심부전에서의 베타차단제의 사용

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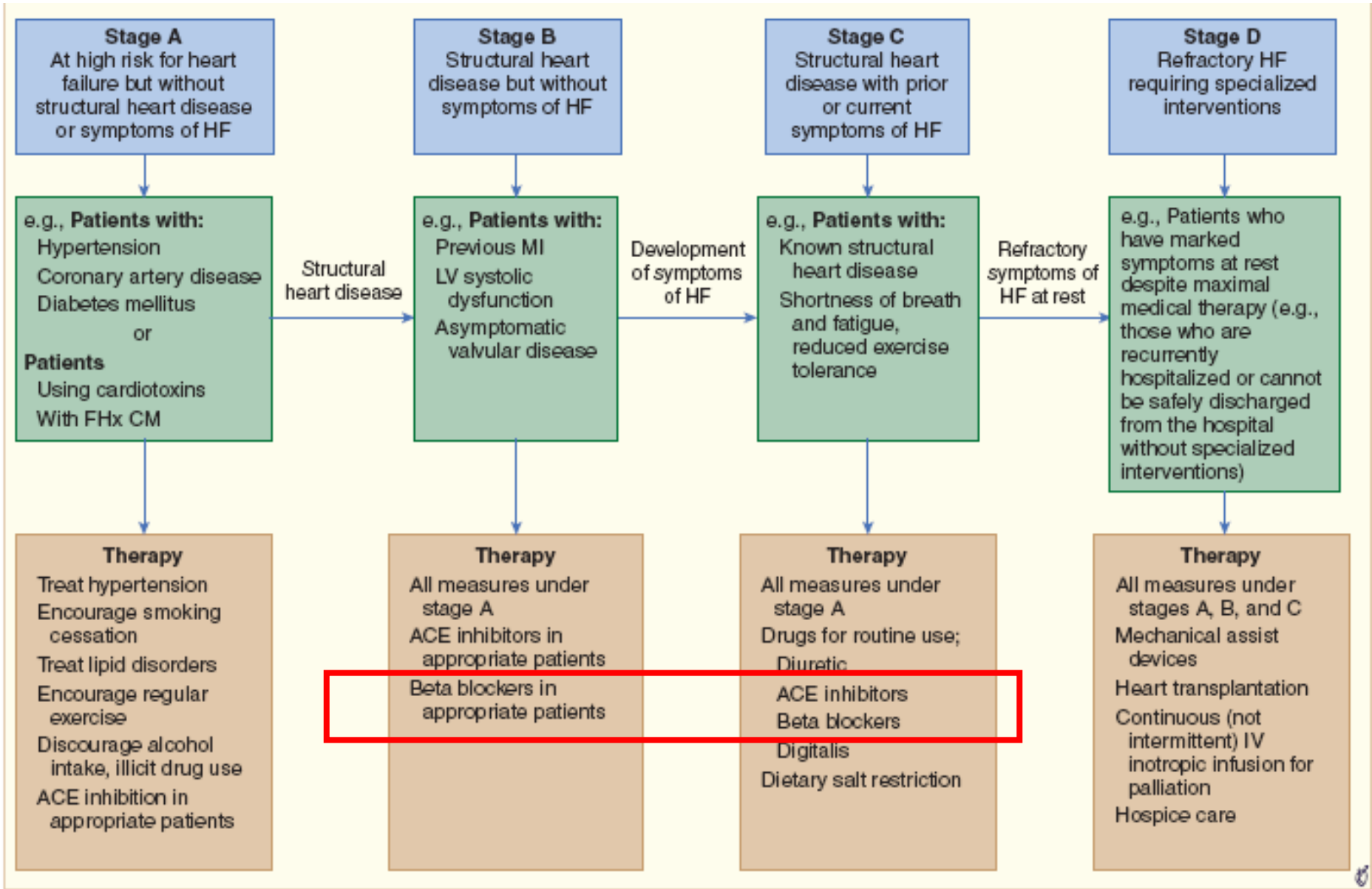
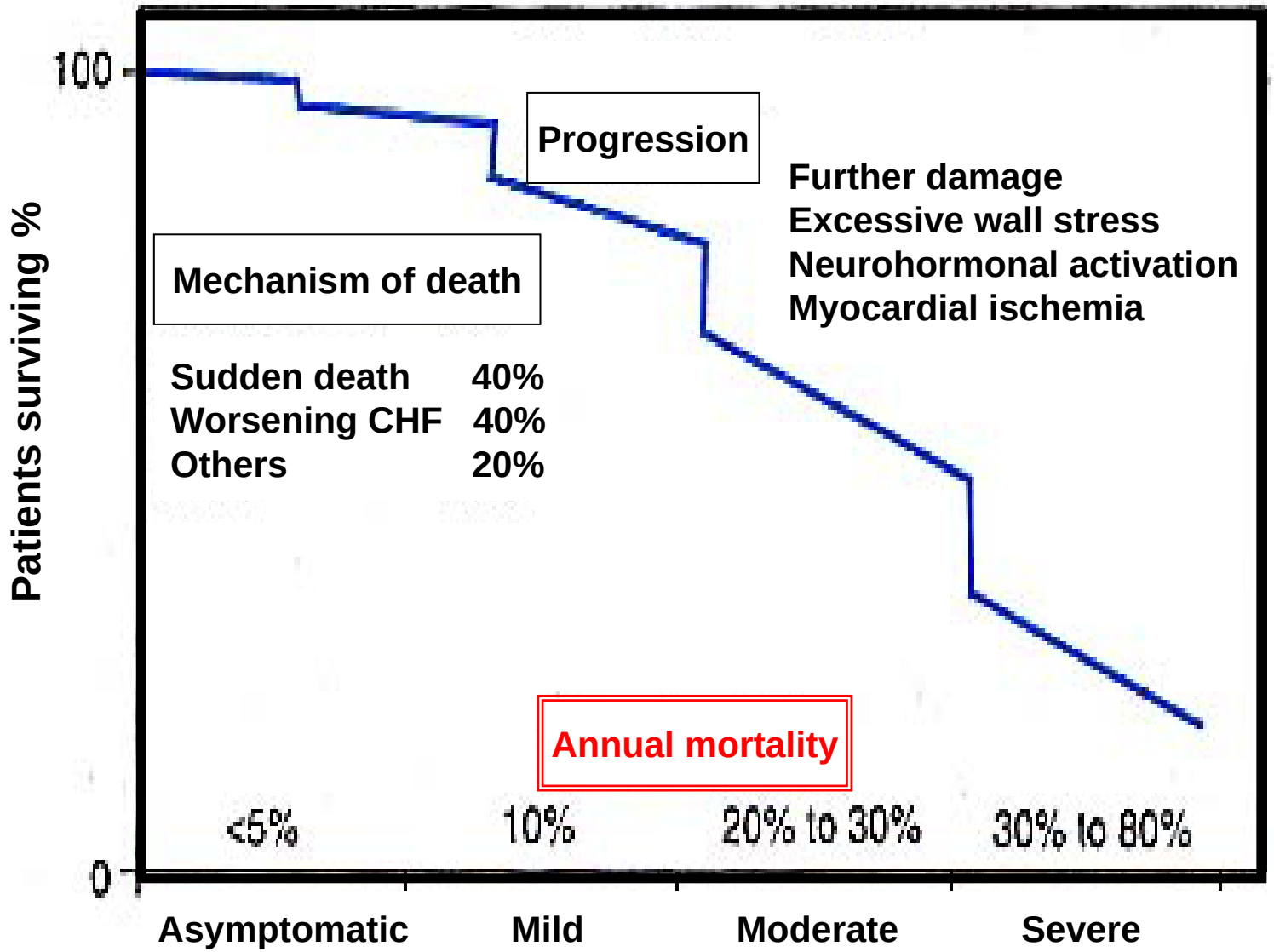
춘계 대한순환기학회 CKD Satellite Symposium
2005년 4월 15일 (금) 12:00

Recommended Therapy by Heart Failure Stage

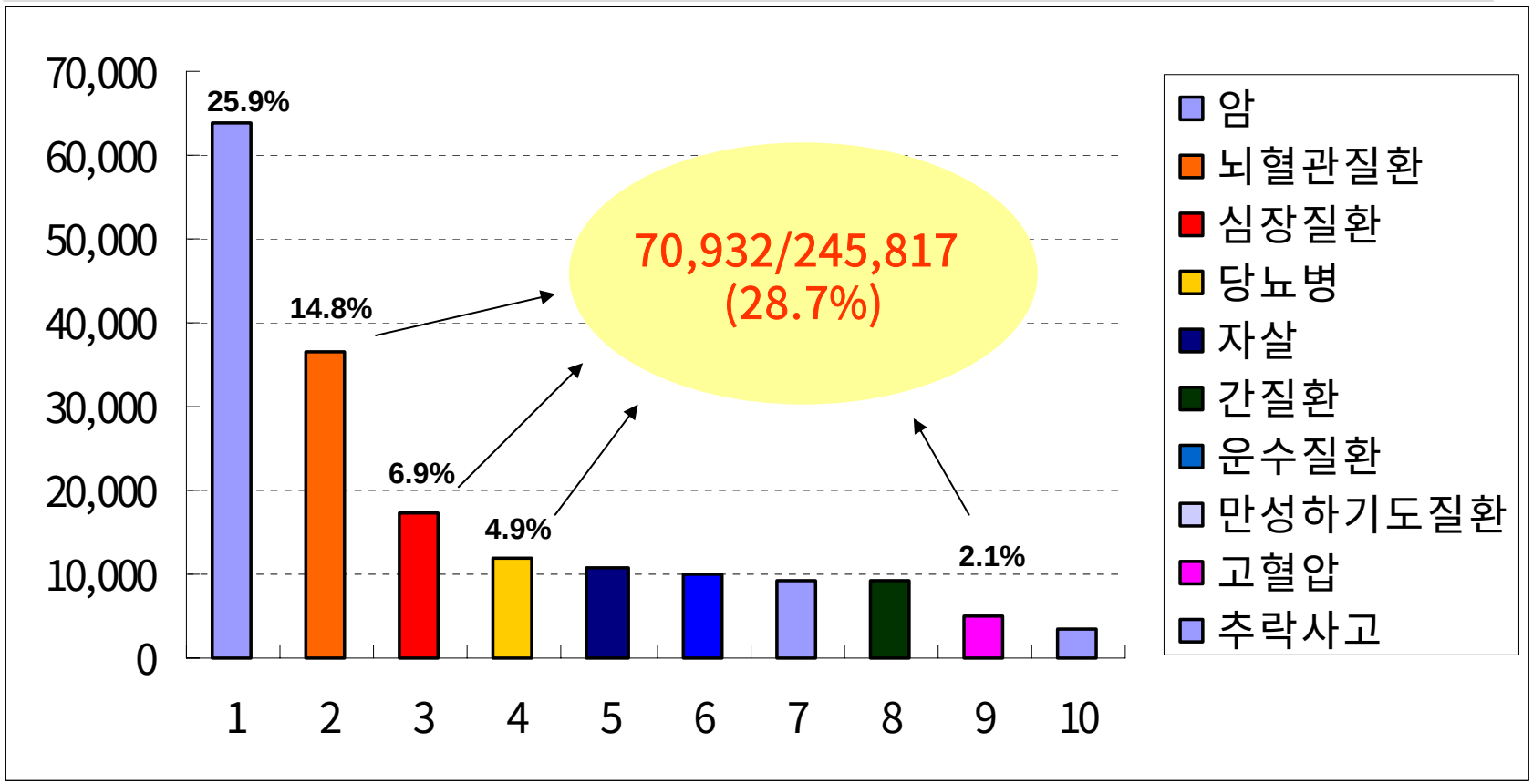


AHA/ACC Task Force on Practice Guideline 2001

Natural History of Heart Failure



2003년도 한국인의 사망원인



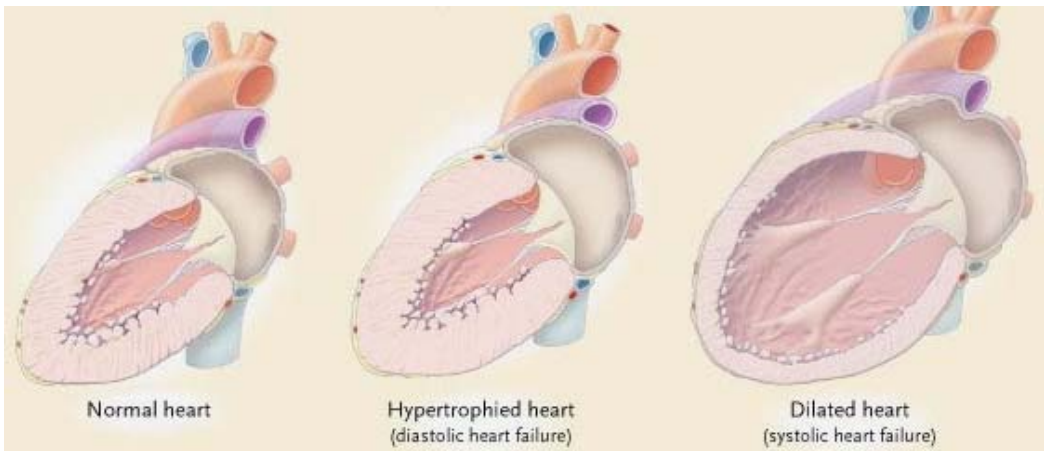
뇌혈관 - 심혈관성 사망률 = 70,932/245,817 (28.7%)

(통계청자료)

Neurohormonal Activation in LV Dysfunction

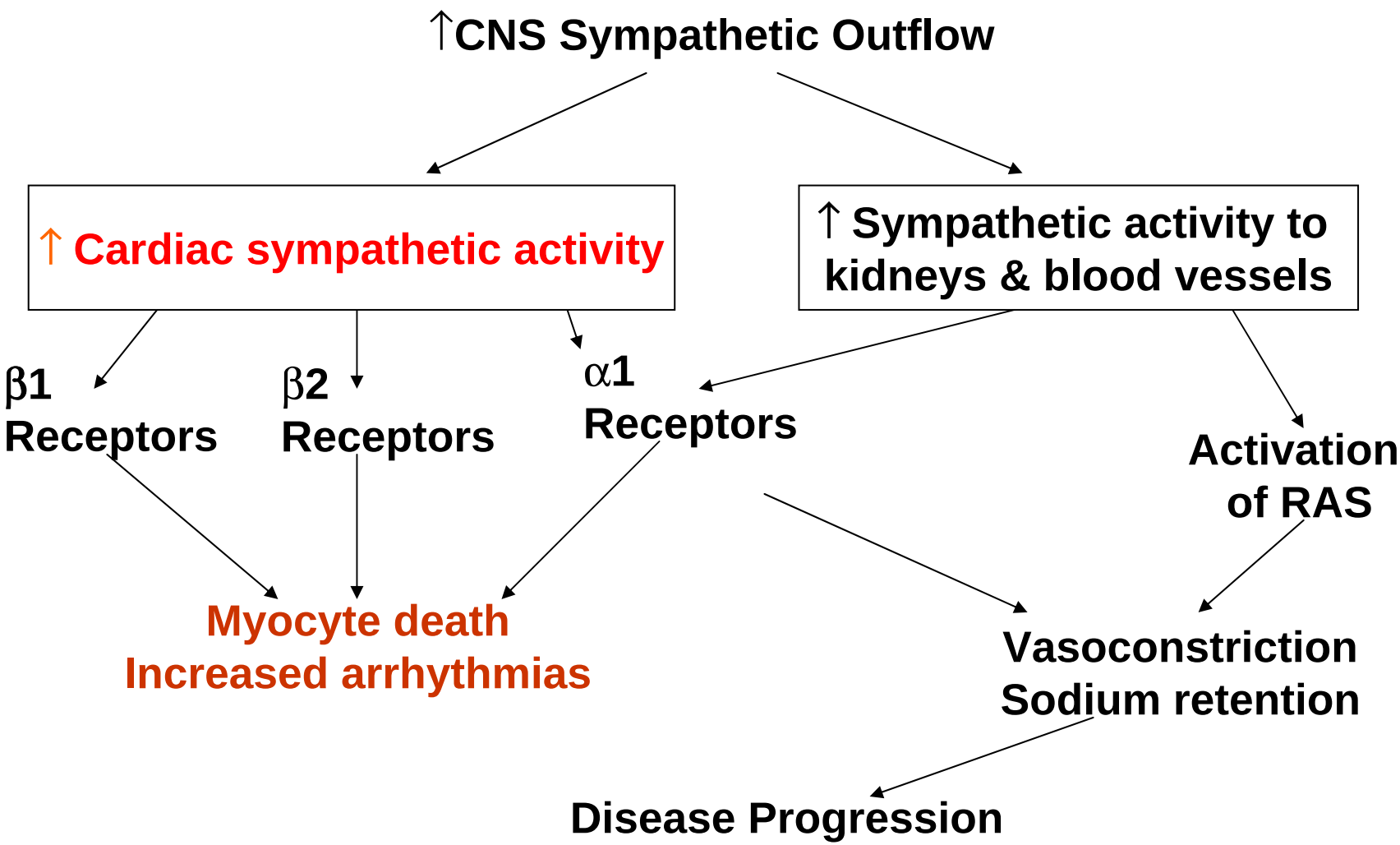
- **Renin-Angiotensin-Aldosterone System**
  - ↑ **Angiotensin II**
- **Sympathetic Nervous System**
  - ↑ **Norepinephrine**

Hypertrophy, Apoptosis, Ischemia, Arrhythmias, Remodeling, Fibrosis

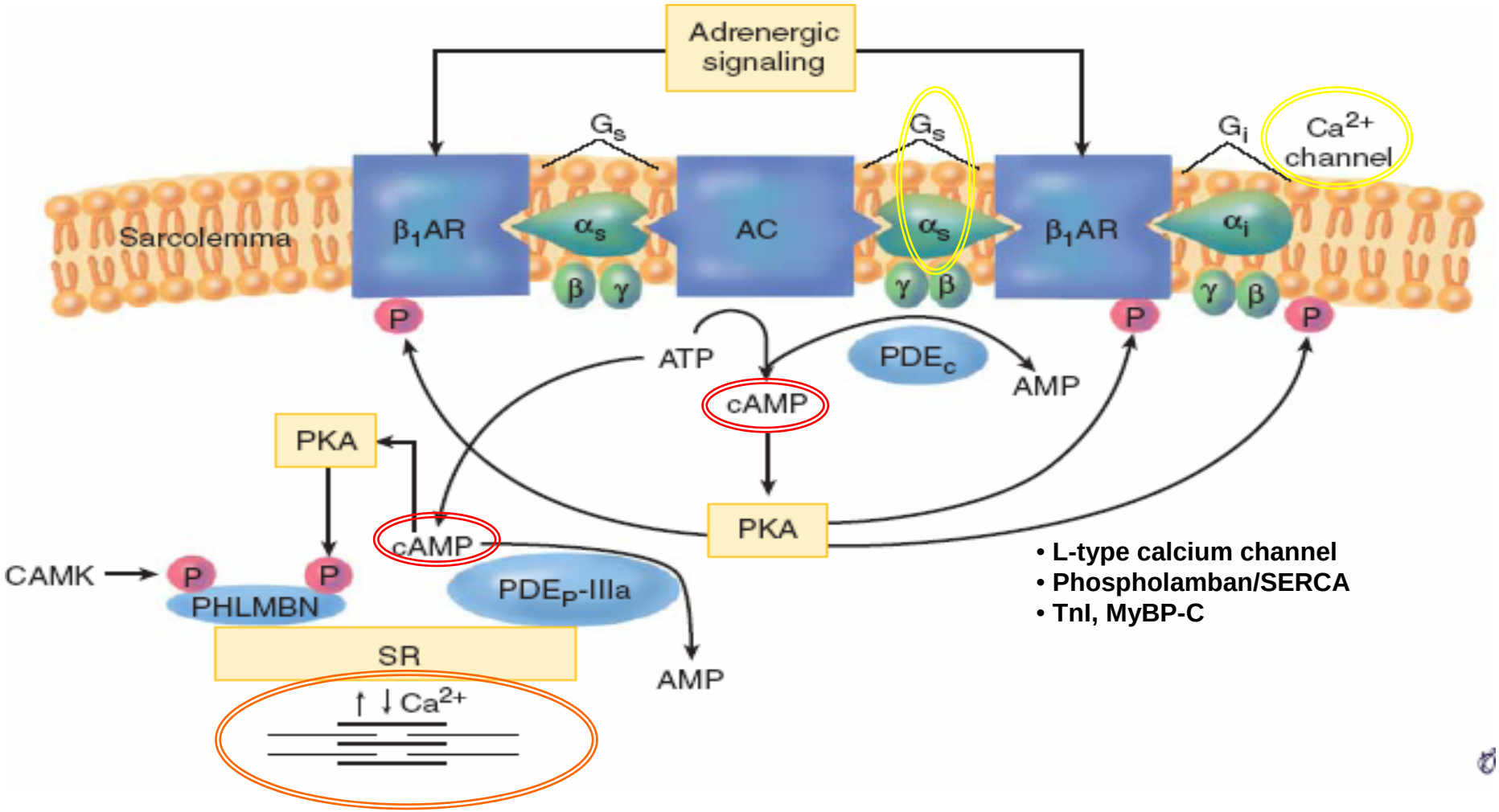


Progressive LV Dysfunction
Morbidity and Mortality

Effect of Sympathetic Activation in Heart Failure

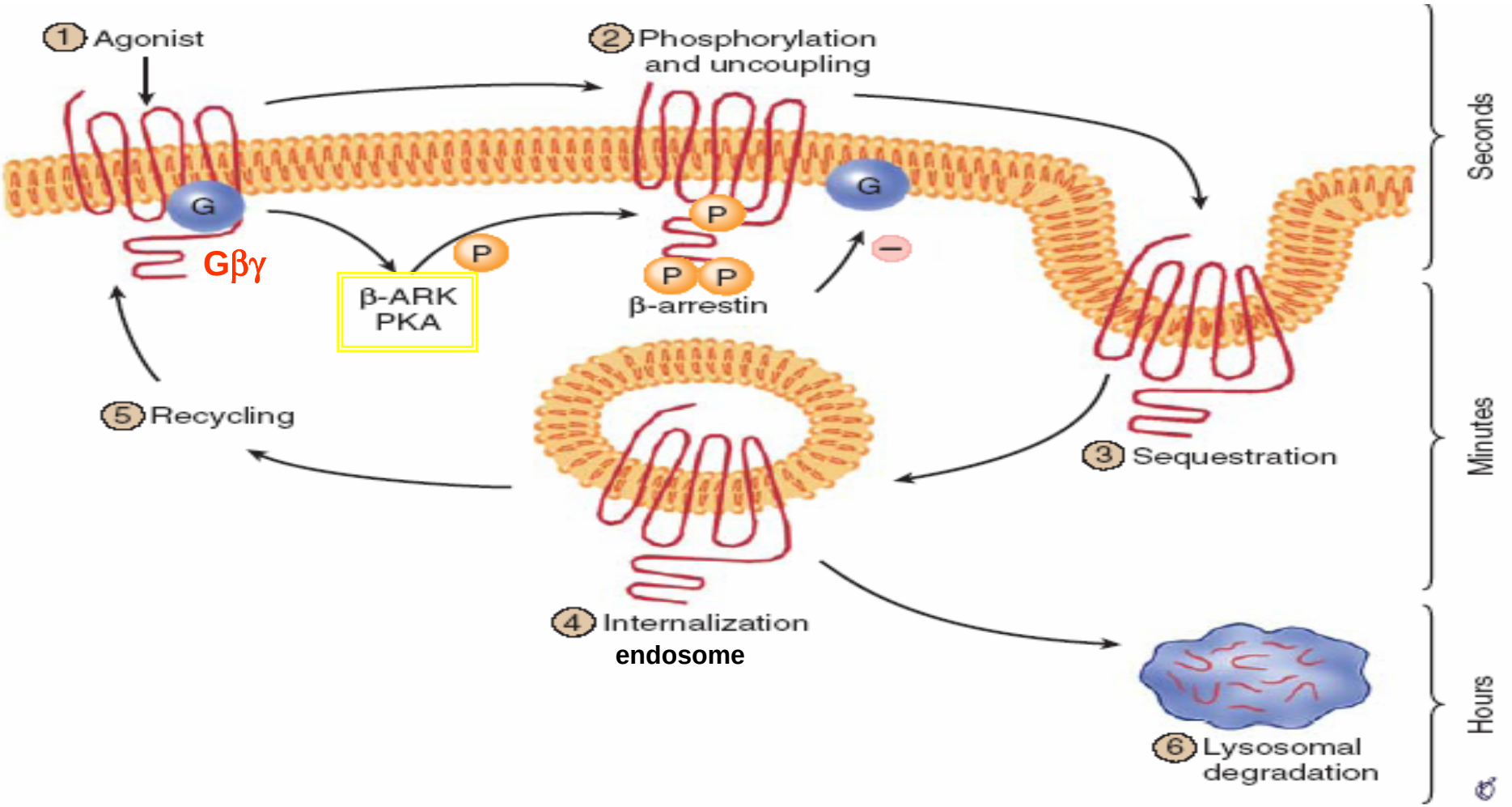


Selected Components of the Cardiac Myocyte β1- and β2-adrenergic Receptor Pathways



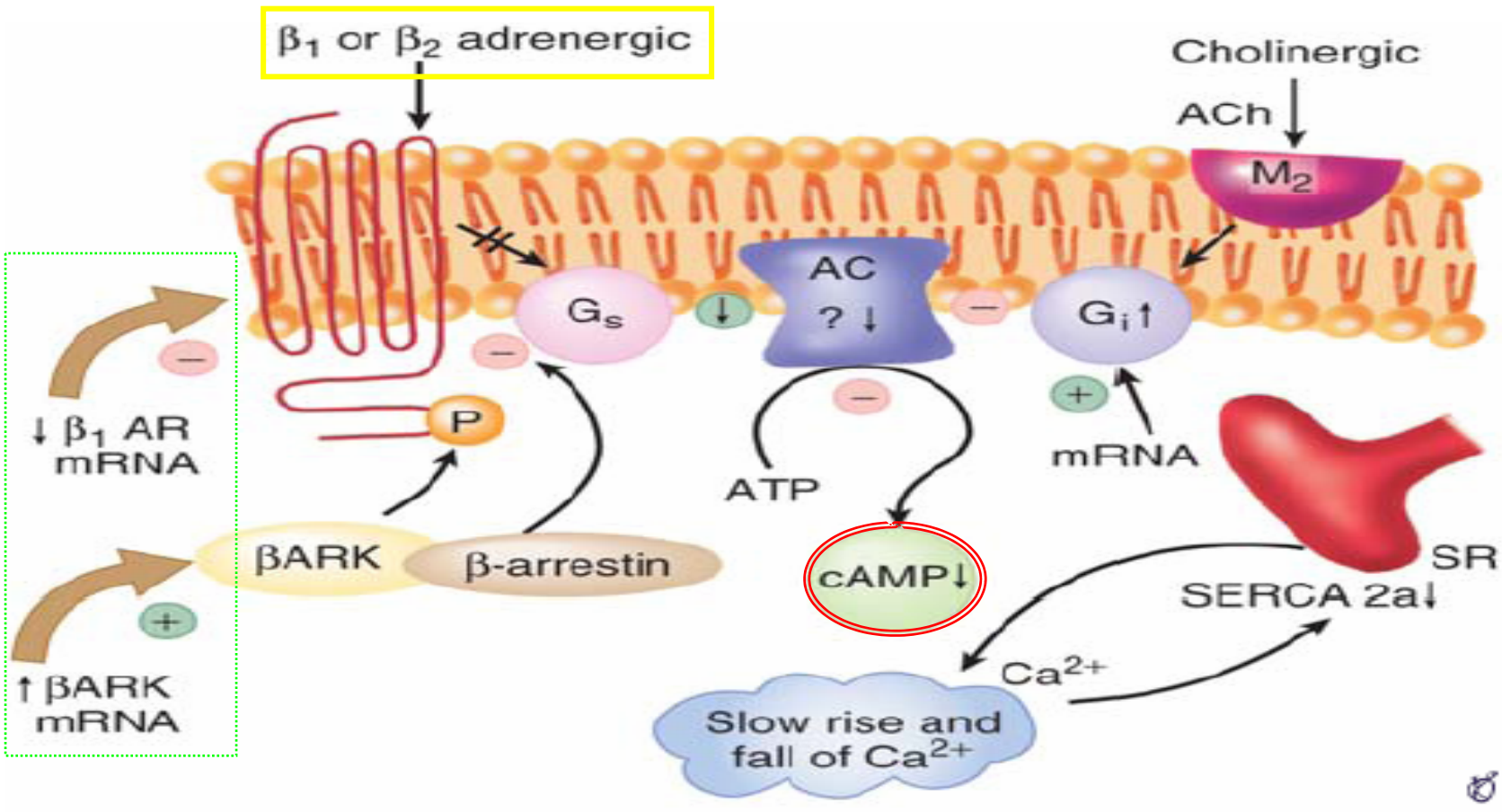
- **L-type calcium channel**
- **Phospholamban/SERCA**
- **TnI, MyBP-C**

Mechanisms of β-adrenergic Receptor Desensitization and Internalization

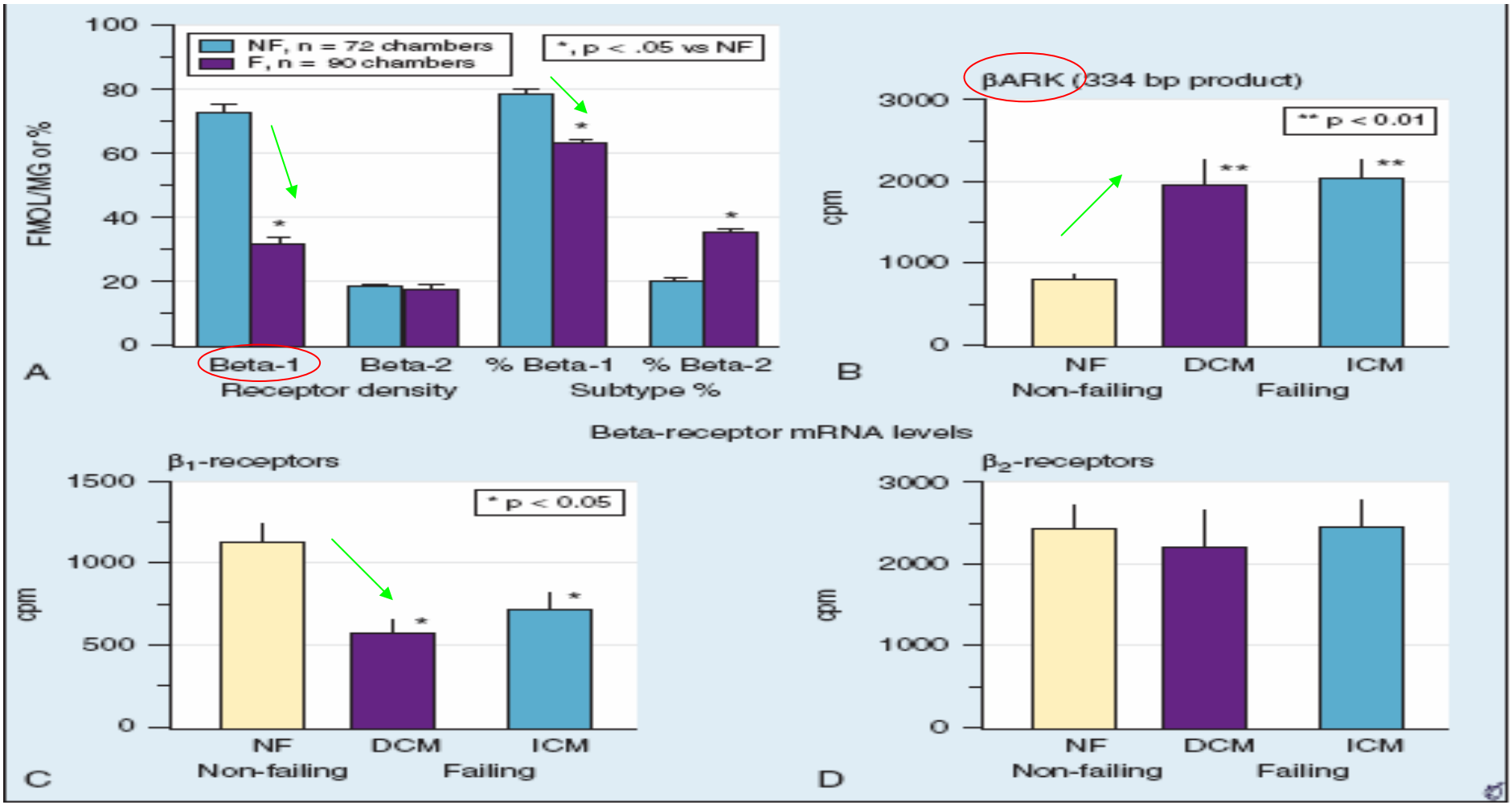


GRK family: GRK2 (βARK1), GRK5 in heart

Proposed Changes in β-adrenergic Receptor Signal System and Sarcoplasmic Reticulum in Severe CHF



Downregulation of β-adrenergic Receptors in Myocardium from Patients with Heart Failure



♥ Beta receptor levels in heart failure

- ♥ **Normal Heart** β_1 **80 :** β_2 **20**
- ♥ **Severe Heart Failure** β_1 **60 :** β_2 **40**

  - ♥ β_1 **receptors to selectively down-regulate secondary to high levels of catecholamine**

  - ♥ β_2 **agonists retain full inotropic activity mediated through a** β_2 **population that is not significantly decreased**

Biological Responses Mediated by Adrenergic Receptors in the Human Heart

Biological Response	Adrenergic Receptor Mediation
Positive inotropic response	β1, β2, α1(minimal)
Positive chronotropic response	β1, β2
Myocyte toxicity	β1>>β2
Myocyte apoptosis	β1
Cardiac myocyte growth	β1>> β2, α1
Fetal gene induction	β1 >> β2, α1
Proarrhythmic	β1, β2, α1

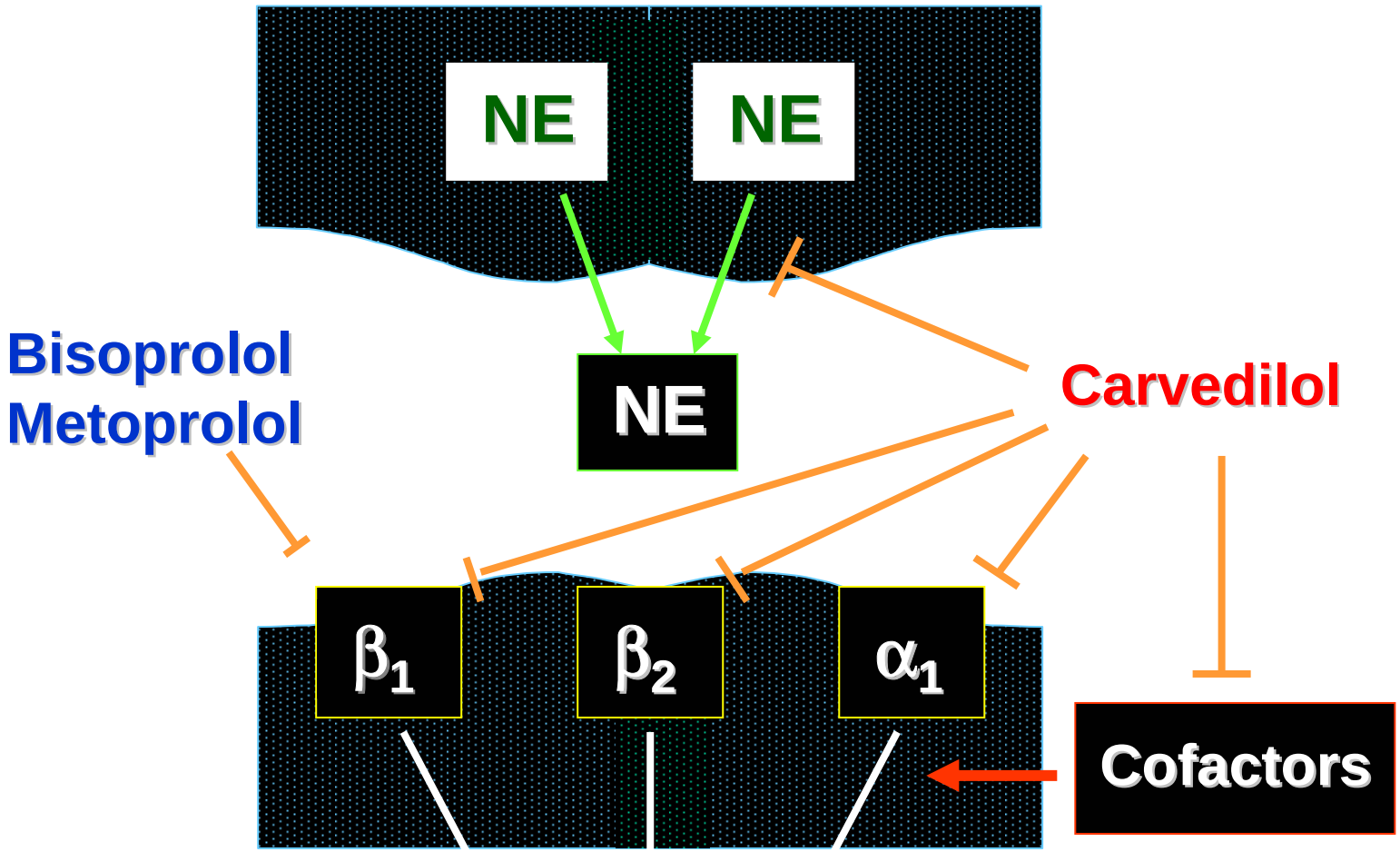
Potential Beneficial Cellular Effects of β-adrenergic Blocker Therapy in Heart Failure

- Upregulation of β_1-receptor
- Correction of Gs and G*i* abnormalities
- Protection against cytosolic Ca^{2+} overload
- Shift in metabolic substrate utilization from Fatty acid to Glucose
- Decrease in Renin release
- Prevention of Myocyte hypertrophy
- Antioxidant effect
- Decrease in Apoptosis
- Antiarrhythmic effects

Adrenergic Receptor Blocking Affinities of β-blocking Agents in Human Receptors

Generation/ Class	Compound	$K(beta_1)^{\dagger}$ (nM)	$K(beta_2)$ (nM)	$Beta_1/Beta_2$ Selectivity	$K(alpha_1)$ (nM)	$Beta_1/Alpha_1$ Selectivity
First/nonselective	Propranolol‡	4.1	8.5	2.1	–	–
Second/selective $beta_1$	Metoprolol	45	3,345	74	–	–
	Bisoprolol	121	14,390	119	–	–
Third/beta blocker–vasodilator	Carvedilol‡	4.0	29	7.3	9.4	2.4
	Bucindolol‡	3.6	5.0	1.4	238	66 (19)*
	Nebivolol	0.7	225	352	330	471

Effects of Different β Blocking Agents



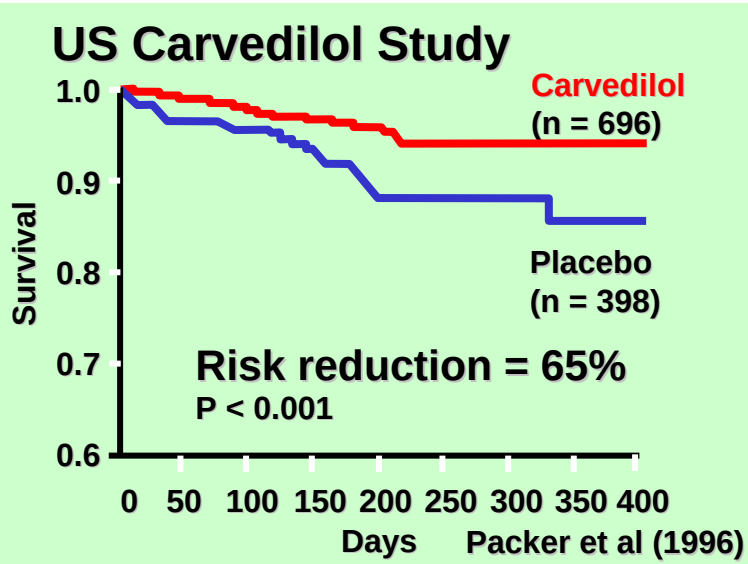
Cardiac cell toxicity

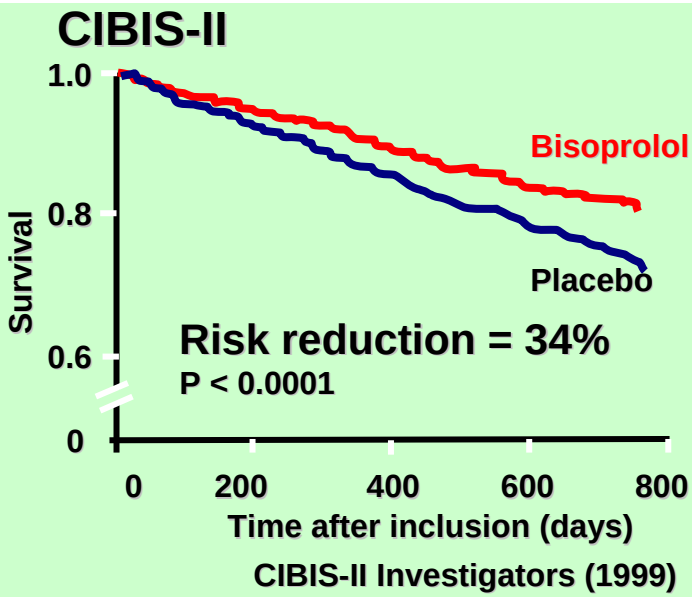
β blocker Trials Conducted in Chronic Heart Failure

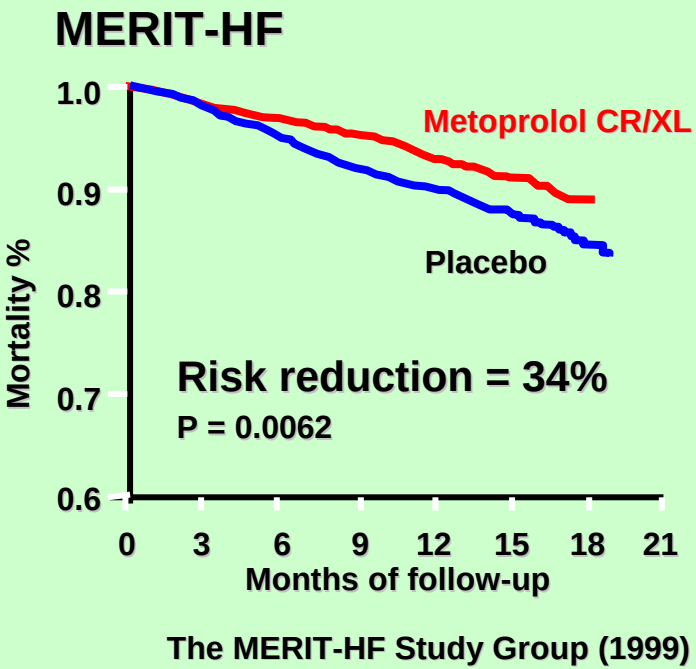
Trial Name	Agent	NYHA Class	Heart Failure Stage, 1-4*	No. of Subjects Enrolled	12-Month Placebo Mortality (%)	12-Month Effect Size (%)
Stage 2 Populations of Patients						
CIBIS-I	Bisoprolol	"III,IV"	2	641	11	↓20
Carvedilol U.S.	Carvedilol	II,III	2	1,094	10	↓66
CIBIS-II	Bisoprolol	"III,IV"	2	2,647	13	↓33
MERIT-HF	Metoprolol CR	II-IV	2	3,991	11	↓35
Stage 3 Populations of Patients						
BEST	Bucindolol	III,IV	3	2,708	17	↓10†
COPERNICUS	Carvedilol	"Severe HF"	3	2,289	18	↓38
Beta blocker totals		II-IV	2-3	13,370	14	↓32
Post-MI Populations of Patients						
CAPRICORN	Carvedilol	I	1	1,959	11	↓23
BEAT	Bucindolol	I	1	343	21	↓12

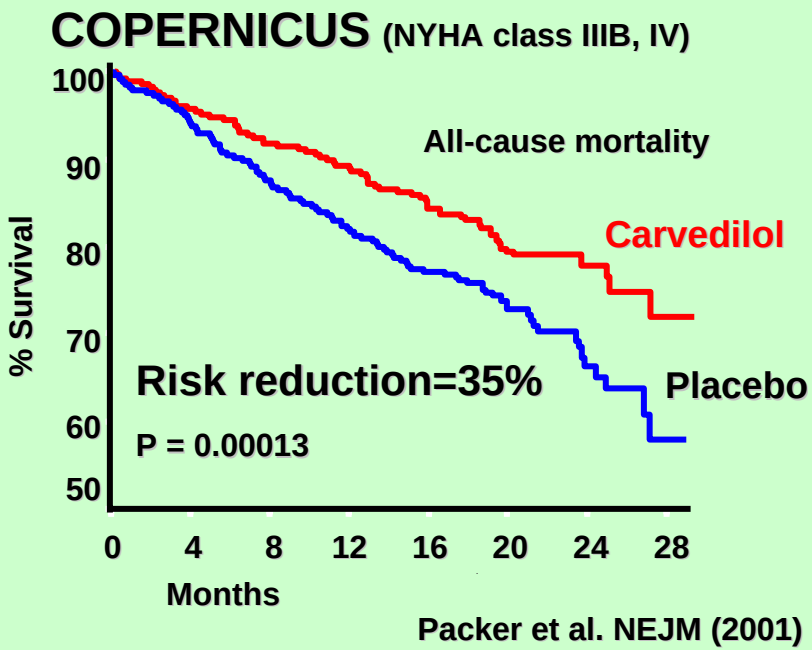
BEAT = bucindolol evaluation in acute myocardial infarction trial; BEST = Beta Blocker Evaluation of Survival Trial; CAPRICORN = Carvedilol Post-Infarct Survival Control in Left Ventriular Dysfunction; CIBIS = Cardiac Insufficiency Bisoprolol Study; COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival; MERIT-HF = Metoprolol CR/XL Randomized Interventional Trial in Congestive Heart Failure; NYHA = New York Heart Association.

b blockers in CHF: All-cause Mortality

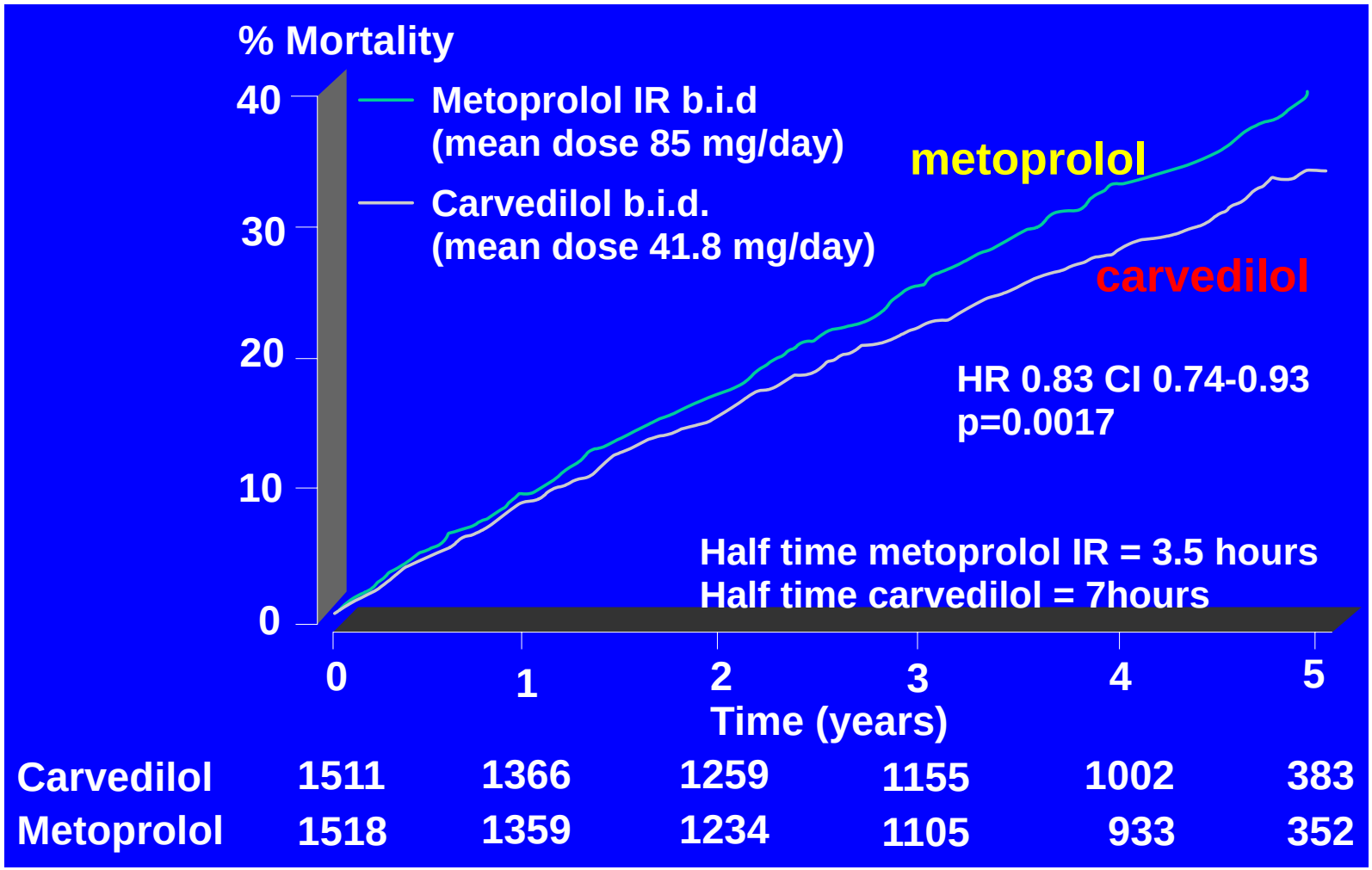








Comparison Carvedilol – Metoprolol IR in Congestive Heart Failure: COMET Trial



LVEF<35%, NYHA functional class II-IV

Poole Wilson PA et al, Lancet 2003;362:7

Class Clinical Effects of β-adrenergic Blocking Agents in Chronic Heart Failure

Effect	Studies	Beta Blockers
Reduction in total mortality	CIBIS-II, MERIT-HF, COPERNICUS	Metoprolol CR/XL, bisoprolol, carvedilol
Reduction in CV mortality	CIBIS-II, MERIT-HF, COPERNICUS, BEST	Metoprolol CR/XL, bisoprolol, carvedilol, bucindolol
Reduction in CV or HF hospitalizations	MDC, MERIT-HF, CIBIS-II, U.S. Carvedilol, BEST	Metoprolol tartrate, metoprolol CR/XL, bisoprolol, carvedilol, bucindolol
Improved HF symptoms	MDC, MERIT-HF, CIBIS-II, U.S. Carvedilol	Metoprolol tartrate, metoprolol CR/XL, bisoprolol, carvedilol
Reduced need for cardiac transplantation	MDC, BEST	Metoprolol tartrate, bucindolol
Reduction in myocardial infarction	BEST	Bucindolol

BEST = Beta Blocker Evaluation of Survival Trial; CIBIS = Cardiac Insufficiency Bisoprolol Study; COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival; CV = cardiovascular; HF = heart failure; MDC = Metoprolol in Dilated Cardiomyopathy; MERIT-HF = Metoprolol CR/XL Randomized Interventional Trial in Congestive Heart Failure.

β blockers Prolong Survival in Elderly with Heart Failure

Parameter	Elderly, n=4617	Nonelderly, n=8112
RR (95% CI)	0.76 (0.64-0.90)	0.66 (0.52-0.85)

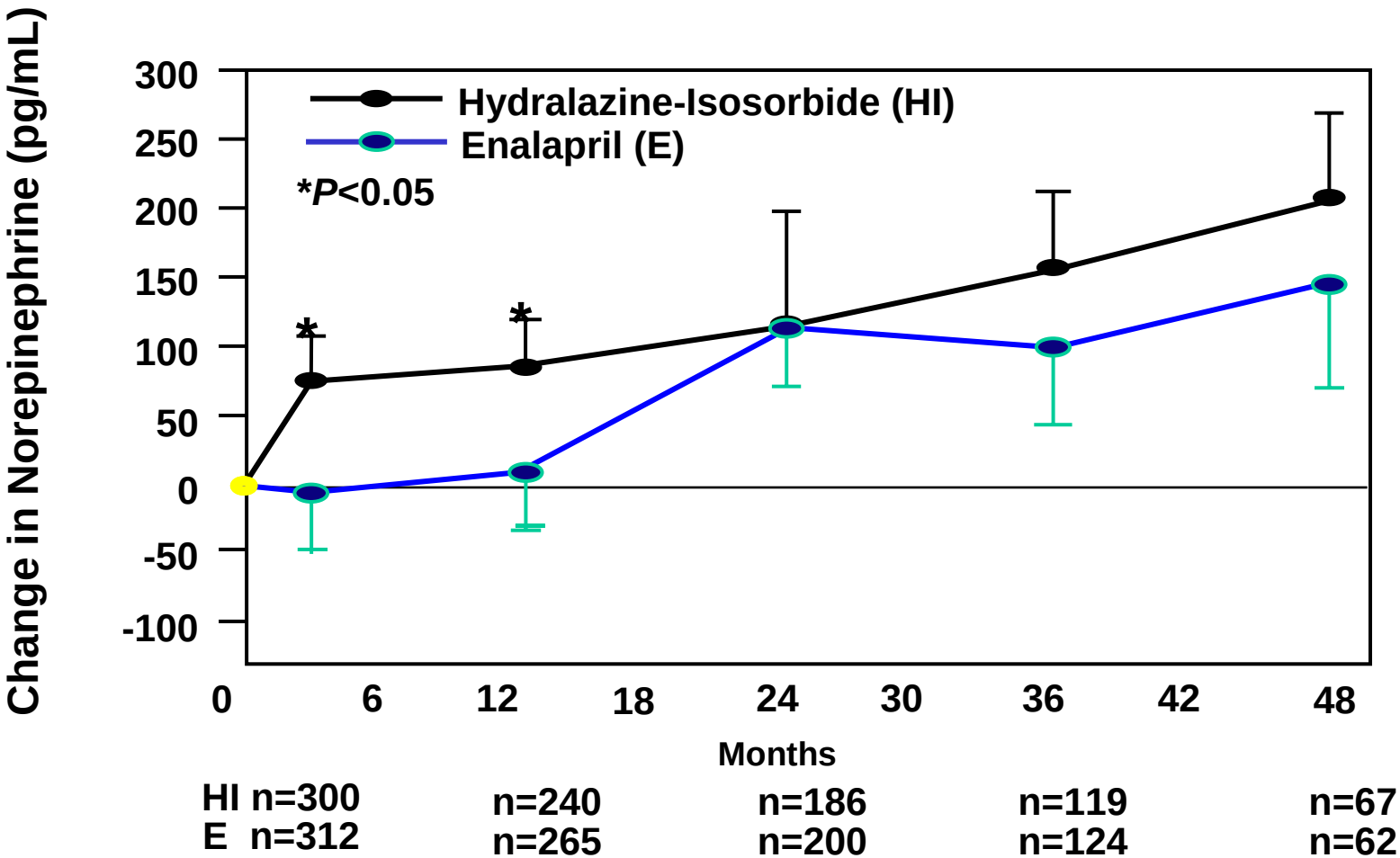
Trial (β blocker used)	n	NHYA Class	LVEF (%)	Duration (months)	Definition of elderly
BEST (bucindolol)	2708	3-4	<35	24	≥ 65 years
Carvedilol US trials (carvedilol)	1094	2-4	<35	6.5 (median)	≥ 59 years
CIBIS-2 (bisoprolol)	2647	3-4	<35	15.6	≥ 71 years
COPERNICUS (carvedilol)	2289	3-4	<25	10.4	≥ 65 years
MERIT-HF (metoprolol)	3991	2-4	<40	12	Upper tertile*

Starting and Target Doses for β Blockers

Agent	Starting Dose	Target Dose <75-85 kg	Target Dose ≥75-85 kg
Metoprolol CR/XL	12.5 or 25 mg PO qd*	200 mg PO qd	200 mg PO qd
Bisoprolol†	1.25 mg PO qd	5 mg PO qd	10 mg PO qd
Carvedilol	3.125 mg PO b.i.d.	25 mg PO b.i.d.	50 mg PO b.i.d.

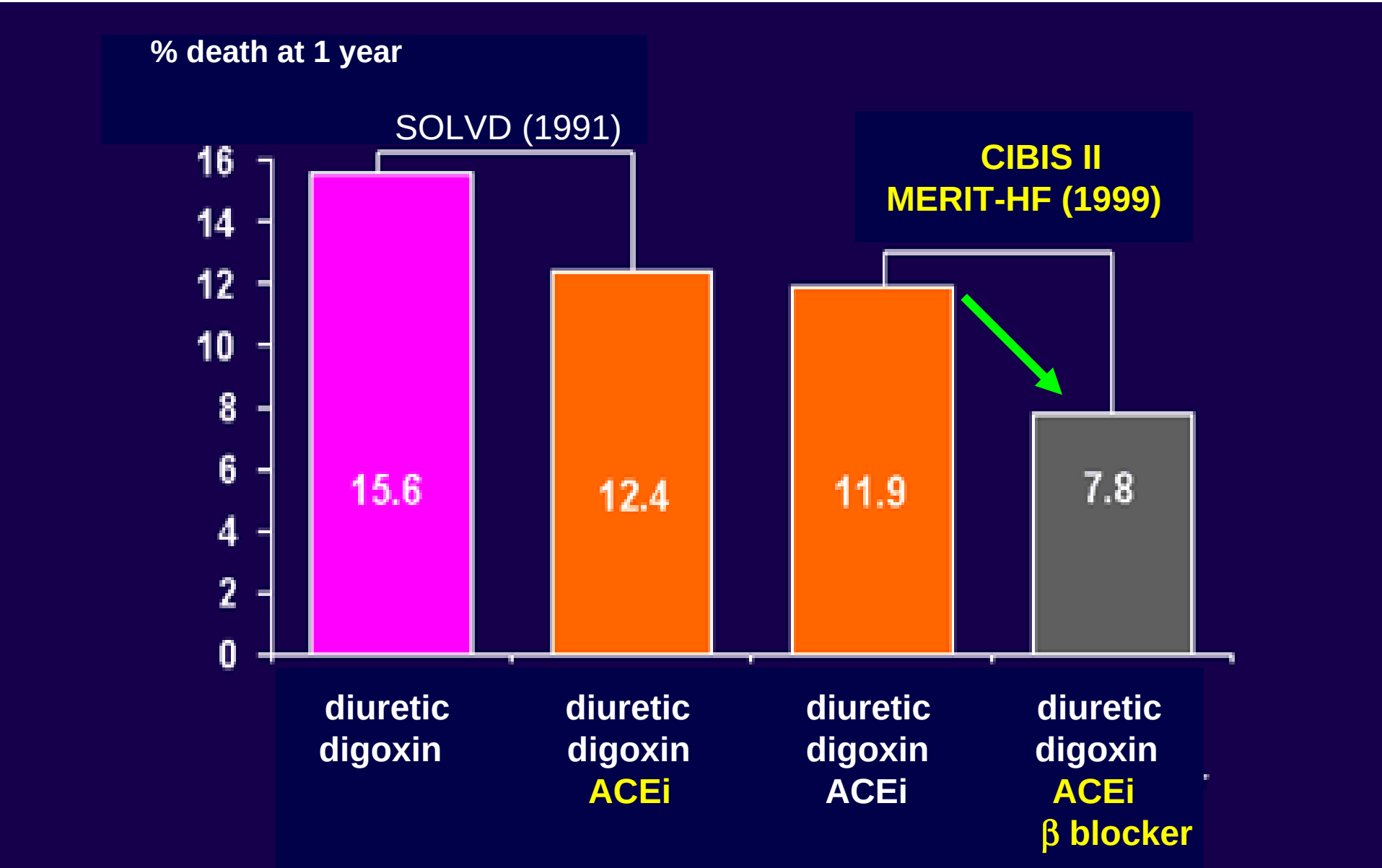
*Starting dose should be half of above if disease is Class III or IV or if the patient has severe right-sided heart failure or is tenuous.

Progressive Adrenergic Activation Despite Use of ACE Inhibitors



Francis et al. *Circulation.* 1993;87:V140-V148.

Mortality Benefit of β Blockers and ACEIs in CHF Trials



Medical Therapies Proven to Reduce Death in Cardiovascular Disease

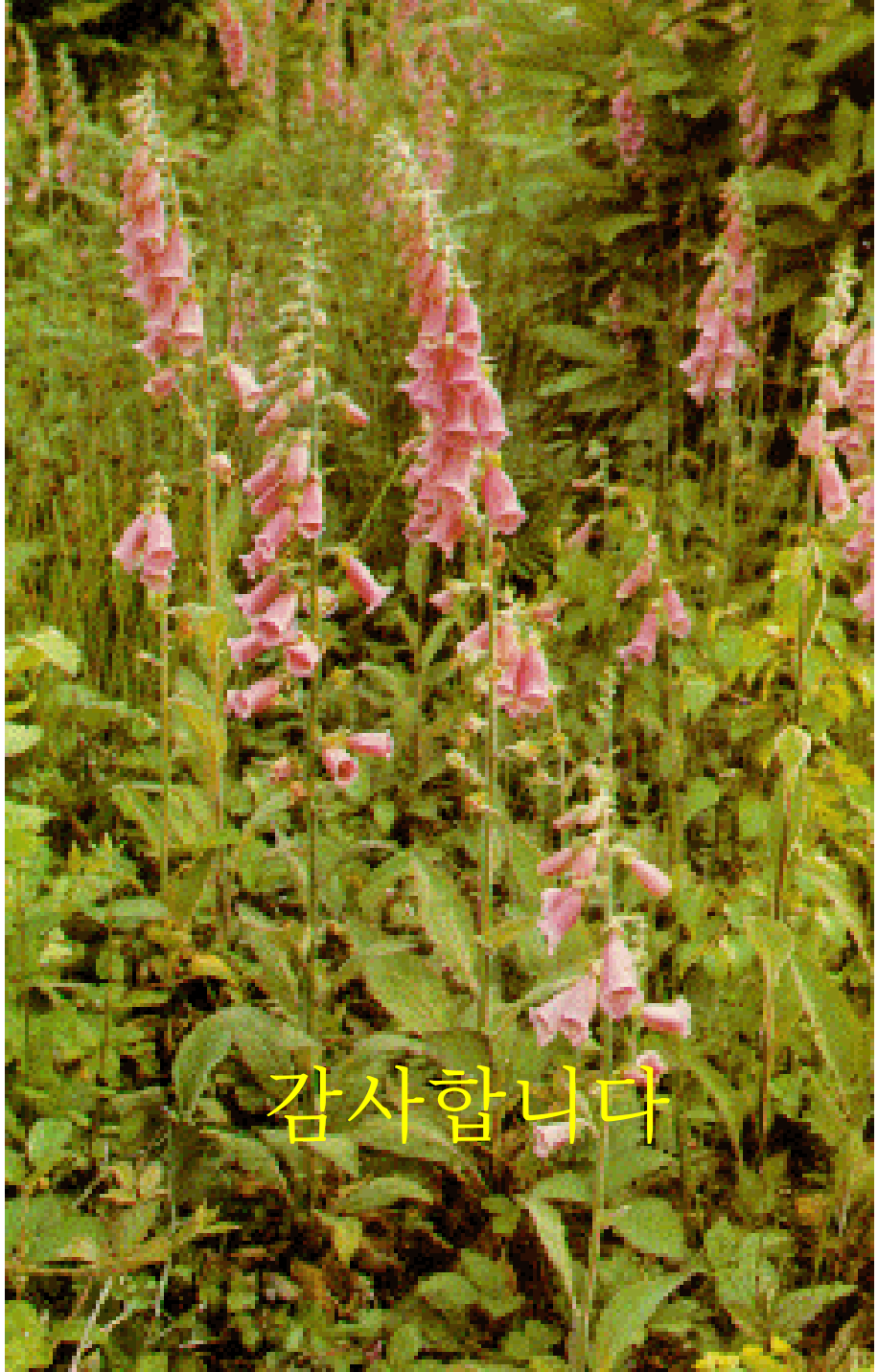
Therapy	Indication	# pts	Reduction in deaths* Relative	Absolute
Aspirin	MI	19,077	23%	2.3%
Thrombolysis	MI	58,000	18%	1.8%
Beta blocker	MI	28,970	13%	1.3%
ACEI	MI (early)	98,500	7%	.5%
ACEI	MI (late)	15,100	17%	2.8%
Statins	2nd prev	17,617	23%	2.7%
ACEI	2nd prev	9297	17%	1.9%
Beta blocker	CHF	12,385	26%	4%
Spironolactone	CHF	1663	30%	11%
ACEI	CHF	12,763	20%	3.8%

Beta blockers in HF

- Stable patients with mild to moderate symptoms without significant congestion
- Additional benefit even in severe but stable HF and post-MI LV dysfunction
- Carvedilol seems better than metoprolol
- Not always beneficial with all kinds of β blockers and study populations

Limitations of β-blocker Therapy in Chronic Heart Failure

- **Contraindications to β-blockade such as reactive airway disease, sinus node or conduction system disease with bradycardia and advanced HF with hemodynamic decompensation**
- **Initiation of therapy and uptitration of β blocking agent can be difficult**
- **Some patient do not respond to β blockade; not yet clear mechanism**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Alterations in β-adrenergic Pathway in the Failing Heart