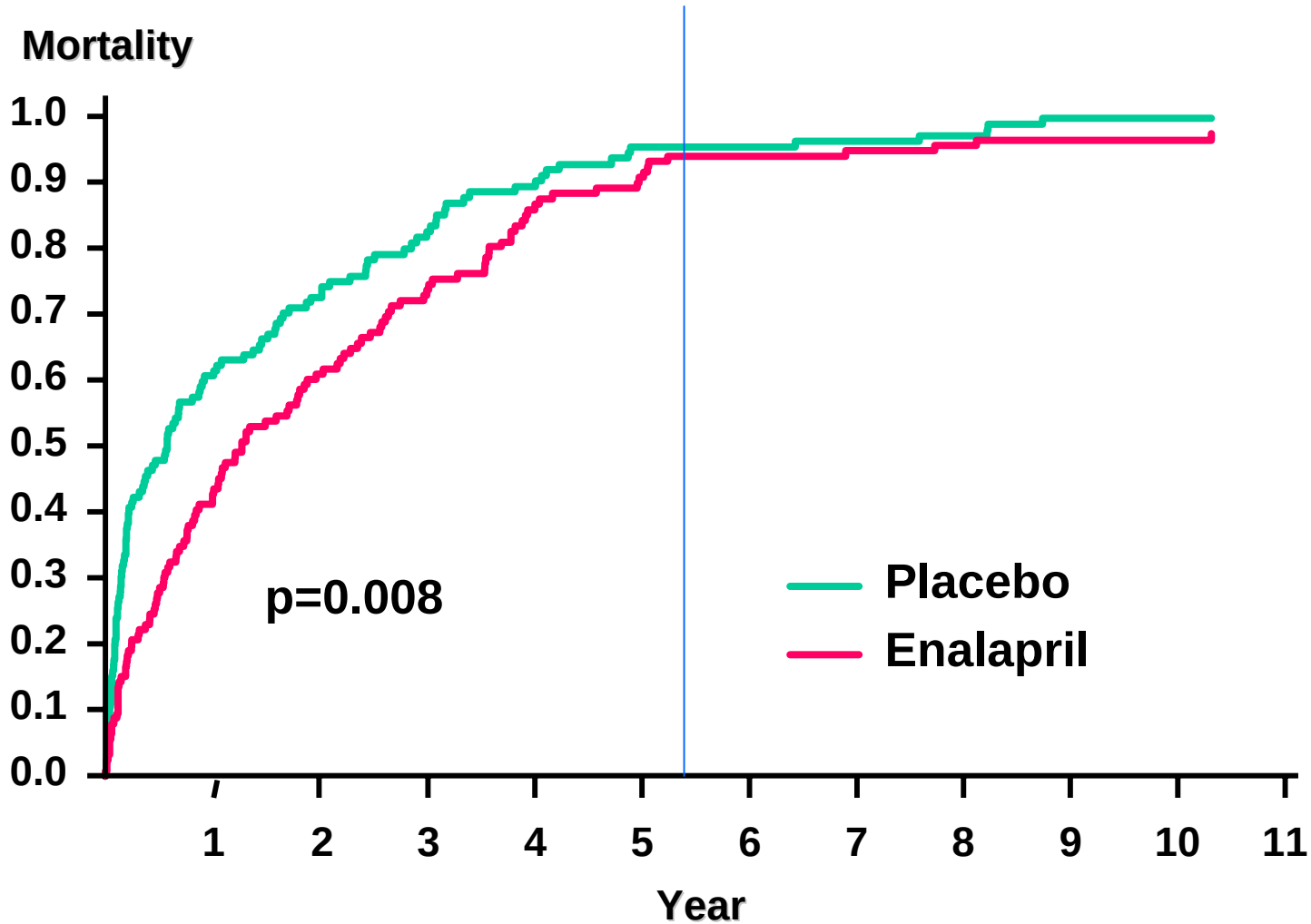
Beta-blocker
vs.
ACE inhibitor

Stages in the Evolution of Heart Failure Treatment



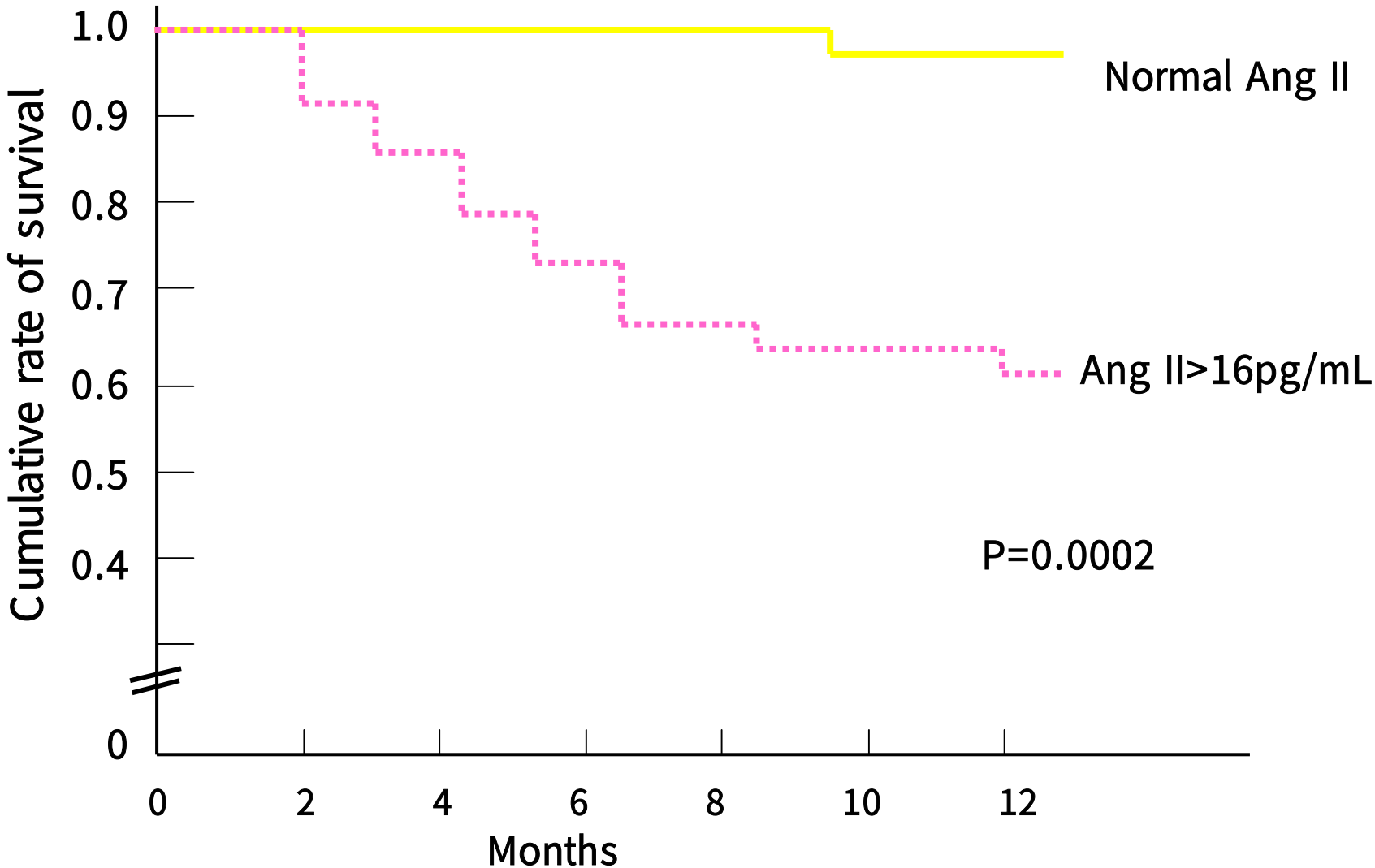
CONSENSUS 10-year follow-up

All randomized patients, original and follow-up



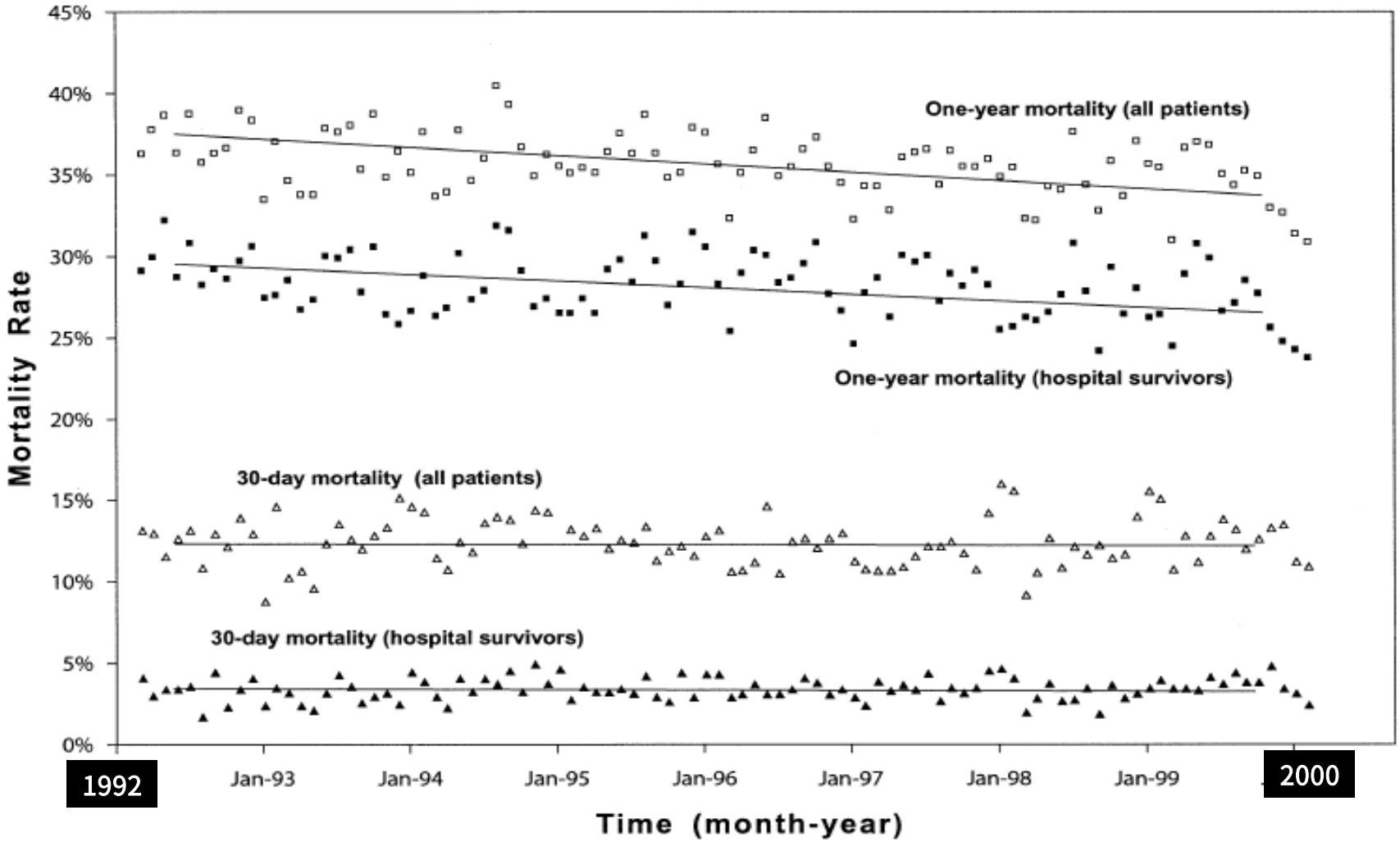
Eur Heart J 1999

Angitensin II in HF with ACEi Tx



European Heart J, 2000;21:53-57

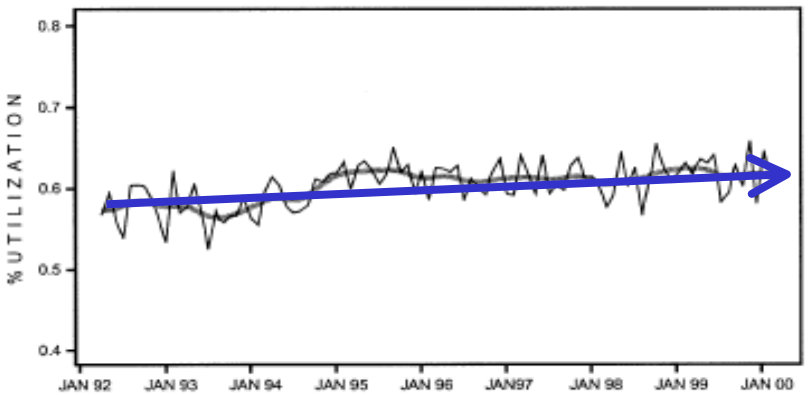
심부전 치료의 변화 추세



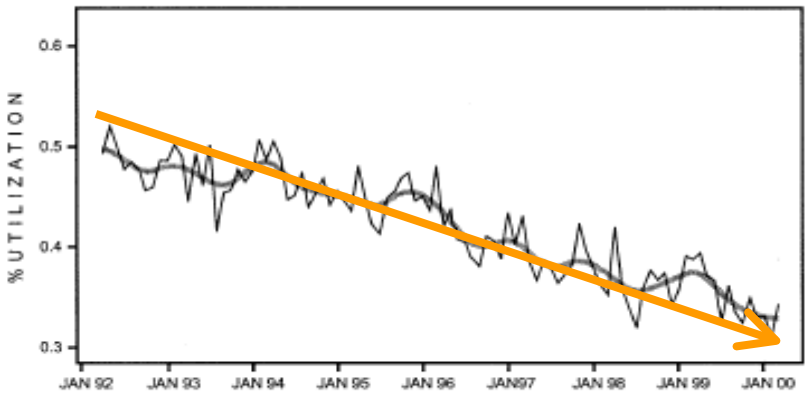
Lee M, Mamdani M and et al. Am J Med. 2004;116:581–589.

심부전 치료의 변화 추세

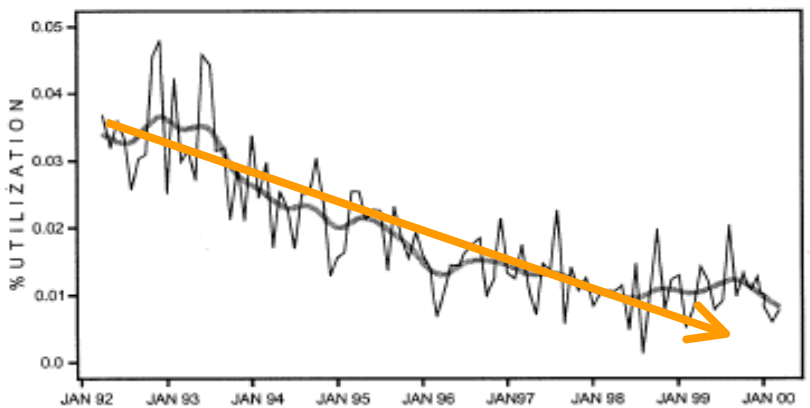
(A) ACE inhibitors or angiotensin receptor blockers



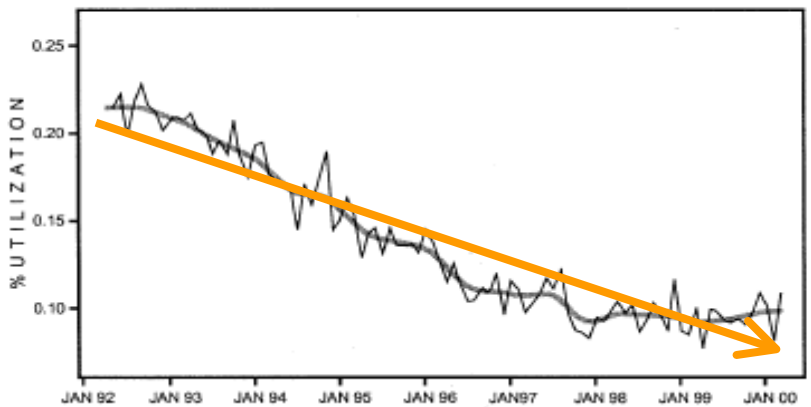
(B) Digitalis



(C) Class I antiarrhythmic agents

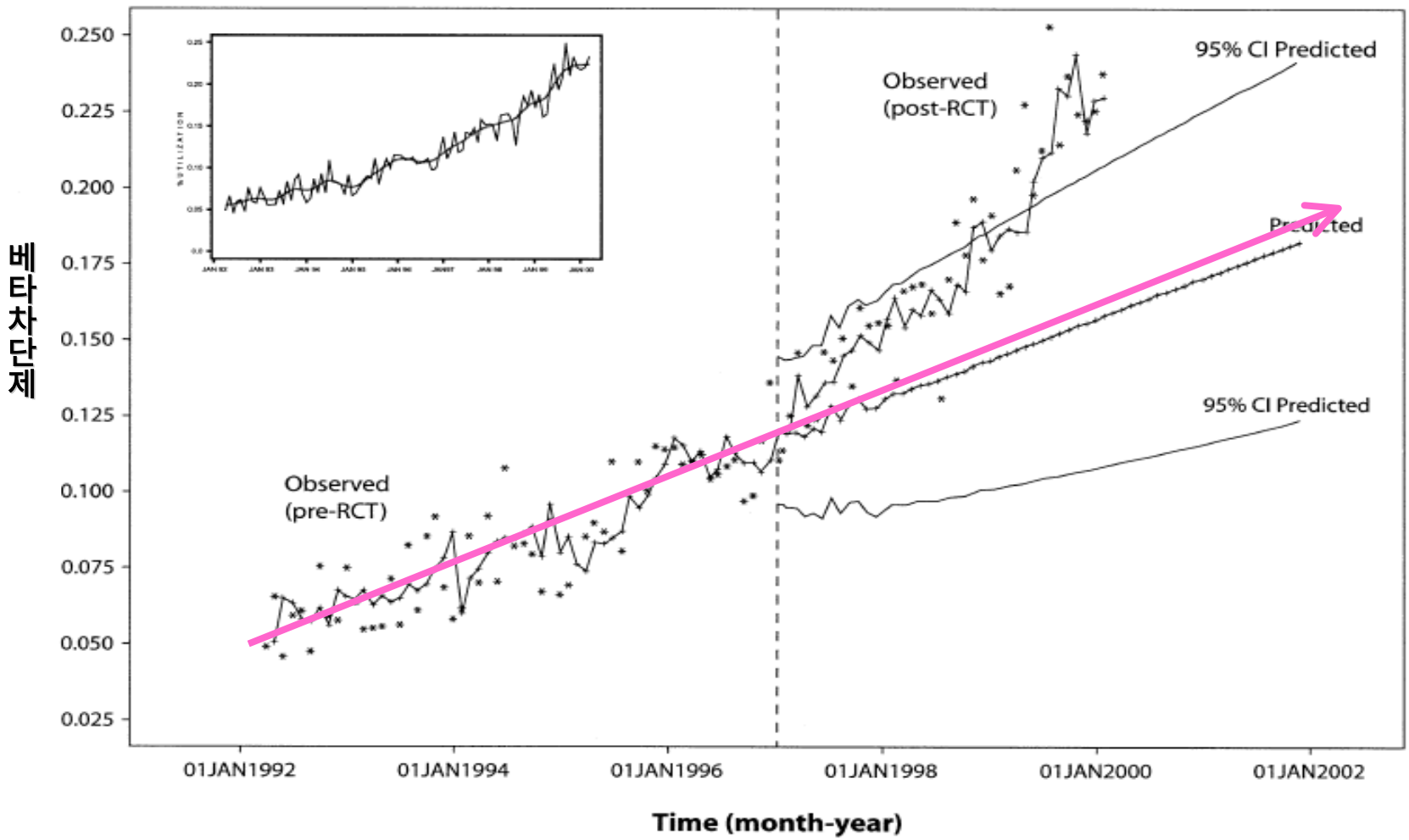


(D) First-generation calcium antagonists



Lee M, Mamdani M and et al. Am J Med. 2004;116:581–

심부전 치료의 변화 추세



Lee M, Mamdani M and et al. Am J Med. 2004;116:581–589.

심부전 치료의 변화 추세

심부전 치료 약제 사용 비율의 변화 추세

약제	Fiscal 1992/1993	Fiscal 1999/2000	*P* Value
	평균사용 빈도 (95% Confidence Interval)		
Beta adrenergic blockers	5.9 (3.9–7.9)	21.5 (17.2–25.8)	<0.001
Calcium channel blockers*	21.3 (19.7–22.9)	9.6 (7.8–11.4)	<0.001
Digitalis preparations	48.6 (45.3–51.9)	34.5 (29.8–39.2)	<0.001
Antiarrhythmic agents†	3.5 (2.1–4.9)	1.4 (0.6–2.2)	<0.001
ACE inhibitors	57.8 (52.3–63.3)	59.1 (55.0–63.2)	0.2
ACE inhibitor or angiotensin receptor blocker	57.8 (52.3–63.3)	61.7 (56.8–66.6)	0.001

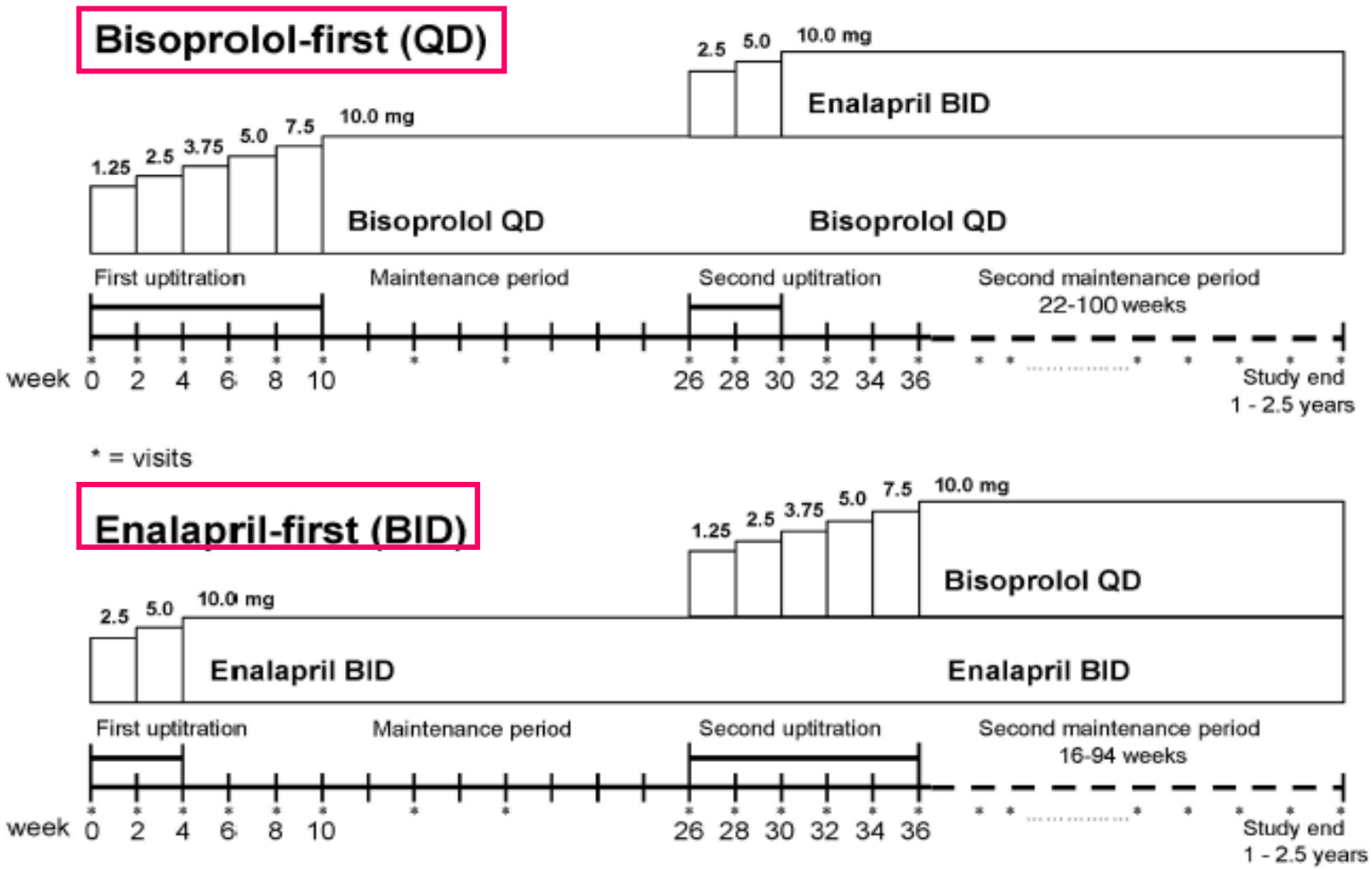
증가

감소

변화 없음

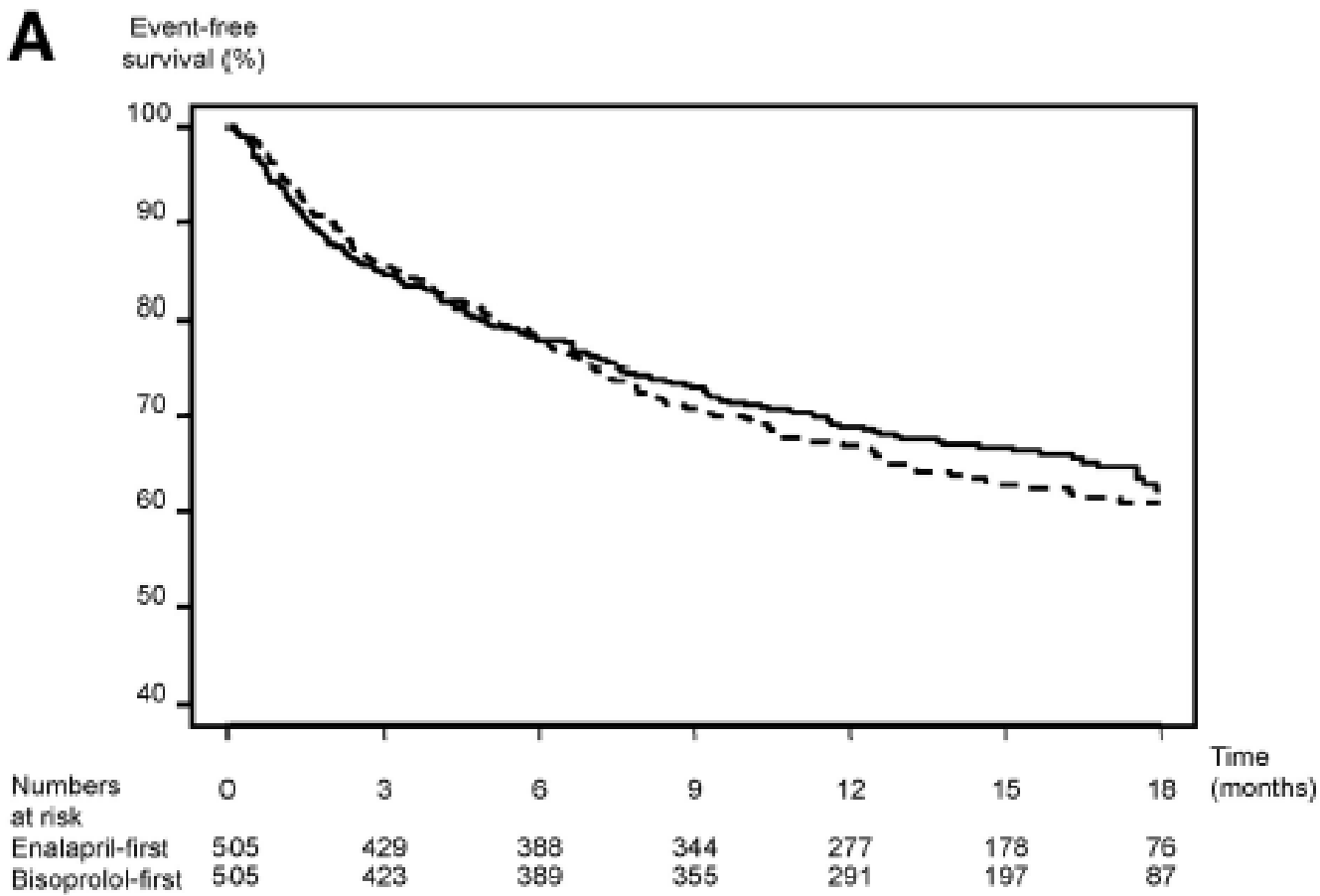
Lee M, Mamdani M and et al. Am J Med. 2004;116:581–589.

Which one first? (beta-blocker:ACEi)



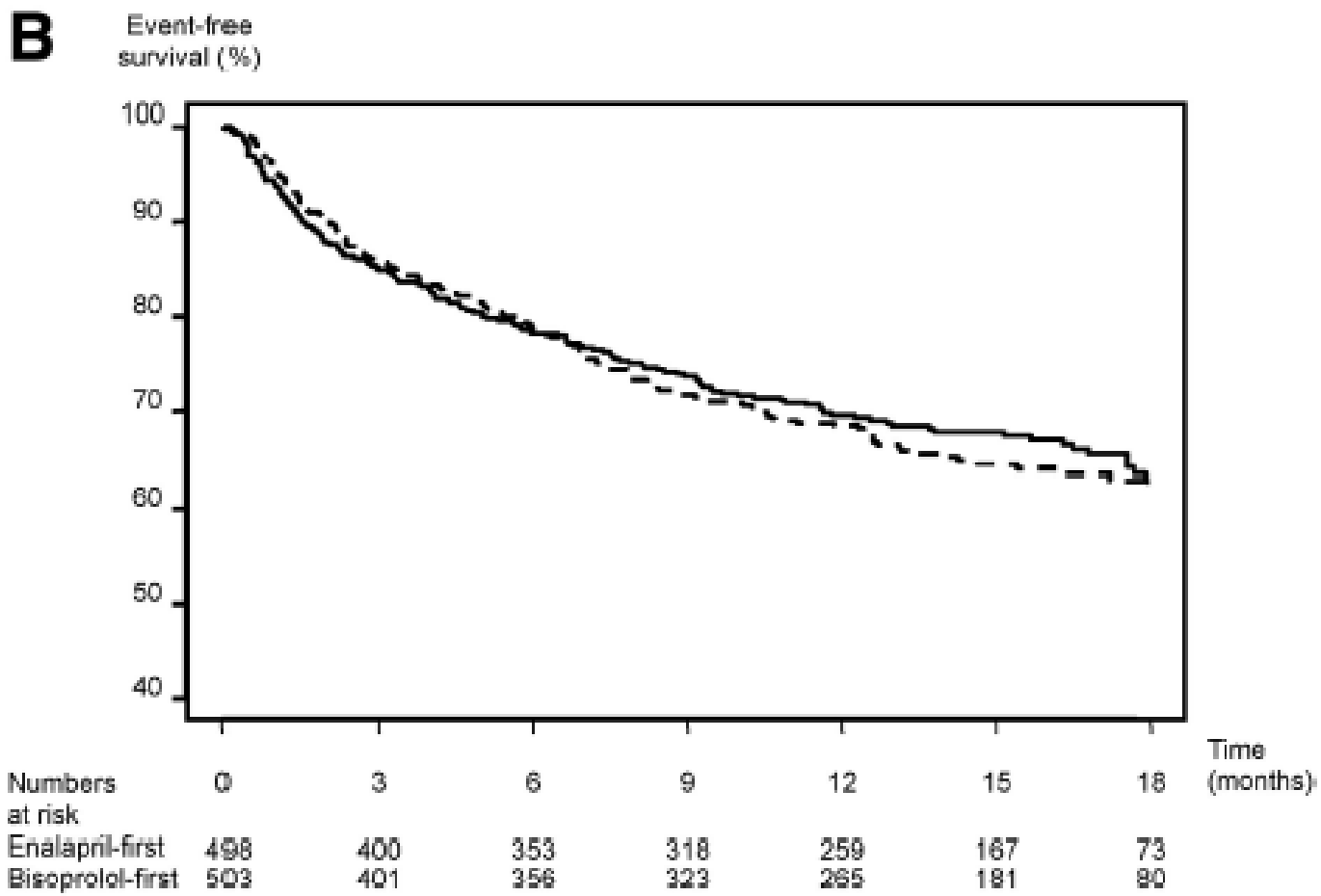
Eur J Heart Fail. 2004;6:493-500

CIBIS III



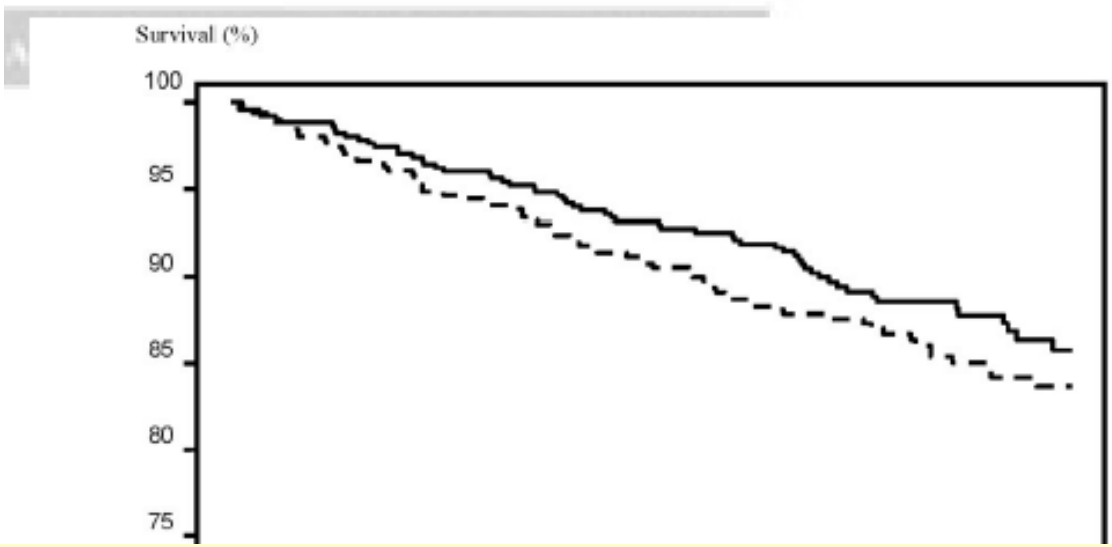
intention-to-treat sample: noninferiority *P*=0.019

CIBIS III



Per-protocol sample: noninferiority *P*=0.046

CIBIS III



Although noninferiority of bisoprolol-first versus e nalapril-first treatment was not proven in the per-protocol analysis, our results indicate that it may be as safe and efficacious to initiate treatm ent for CHF with bisoprolol as with enalapril.

Modulation of ß-AR in HF

- **Down-regulation**

  β-수용체의 수적감소

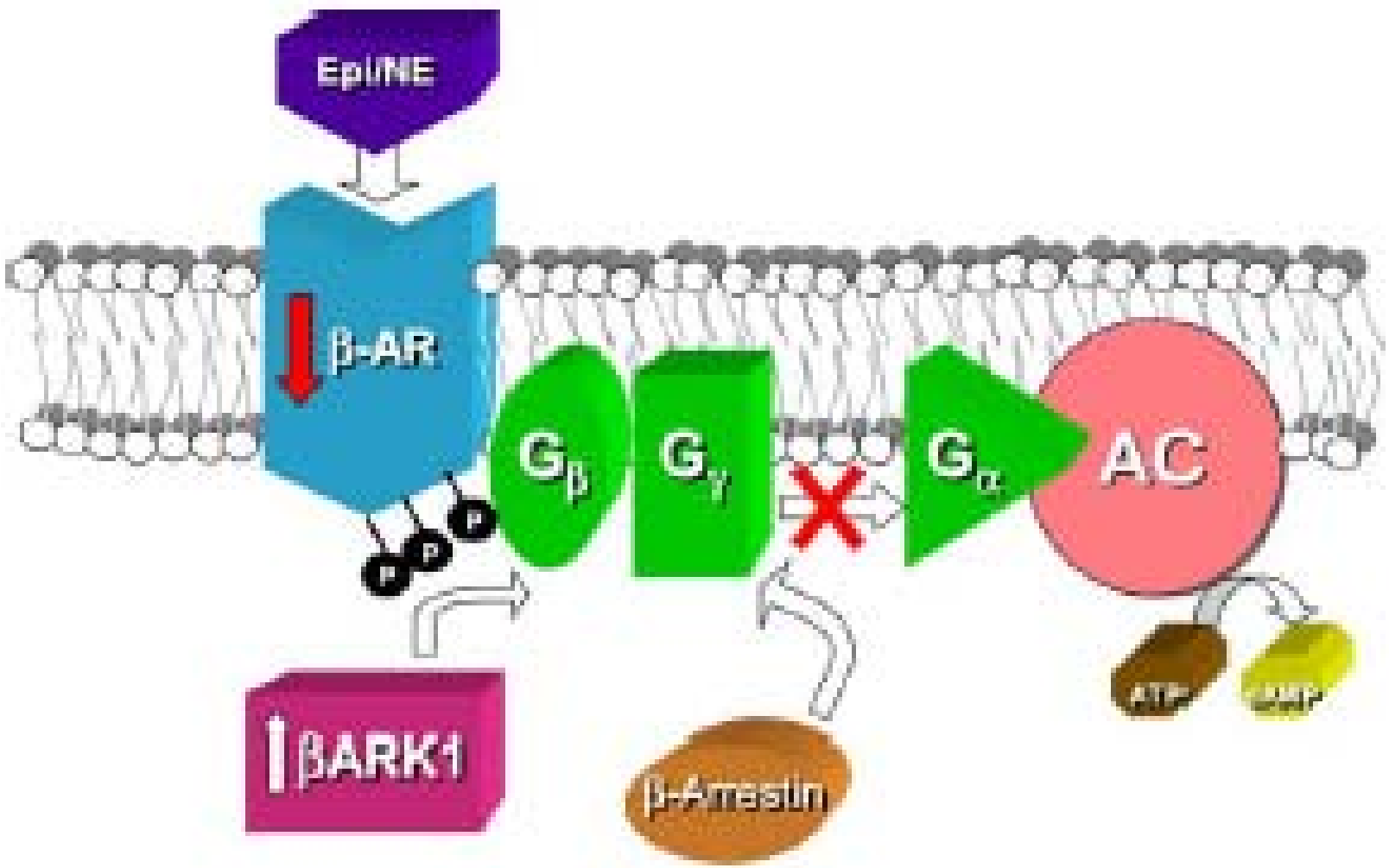
- **Desensitization**

  수용체 기능 저하

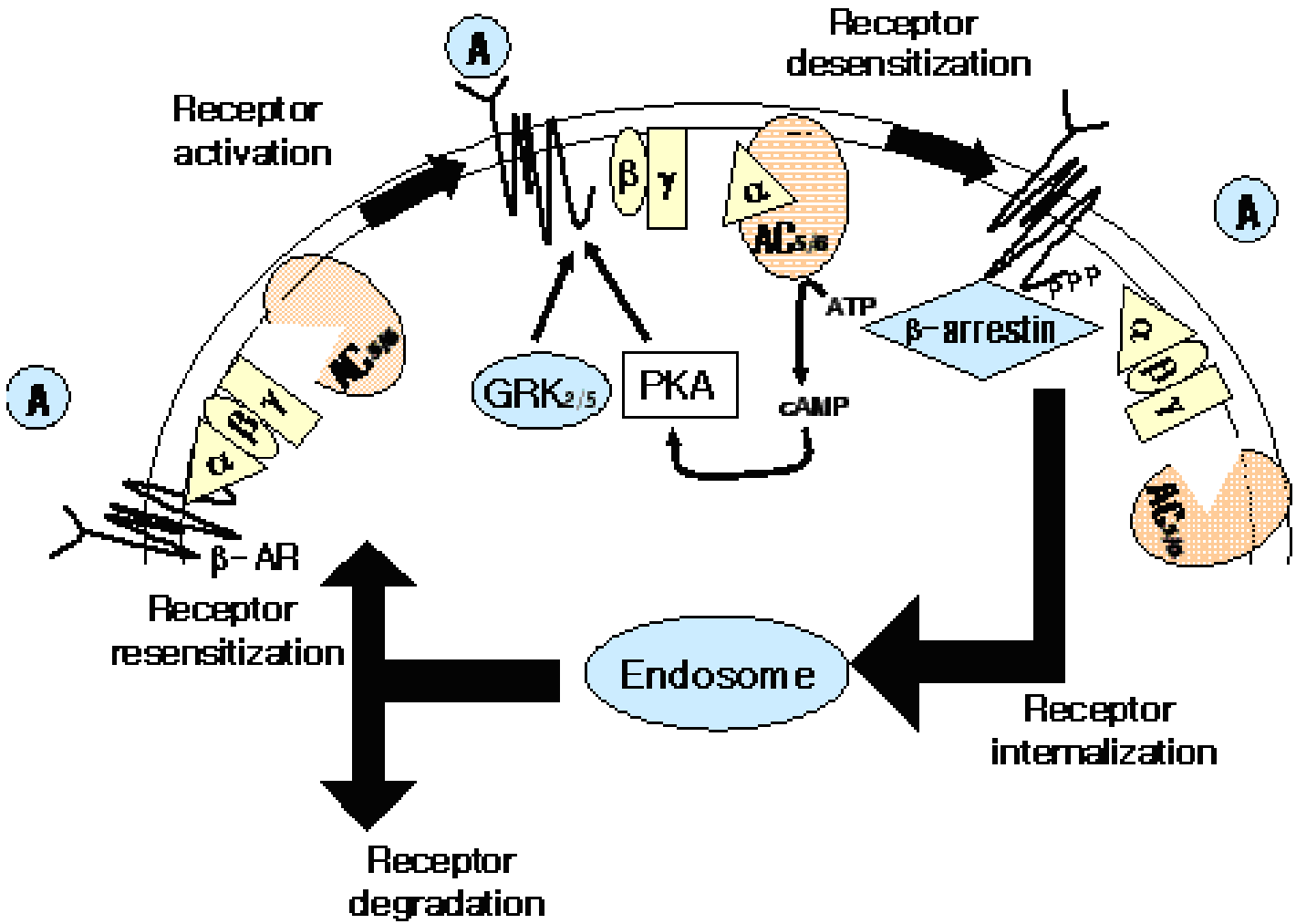
  – Heterologous desensitization by **PKC, PKA**

  – Homologous desensitization by **βARK1, GRK5**

G Protein-coupled Receptor Kinases (GRKs)



ß-Adrenergic Receptor

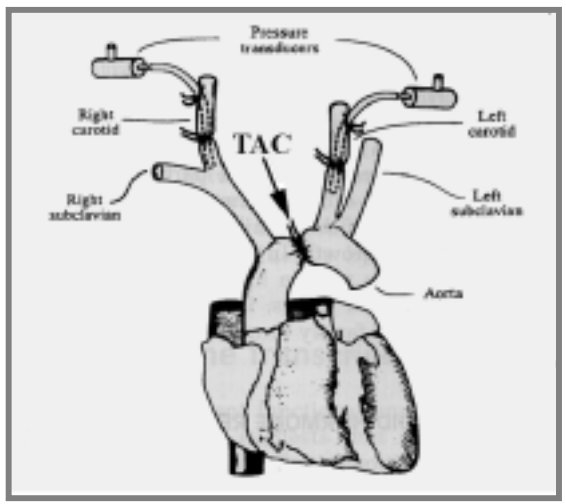


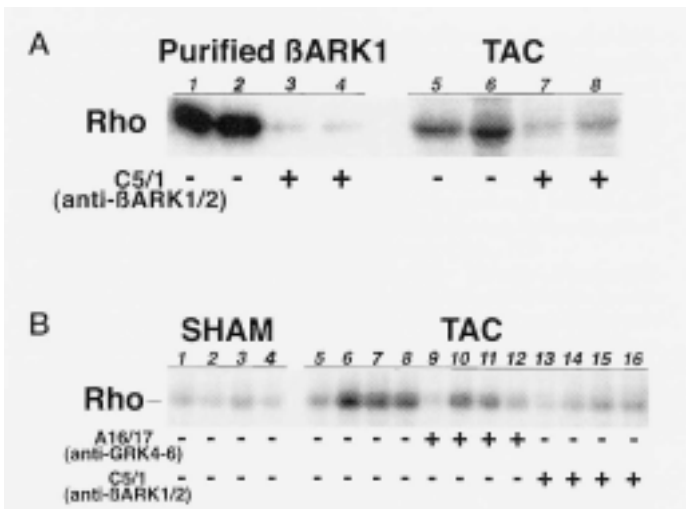
G Protein-coupled Receptor Kinases (GRKs)

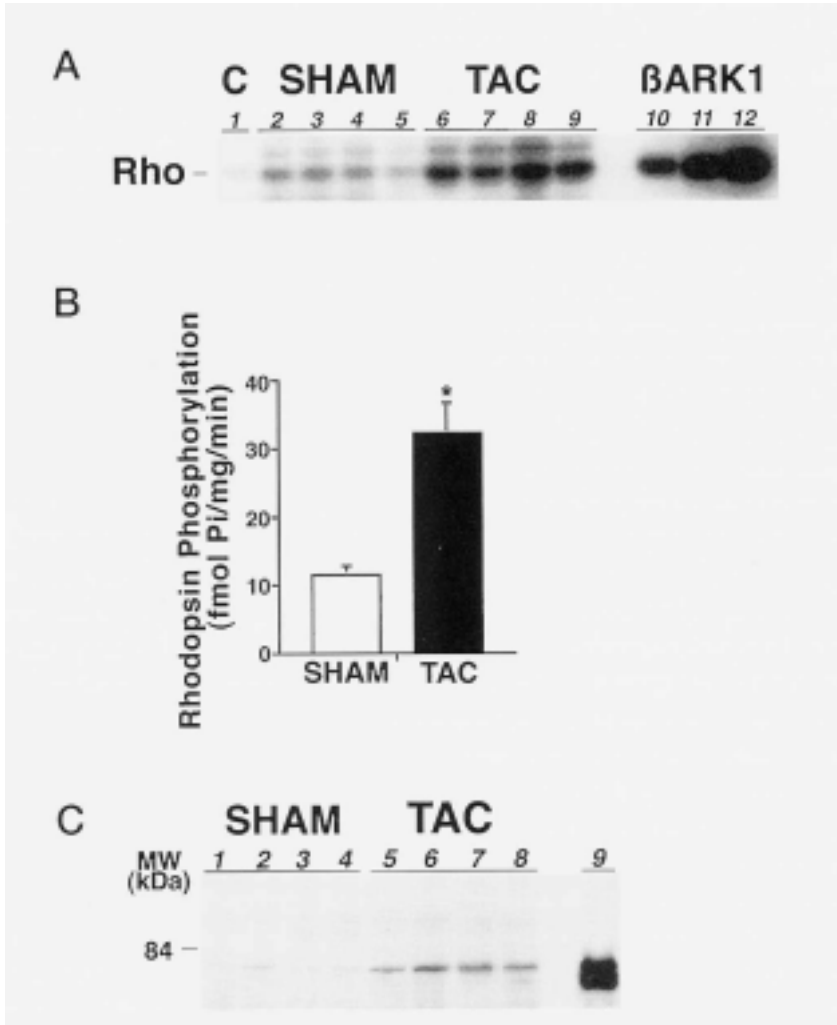
Kinase	Substrate specificity	Localization
GRK1(*RK*)	Rho >> βAR	Retina
GRK2(β*ARK1*)	βAR,m2R,αAR>Rho	Heart,lung,brain
GRK3(β*ARK2*)	βAR,m2R,αAR>Rho,Olf	Brain>heart,lung
GRK4(*IT11*)	?	Testis
GRK5	βAR>m2R,αAR>Rho	Heart,lung>muscle
GRK6	βAR>Rho	Brain,muscle>heart

GRKs in Cardiac Hypertrohpy

- Choi DJ. J Biol Chem. 272(27):17223 - 9 -

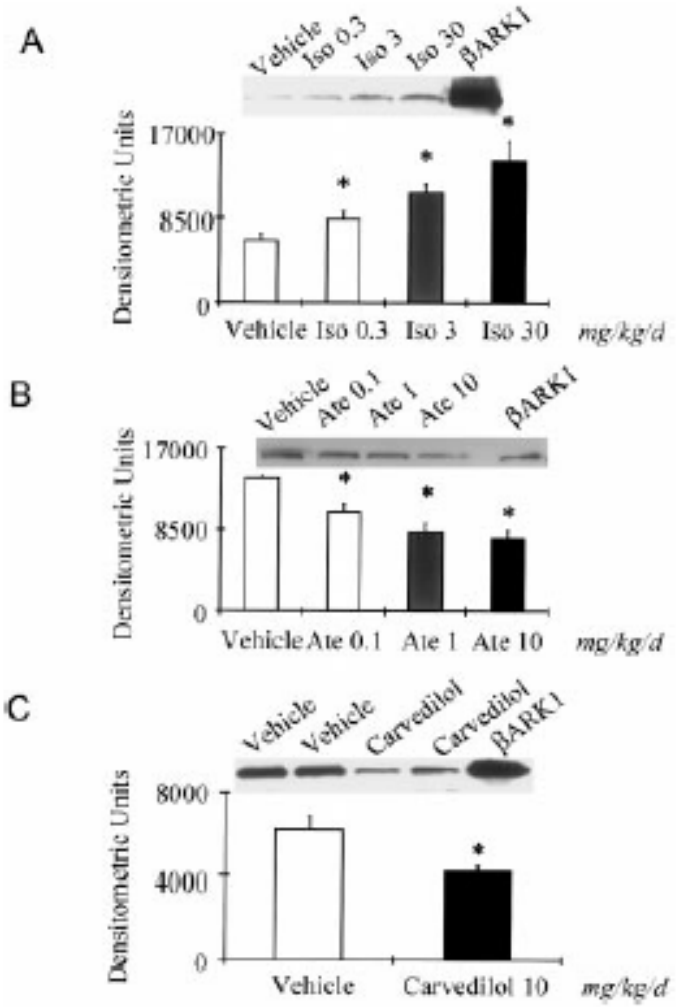


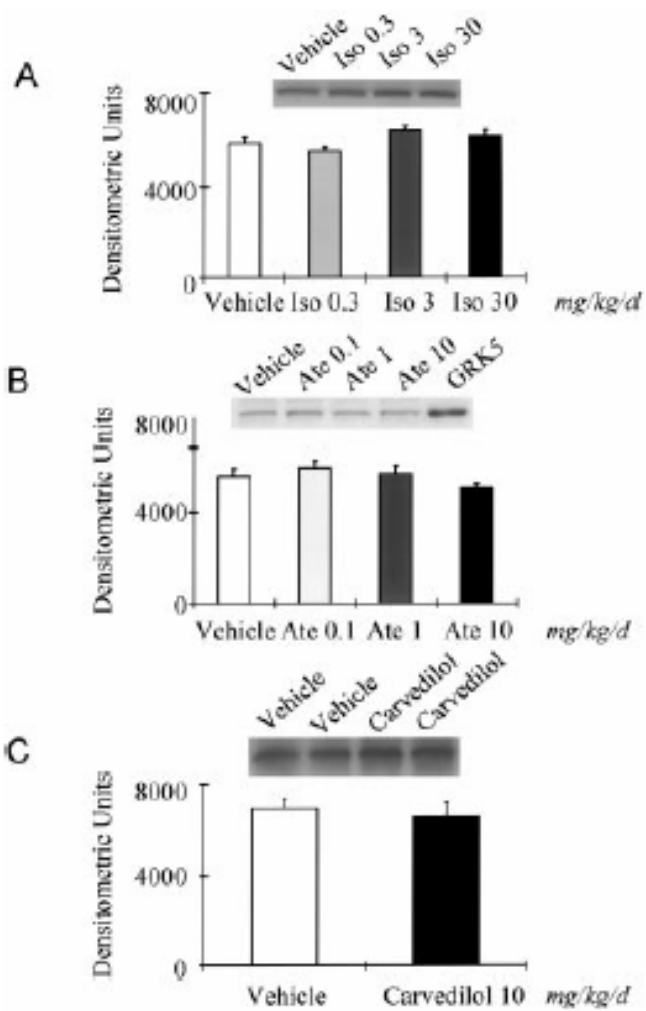




Effect of β-blocker on βARK1

Iaccarino G, et al. Circulation 1998;98:1783-1789





βARK1 in human Cardiac Hypertrophy

Hypertensive left ventricular hypertrophy: relation to β-adrenergic receptor kinase-1 (βARK1) in peripheral lymphocytes

Sung-Ji Park[a], Dong-Ju Choi[c] and Choong Won Kim[b]

Background Left ventricular hypertrophy (LVH) is associated with increased cardiovascular risk and altered sympathetic regulation in hypertension.

Objectives To determine whether the level of β-adrenergic receptor kinase-1 (βARK1) in lymphocytes is related to LVH in patients with hypertension.

Methods Forty-nine patients with untreated essential hypertension were recruited to the study and classified into two groups: left ventricular hypertrophy (LVH: left ventricular mass index ⩾ 134 g/m^2 in men and ⩾ 110 g/m^2 in women; ages 52.4 ± 12.8 years, $n = 25$) and non-LVH (NLVH: left ventricular mass index < 134 g/m^2 in men and < 110 g/m^2 in women; ages 50.8 ± 13.1 years, $n = 24$). activity from LVH was enhanced 1.7-fold compared with NLVH (1.03 ± 2.16 and 1.79 ± 1.87 pmol phosphate/min per mg protein, respectively; $P < 0.05$, $n = 7$ for each group).

Conclusions The concentration of βARK1 in lymphocytes is greater in hypertensive individuals with LVH than in those without LVH and parallels the degree of hypertrophy. Generalized alterations in β-adrenergic signalling, including βARK1, could be a major contributory factor in the development of LVH in hypertension, and the concentration of βARK1 in lymphocytes can reflect the development of LVH in a patient with hypertension.
J Hypertens 22:1025–1032

βARK1 in human Cardiac Hypertrophy

Fig. 1

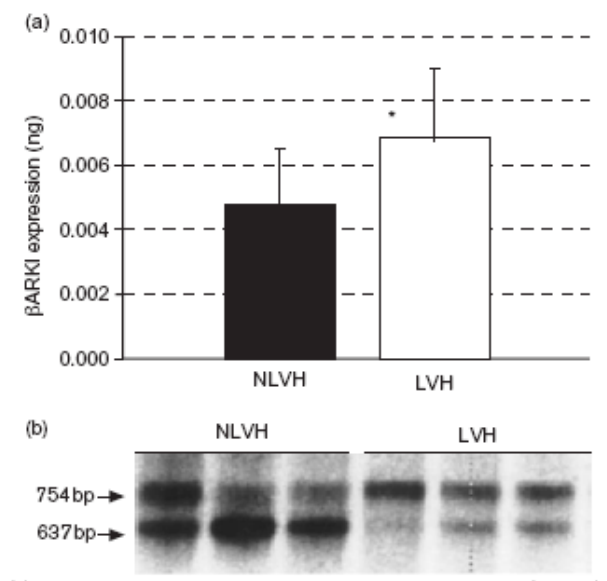


Fig. 2

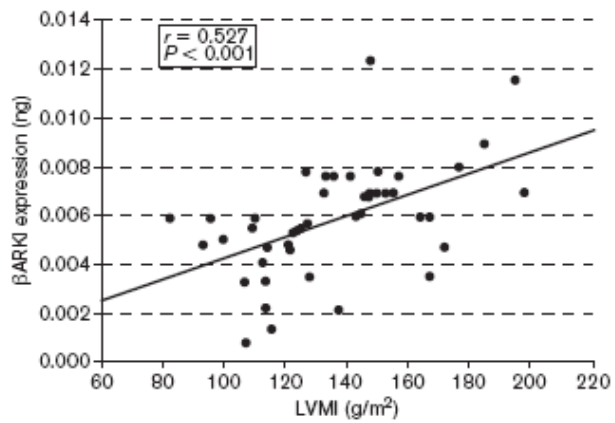
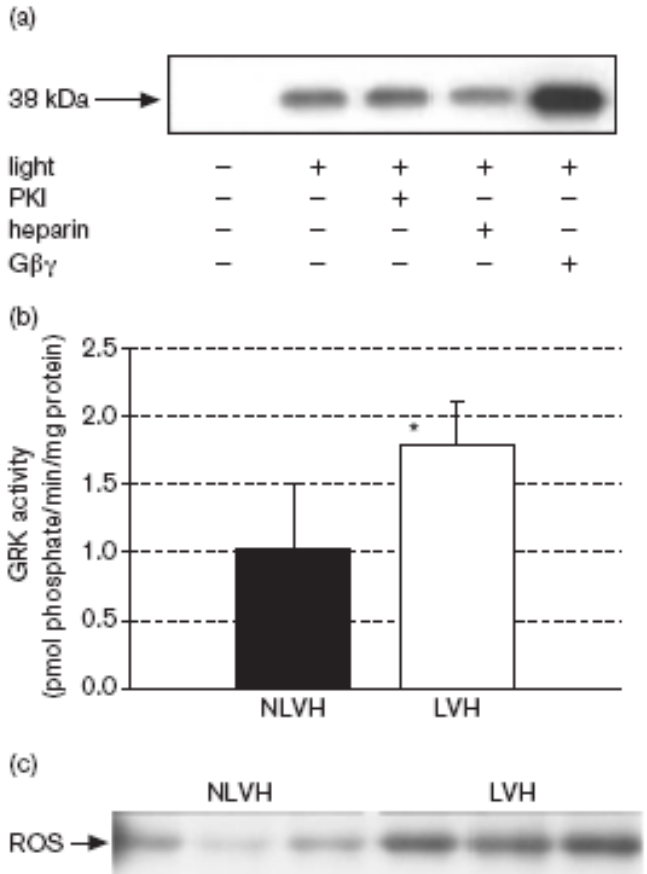


Fig. 5



βARK1 in human HF

European Heart Journal (2005) 26, 1752–1758
doi:10.1093/eurheartj/ehi429

Clinical research

Elevated myocardial and lymphocyte GRK2 expression and activity in human heart failure

Guido Iaccarino[1], Emanuele Barbato[1†], Ersilia Cipolletta[1], Vincenzo De Amicis[1], Kenneth B. Margulies[2‡], Dario Leosco[1], Bruno Trimarco[1*], and Walter J. Koch[3*]

[1] *Department of Medicina Clinica Scienze Cardiovascolari ed Immunologiche, Federico II University, Via Pansini 5, 80131 Napoli, Italy;* [2] *Department of Medicine (Cardiology), Temple University Medical Center, Philadelphia, PA, USA; and* [3] *Department of Medicine, Center for Translational Medicine, Thomas Jefferson University, 1025 Walnut Street, Room 410, Philadelphia, PA 19107, USA*

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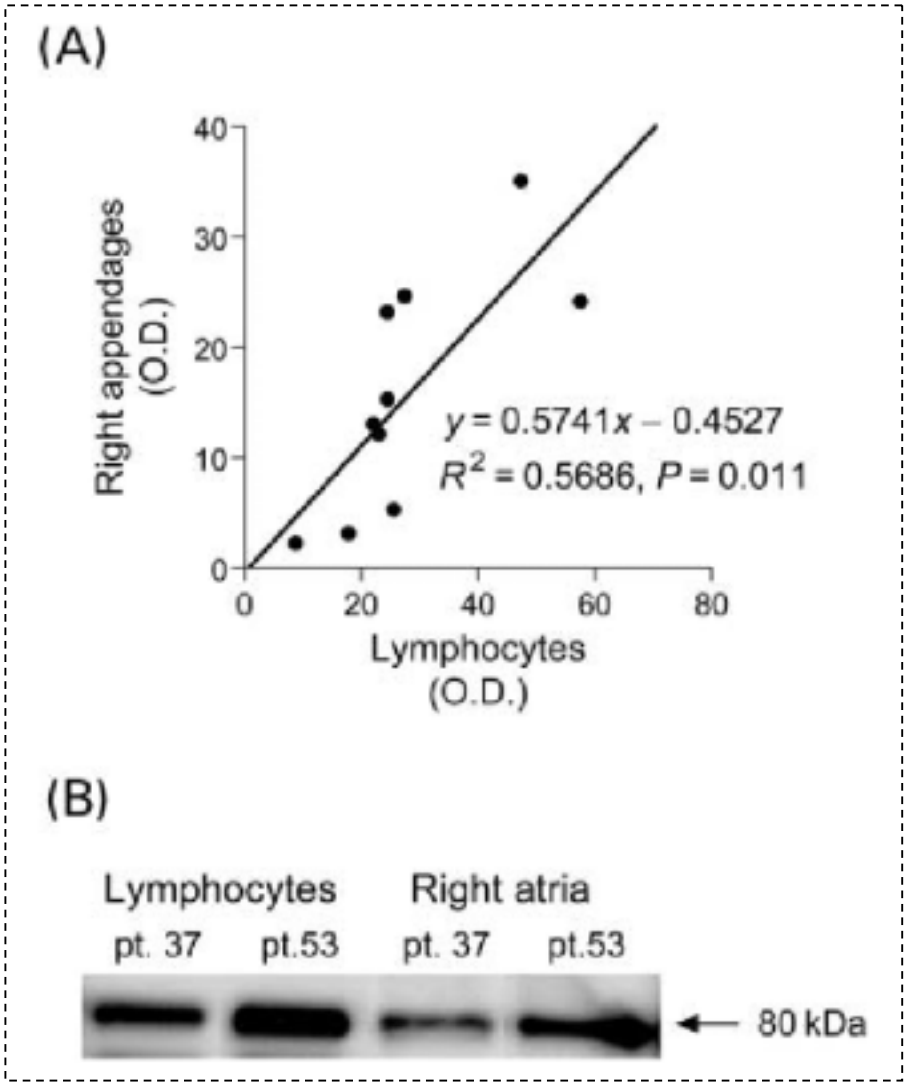
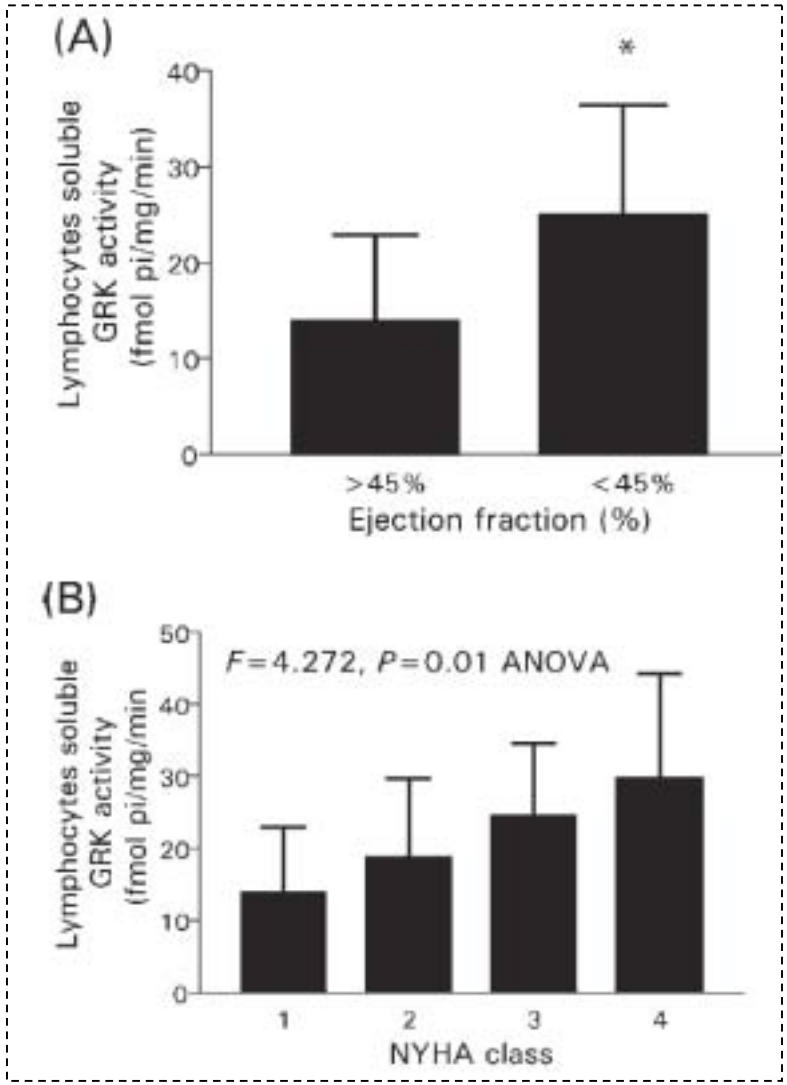
See page 1695 for the editorial comment on this article (doi:10.1093/eurheartj/ehi355)

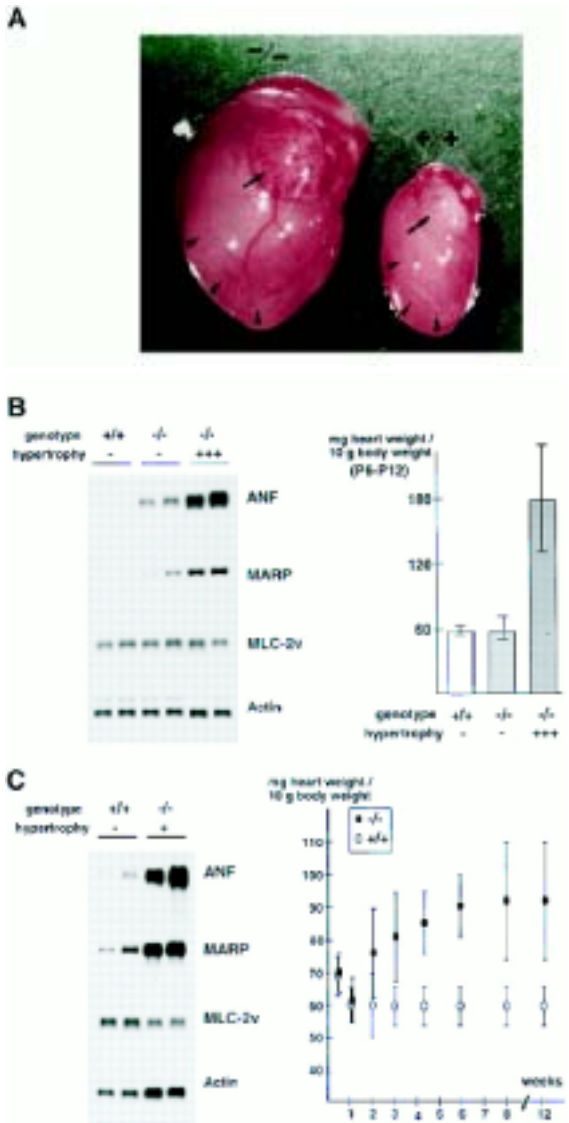
βARK1 in human HF

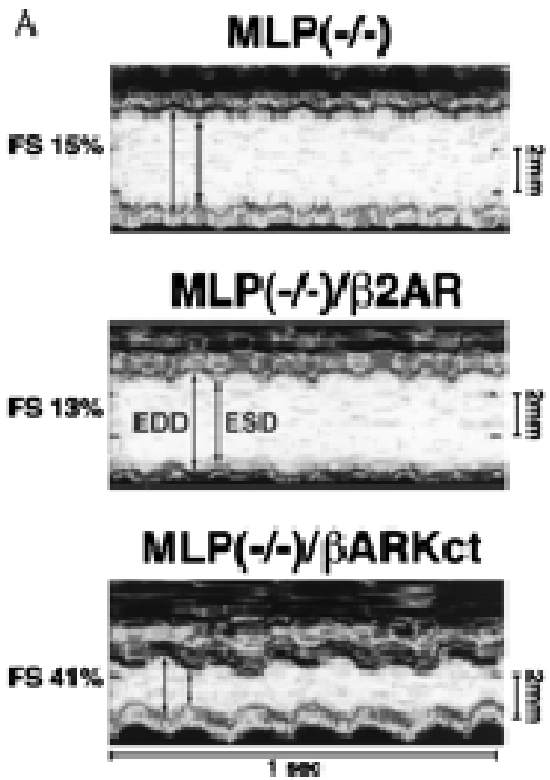


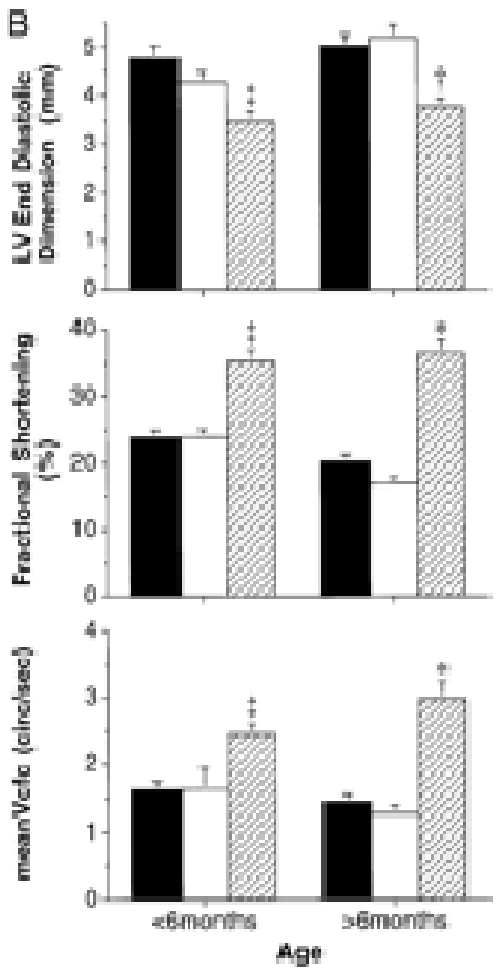


GRK2 in **HF model (MLP knock-out)**

- *Choi DJ and Rockman H. PNAS 1998:7000 - 5*







Recent Update beta-blocker in HF

β-blocker should be considered in all HF.

1. **NYHA FC II-IV**
2. **Reduced LVEF**
3. **Stable, mild to severe HF**
4. **Ischemic or non-ischemic**
5. **On standard Tx: diuretis and ACEi**

Class I recommendation, evidence level A

Recent Update beta-blocker in HF

Recommended β-blocker in HF

1. **Carvedilol**
2. **Bisoprolol**
3. **Metoprolol succinate *(not tartrate)***
4. **Nebivolol *(ESC2005)***

Class I recommendation, evidence level A

Future directions

1) Which beta-blocker is better? Or new one?

β1/β2, α1, anti-oxydant, inverse agonism…

2) β-blocker prior to ACEi?

After CIBIS III

3) Other than β-blocker for modulating β-AR system?