Baseline disease oriented management of heart failure

Prevention & Management of Hypertensive Heart Failure

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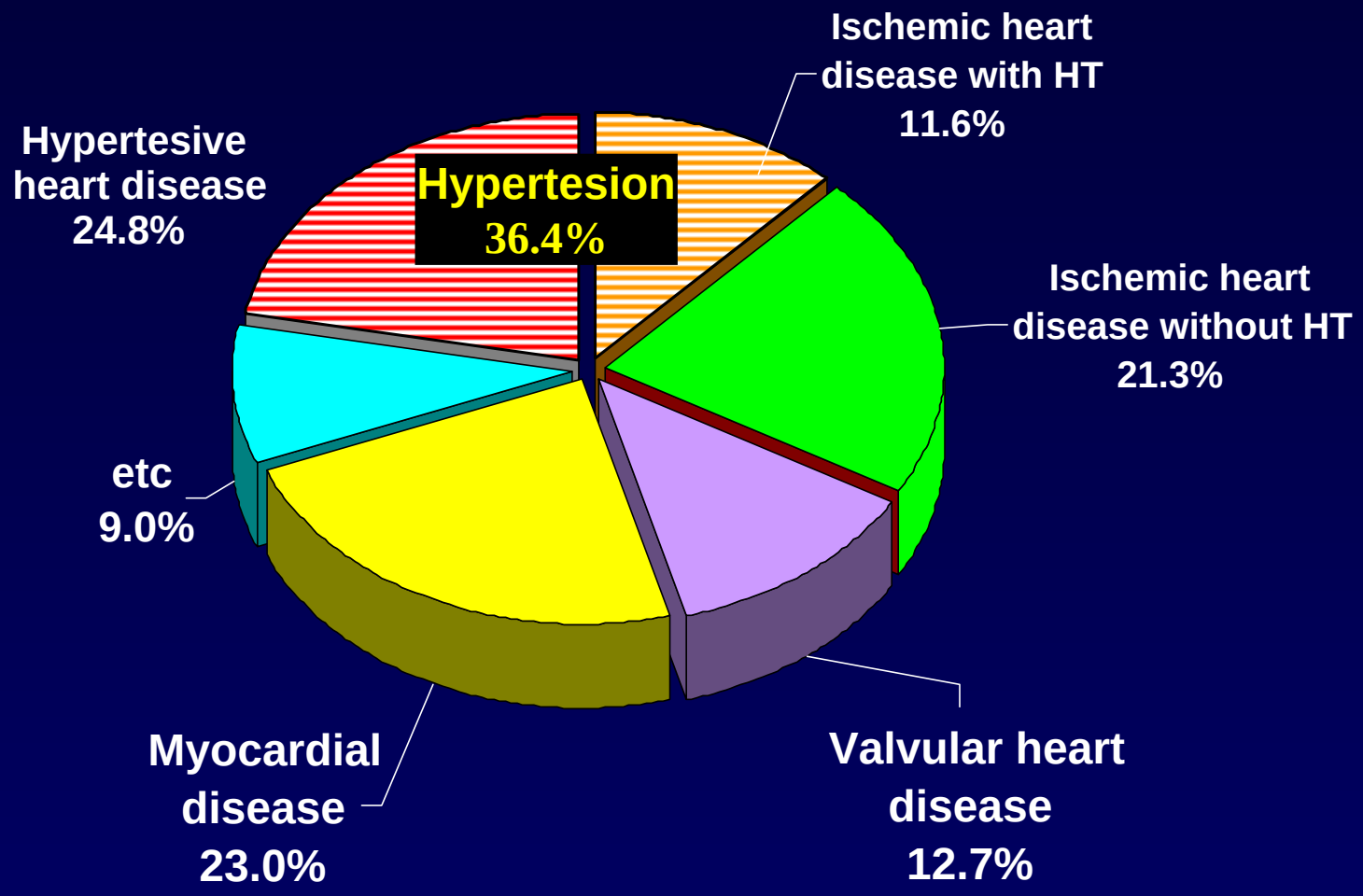
Hypertension in Hospital Based Epidemiologic Study

Underlying cause of CHF in Korea (multicenter survey)

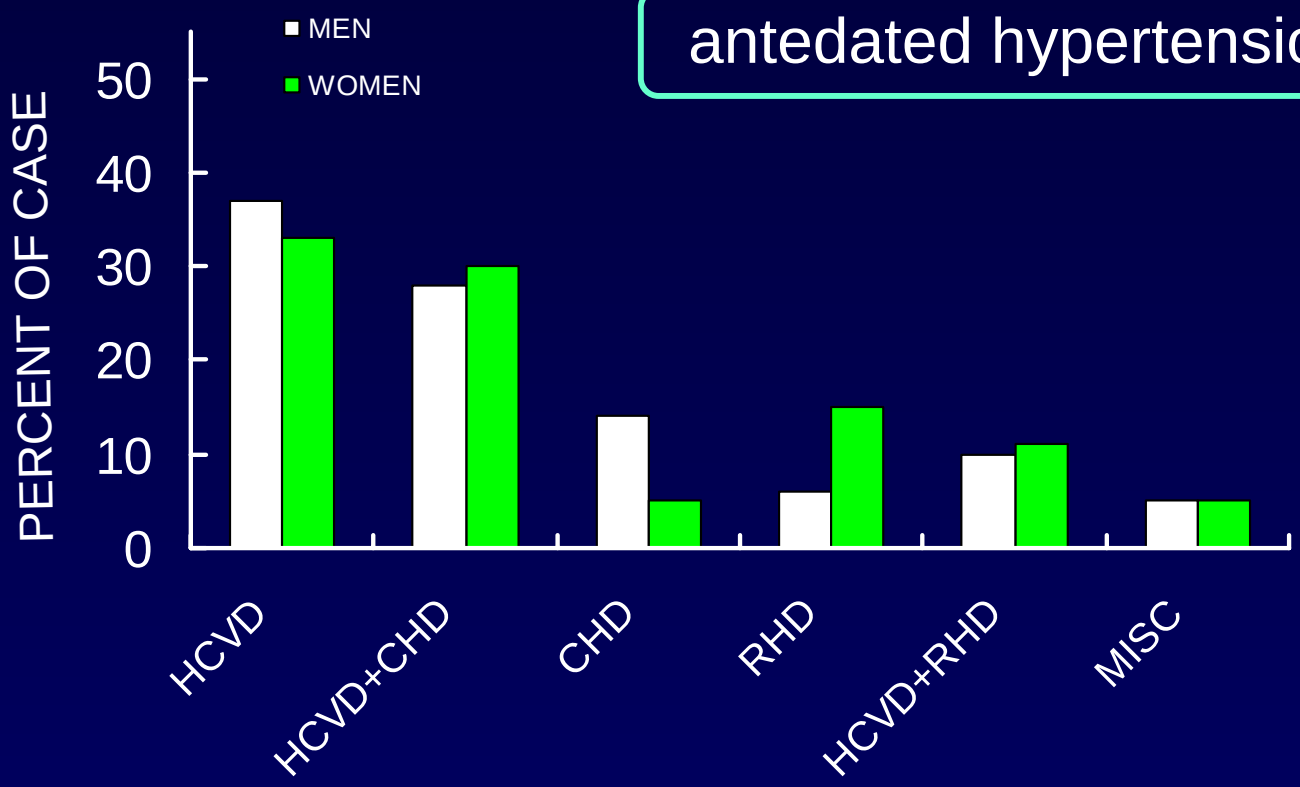
Korean J Circ 2003



Hypertension, leading cause of heart failure

Etiology of CHF (Framingham Study)

McKee ET et al. N Engl J Med *1971*



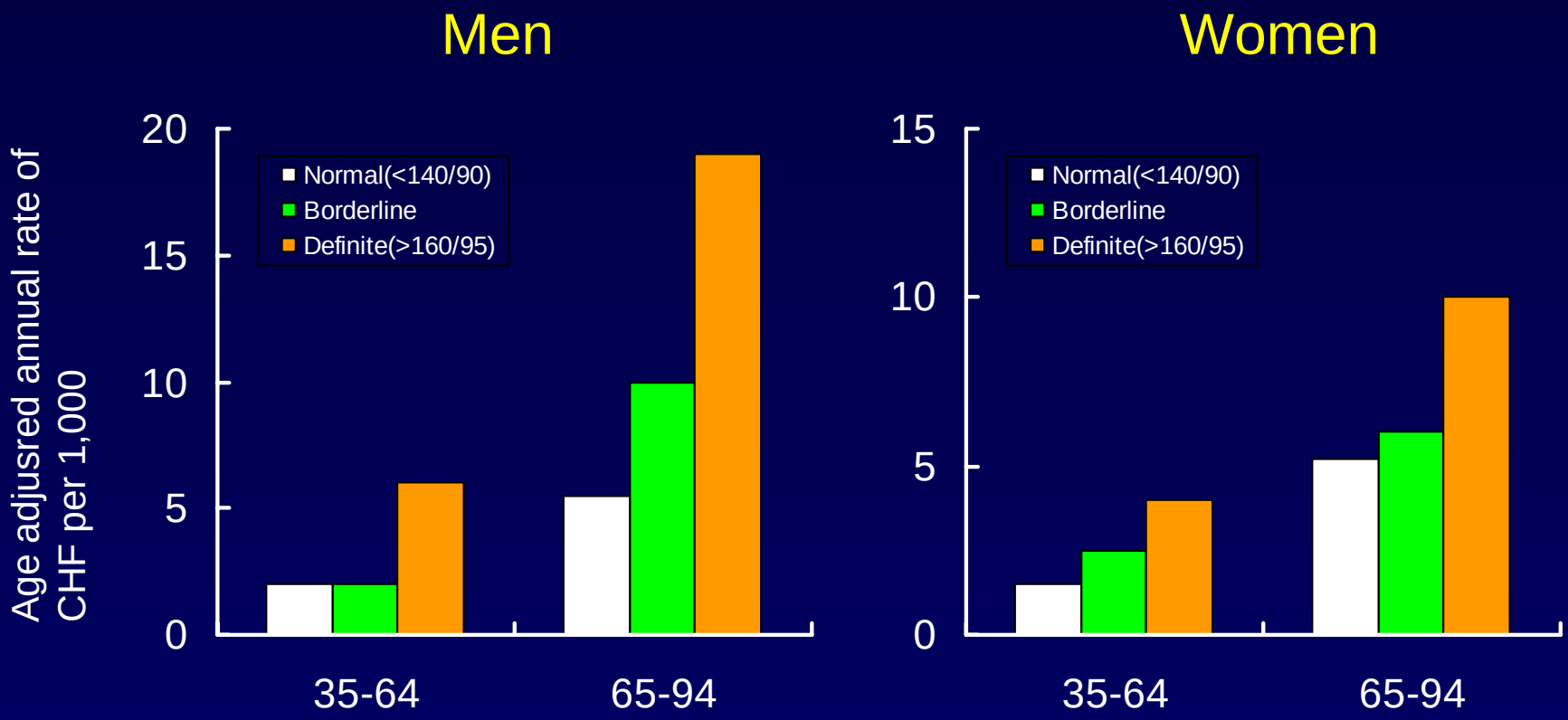
antedated hypertension in 75%

HCVD: hypertensive cardiovascular disease
CHD: coronary heart disease
RHD: rheumatic heart disease

Hypertension, still leading cause of heart failure

Effect of hypertension on the risk of heart failure (Framingham Study)
Levy D et al. *JAMA 1996*

375/392(91%) prior hypertension
2 fold in men & 3-fold in women



ACC/AHA Guideline For Treatment of Heart Failure
Staged Approach

Stage	Description	Examples
A	High risk of developing HF No structural or functional abnormality	Hypertension, CAD, DM, cardiotoxic drug, Alcohol abuse, Hx of rheumatic fever, FHx CMP
B	Structural heart disease strongly associated with developing HF Never symptoms or signs	LV hypertrophy or fibrosis, LV dilation or hypocontractility, Asymptomatic VHD Previous MI
C	Current or past history of HF with underlying structural disease	Symptom due to LV systolic dysfunction Aysmptomatic patients but treated due to previous symptom
D	Advanced structural heart disease with far advanced structural disease Marked symptom despite maximal medical therapy	Frequent hospitalization, home continuous IV support, waiting transplantation, mechanical device assist

ACC/AHA Guideline For Treatment of Heart Failure
Staged Approach for patients with *hypertension*

Stage	Description	Management
A	Untreated or inappropriately treated hypertnsion	Control of blood pressure Modification of risk factors of atherosclerotic vascular disease
B	Concentric or eccentric LVH without Sx Asymptomatic LV dysfunction	Regression of LVH Preventing progression to symptomatic HF
C	Symptomatic LV systolic dysfunction HF with preserved systolic function	Relieve symptom of heart failure & improve survival
D	End stage heart failure	Relieve Sx and improve quality of life

Prevention of Heart Failure in Patients with Hypertension (Stage A)

Stage	Description	Examples
A	Untreated or inappropriately treated hypertension	Control of blood pressure Modification of risk factors of atherosclerotic vascular disease
B	Concentric or eccentric LVH without Sx Asymptomatic LV dysfunction	Regression of LVH Preventing progression to symptomatic HF
C	Symptomatic LV systolic dysfunction HF with preserved systolic function	Relieve symptom of heart failure & improve survival
D	End stage heart failure	Relieve Sx and improve quality of life

Large Randomized Controlled Trials Comparing Different Antihypertensive Agents for Preventing Heart Failure

Study	Medication (initial dose, mg/d)	Event rate				
		Heart Failure	MI	Stroke	Major CV event	CV mortality
STOP-2	Beta blocker	16.4/1000py	14.1	22.2	44.1	19.8
	ACEi	13.9†	12.2 †	20.2	41.9	20.5
	CCB*	17.5	16.7	19.5	43.6	19.2
INSIGHT	Nifedipine GITS(30)	0.9%¶	2.4%	2.0%	6.3%	1.9%
	HCTZ(25)	0.3%	2.0%	2.3%	5.8%	1.2%
NORDIL	Diltiazem	2.5/1000py	7.4	6.4	20.2	5.2
	Thiazide/β blocker	2.1	6.3	7.9§	19.2	4.5
CAPP	Captopril(50)	1.4%	3.0%	3.5% §	15.2%	1.3%
	Atenolol or metoprolol(50-100) +HCTZ diuretics	1.2%	3.0%	2.7%	14.6%	1.5%

*atenolol(50), pindolol (5) or thiazide(25)/ Enalapril or lisinopril(10)/ Felodipine or isradipine(2.5)
† $p<0.025$ compared to CCB group
¶ $p=0.028$ compared to HCTZ for nonfatal heart failure
§ $p=0.04$ for comparison between the two groups

HOPE: Heart Outcomes Prevention Evaluation study
- TRIAL DESIGN -

Treatment

Multicenter, multinational, randomized, double-blind, placebo-controlled parallel-group, two-by-two factorial study

High risk subjects!

Patients

55 years or older with history of vascular disease or diabetes mellitus, plus one other cardiovascular risk factor; patients with stroke or MI in previous month, heart failure or evidence of low ejection fraction excluded

Follow up and primary endpoint

Mean 5.0 years follow up for ramipril (4.5 for vitamin E). Primary endpoint composite of MI, stroke or cardiovascular death

HOPE: Heart Outcomes Prevention Evaluation study
- TRIAL DESIGN continued -

Ramipril up to 10mg

Treatment

9297 patients (2480 women, 6817 men) randomly assigned to receive one of four treatments for 5 years:

- **Ramipril** 2.5 mg for 1 week, 5 mg for 3 weeks, then 10 mg + **vitamin E** 400 IU daily
- **Ramipril** 2.5 mg for 1 week, 5 mg for 3 weeks, then 10 mg + **placebo** matching vitamin E treatment
- **Placebo** matching ramipril treatment + **vitamin E** 400 IU daily
- **Placebo** matching ramipril treatment + **placebo** matching vitamin E treatment

HOPE: Heart Outcomes Prevention Evaluation study
- RESULTS -

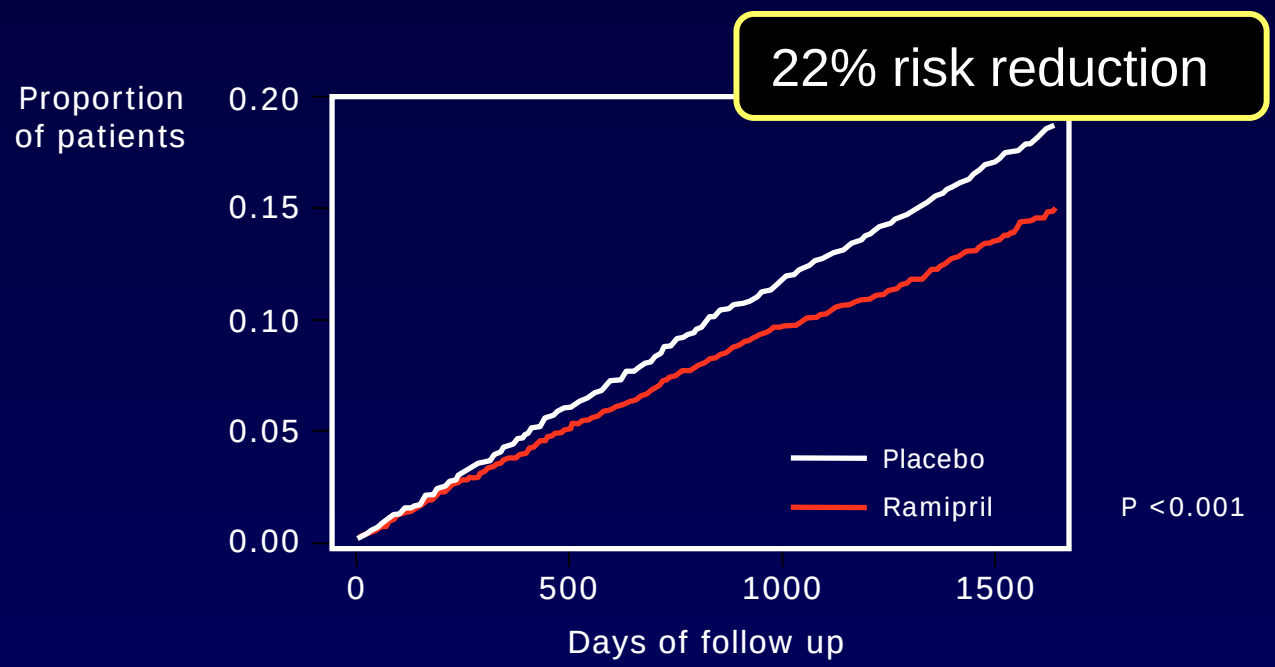
- Termination 6 mo earlier
- 22% risk reduction
- Prevent new DM

Ramipril vs. placebo

- Study halted 6 months early on recommendation of monitoring board because of consistent benefit of ramipril:
  - Composite primary endpoint of MI, stroke or death from cardiovascular causes significantly lower in ramipril group (14.0 vs. 17.8%, relative risk 0.78, P<0.001)
  - Individual primary endpoints (MI, stroke, death from cardiovascular causes), all-cause mortality, and secondary outcomes of revascularization and complications related to diabetes, significantly lower in ramipril group
- New diagnosis of diabetes significantly lower in ramipril group (3.6 vs. 5.4%, relative risk 0.66, P<0.001)
- Drug well tolerated as defined by permanent discontinuation of treatment (28.9% of ramipril group versus 27.3% placebo)

HOPE: Heart Outcomes Prevention Evaluation study
- RESULTS continued -

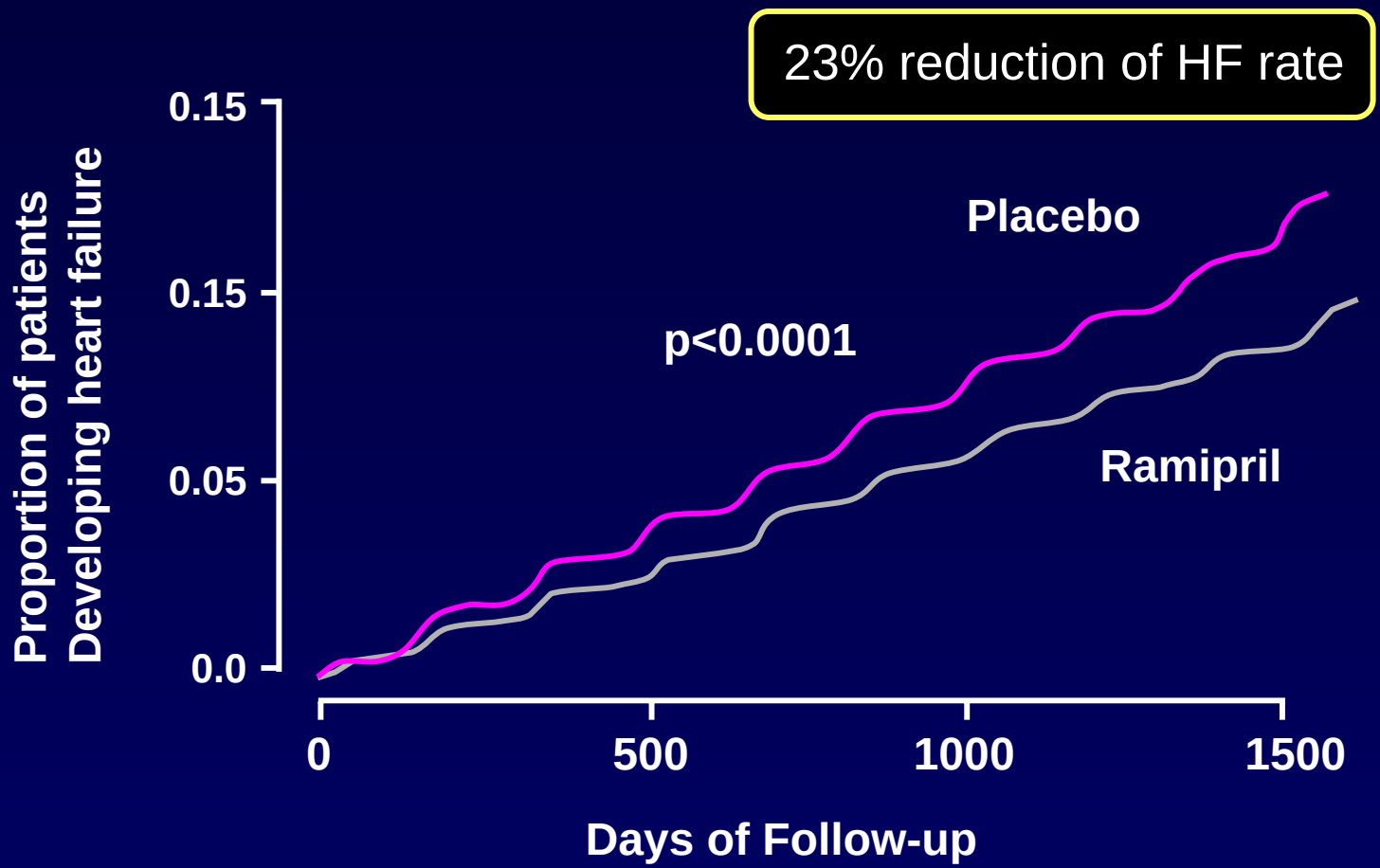
MI, stroke or death from cardiovascular causes



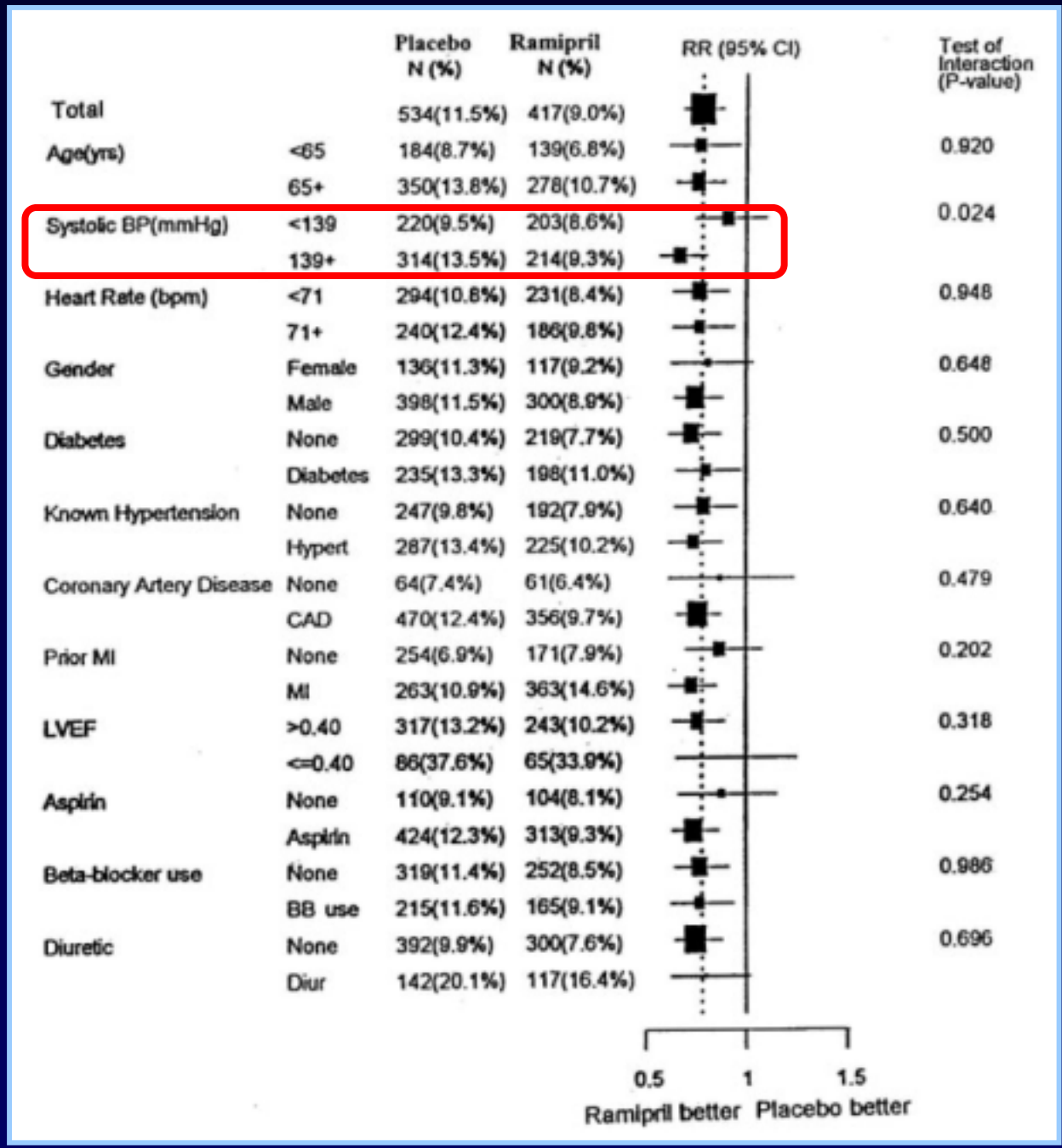
The Hope Study Investigators. *N Engl J Med* 2000;**342**:145–53.

Prevention of Heart Failure in HOPE study

Malcolm J et al. Circulation 2003

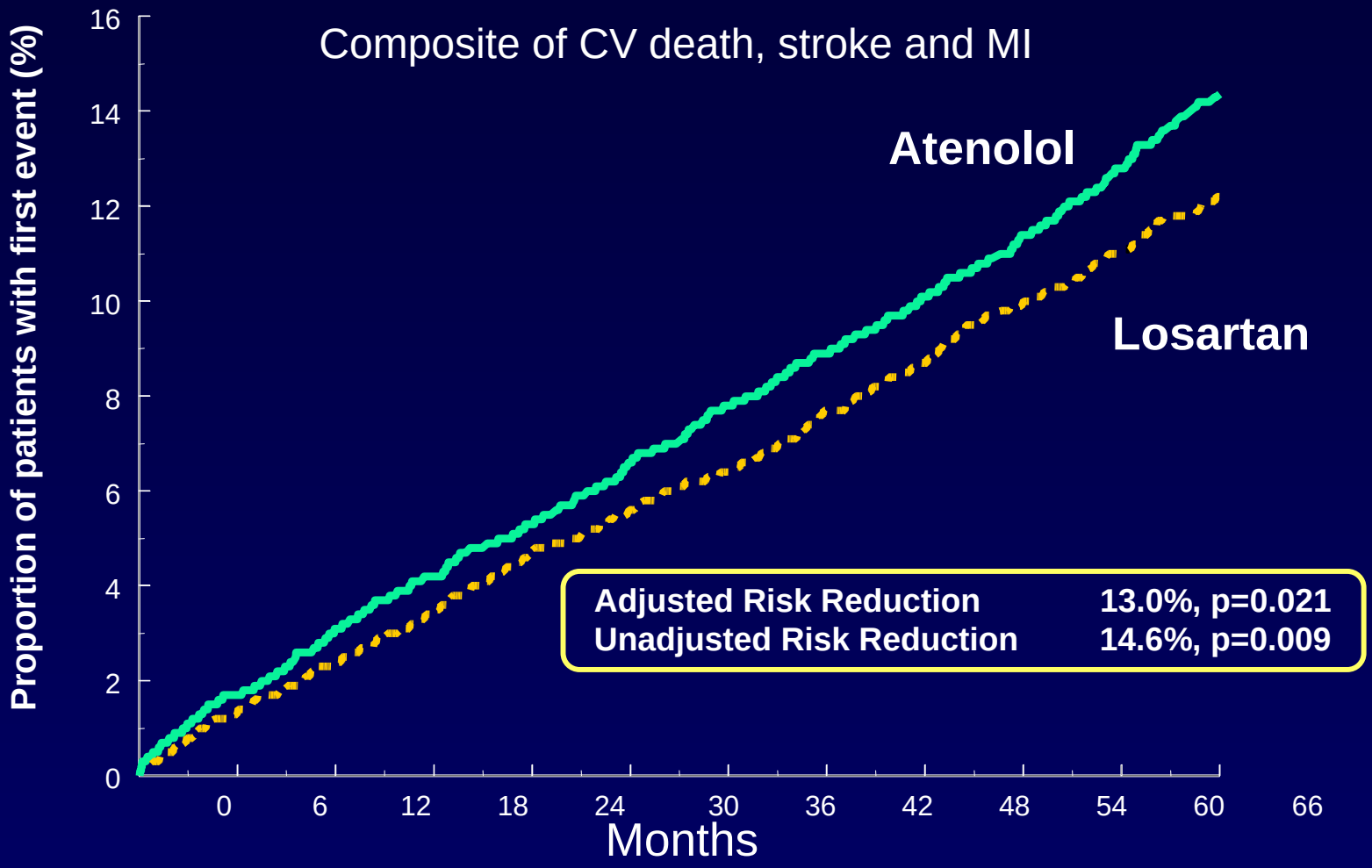


Malcolm J et al.
Circulation 2003



LIFE: losartan vs atenolol

Dahlöf B et al *Lancet* 2002



LIFE: losartan vs atenolol

Dahlöf B et al *Lancet* 2002

End points

Admission due to heart failure
Losartan 7.1% / Atenolol 7.5%

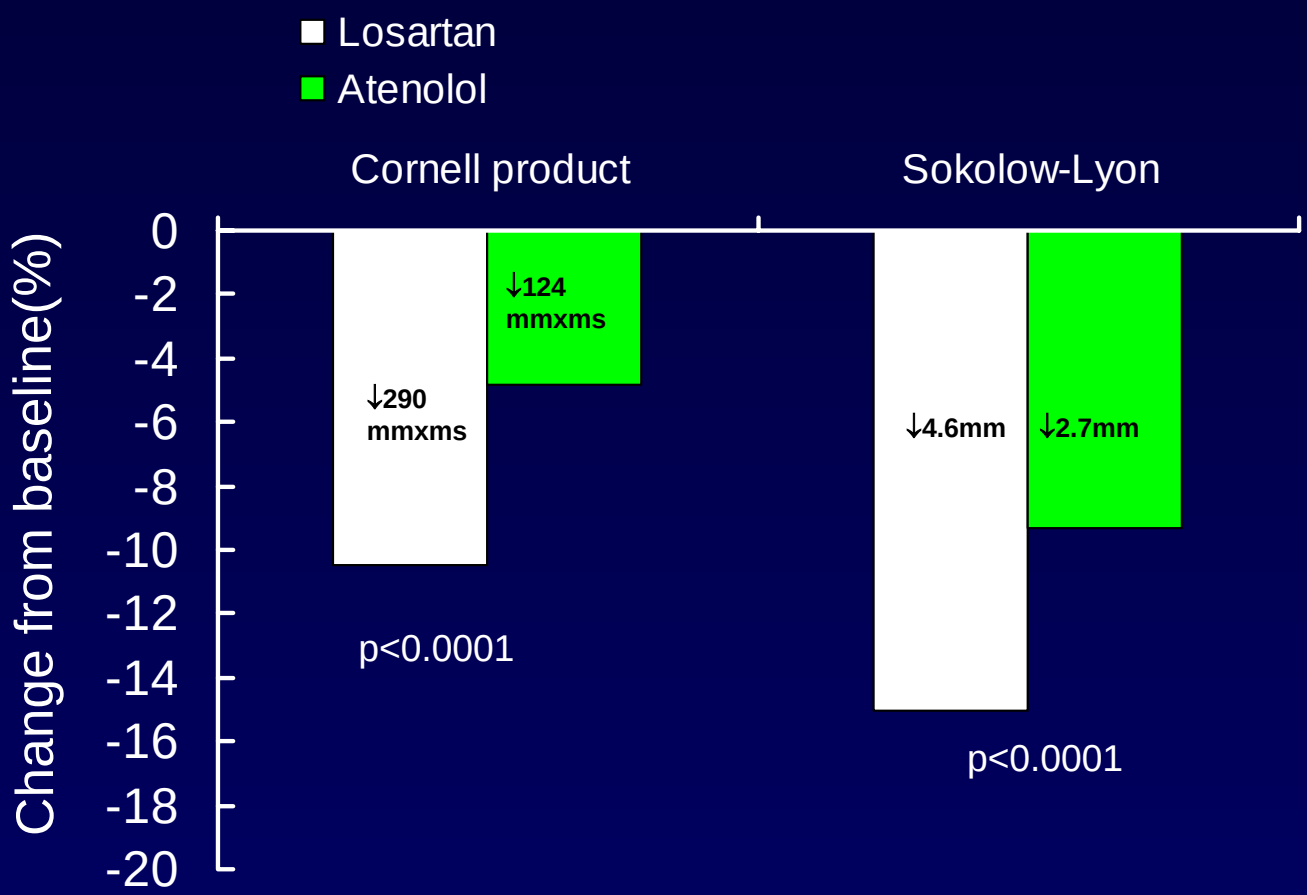
Endpoint	Losartan (n=4605)		Atenolol (n=4588)		Adjusted hazard ratio (95% CI)†	p	Unadjusted hazard ratio (95% CI)	p
	n	Rate*	n	Rate				
Primary composite endpoint‡	508 (11%)	23·8	588 (13%)	27·9	0·87 (0·77–0·98)	0·021	0·85 (0·76–0·96)	0·009
Cardiovascular mortality	204 (4%)	9·2	234 (5%)	10·6	0·89 (0·73–1·07)	0·206	0·87 (0·72–1·05)	0·136
Stroke	232 (5%)	10·8	309 (7%)	14·5	0·75 (0·63–0·89)	0·001	0·74 (0·63–0·88)	0·0006
Myocardial infarction	198 (4%)	9·2	188 (4%)	8·7	1·07 (0·88–1·31)	0·491	1·05 (0·86–1·28)	0·628
Other prespecified endpoints								
Total mortality	383 (8%)	17·3	431 (9%)	19·6	0·90 (0·78–1·03)	0·128	0·88 (0·77–1·01)	0·077
Admitted to hospital for:								
Angina pectoris	160 (3%)	7·4	141 (3%)	6·6	1·16 (0·92–1·45)	0·212	1·13 (0·90–1·42)	0·284
Heart failure	153 (3%)	7·1	161 (4%)	7·5	0·97 (0·78–1·21)	0·765	0·95 (0·76–1·18)	0·622
Revascularisation	261 (6%)	12·2	284 (6%)	13·3	0·94 (0·79–1·11)	0·441	0·91 (0·77–1·08)	0·292
Resuscitated cardiac arrest	9 (0·2%)	0·4	5 (0·1%)	0·2	1·91 (0·64–5·72)	0·250	1·80 (0·60–5·36)	0·294
New-onset diabetes§	241 (6%)	13·0	319 (8%)	17·4	0·75 (0·63–0·88)	0·001	0·75 (0·63–0·88)	0·001

*Per 1000 patient-years of follow-up. †For degree of left ventricular hypertrophy and Framingham risk score at randomisation. ‡Cardiovascular mortality, stroke, and myocardial infarction (numbers of patients with a first primary event). §In patients without diabetes at randomisation (losartan, n=4019; atenolol, n=3979).

LIFE

Dahlöf B et al *Lancet* 2002

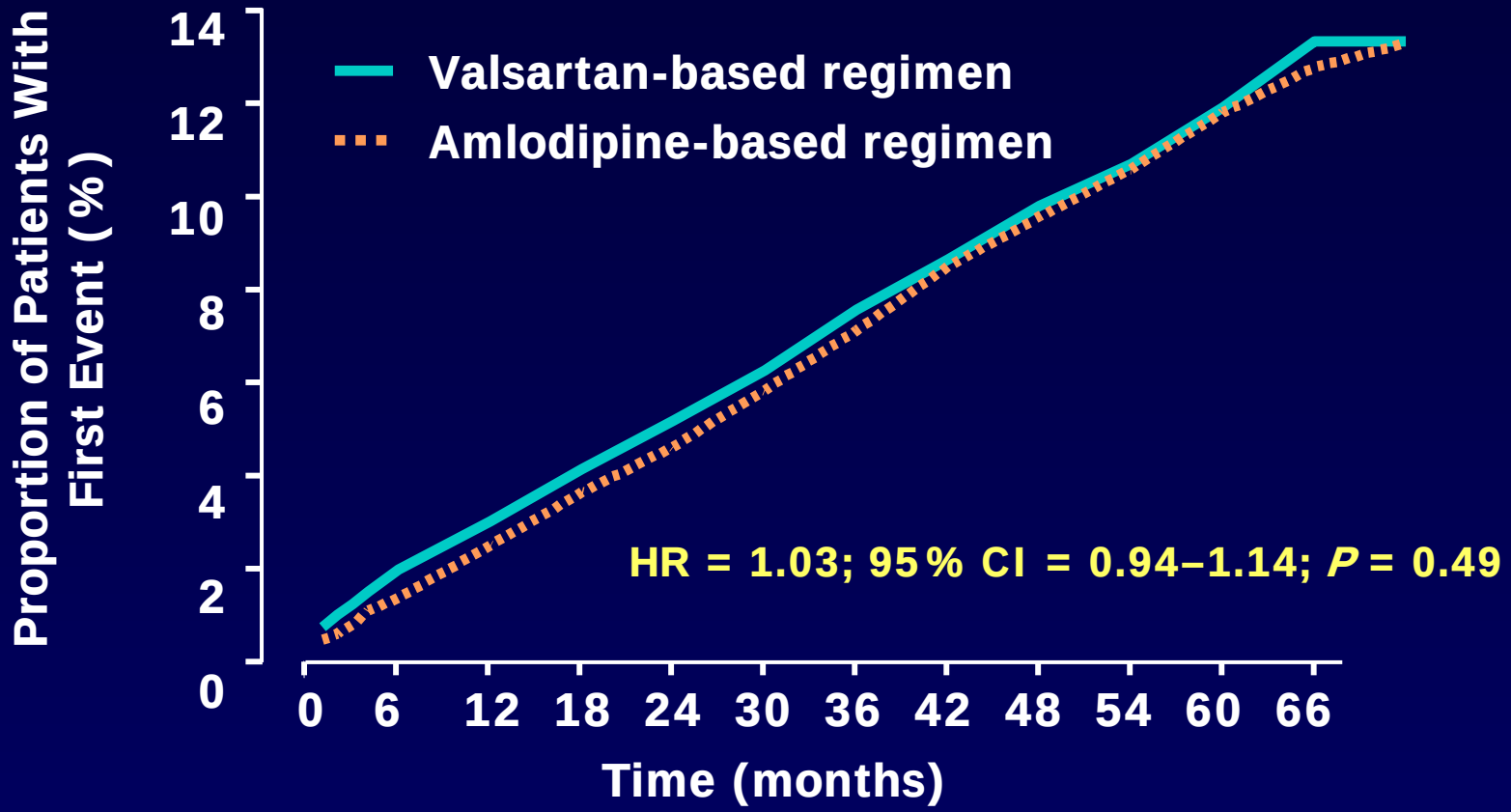
Regression of LVH



VALUE

- **Primary endpoint**
  - **composite cardiac morbidity and mortality**
  -
- **Secondary endpoints**
  - **fatal/non-fatal myocardial infarction**
  - **fatal/non-fatal stroke**
  - **fatal/non-fatal heart failure**
- **Pre-specified analyses**
  - **all-cause mortality**
  - **new onset diabetes**

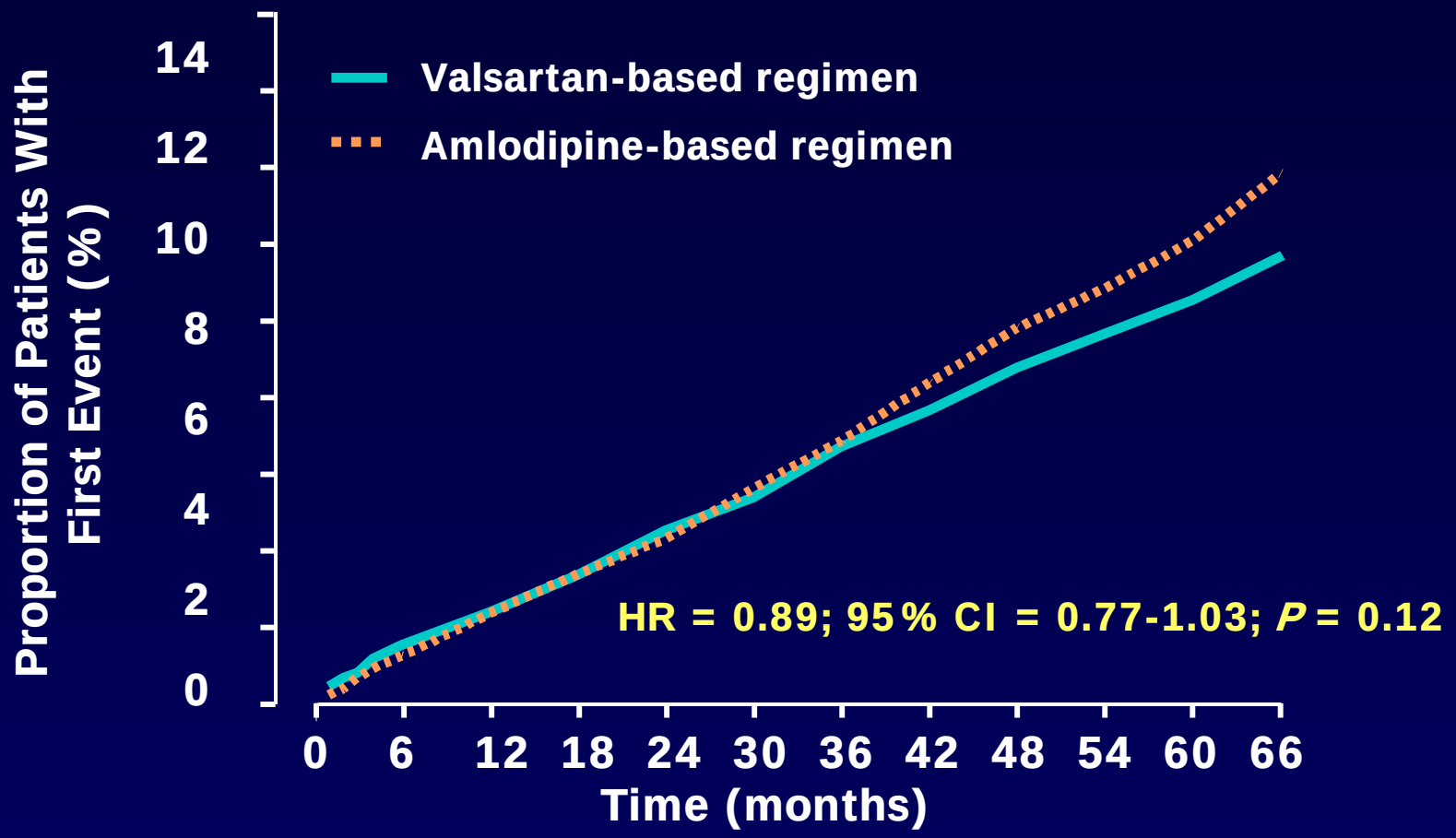
VALUE: Primary Composite Cardiac Endpoint



Julius S et al. *Lancet*. June 2004;363

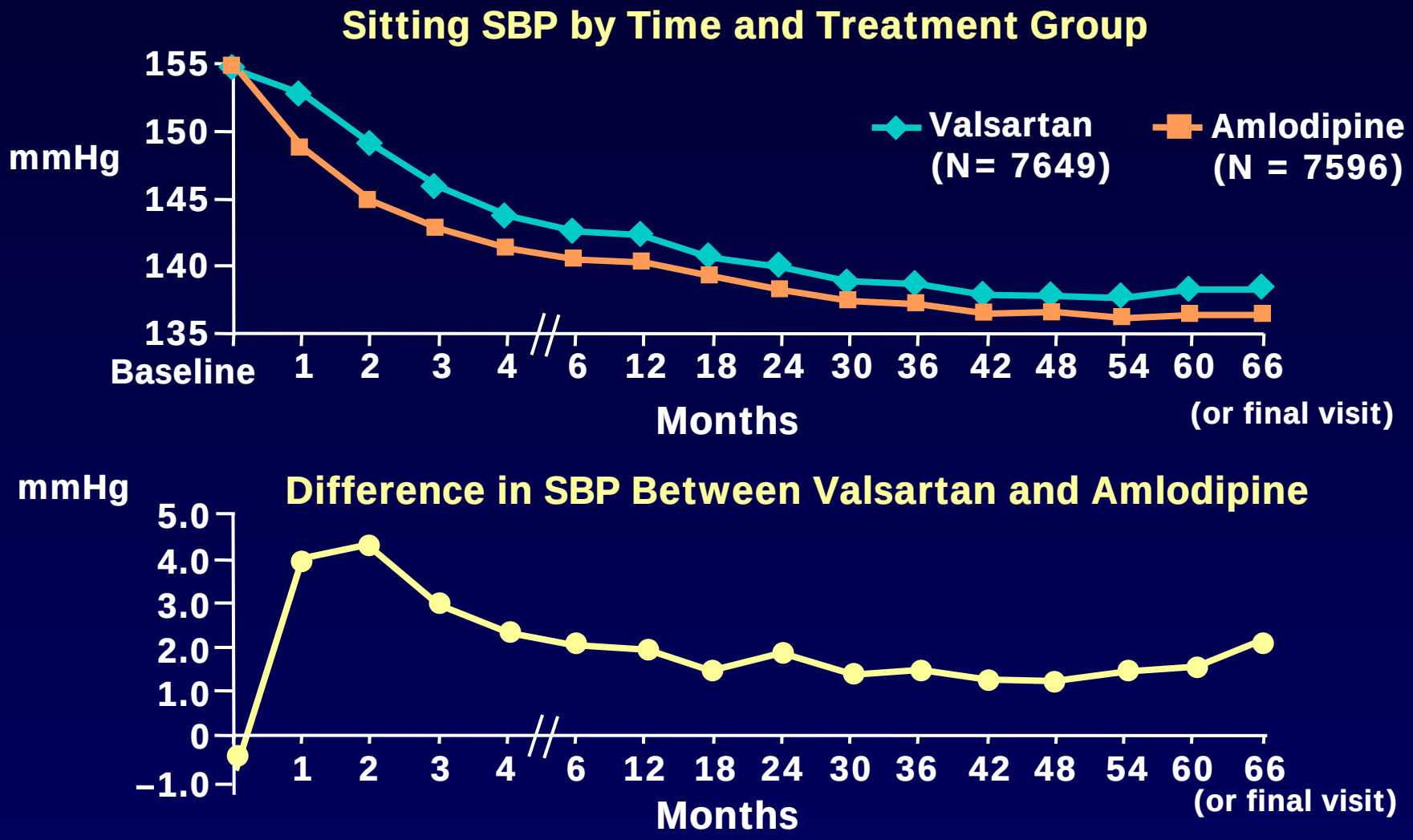
VALUE: Heart Failure

Hospitalisation for HF or death from HF



Julius S et al. *Lancet*. June 2004;363.

VALUE: Systolic Blood Pressure in Study



Julius S et al. *Lancet*. June 2004;363.

The Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

JAMA 2002;288

ALLHAT trial

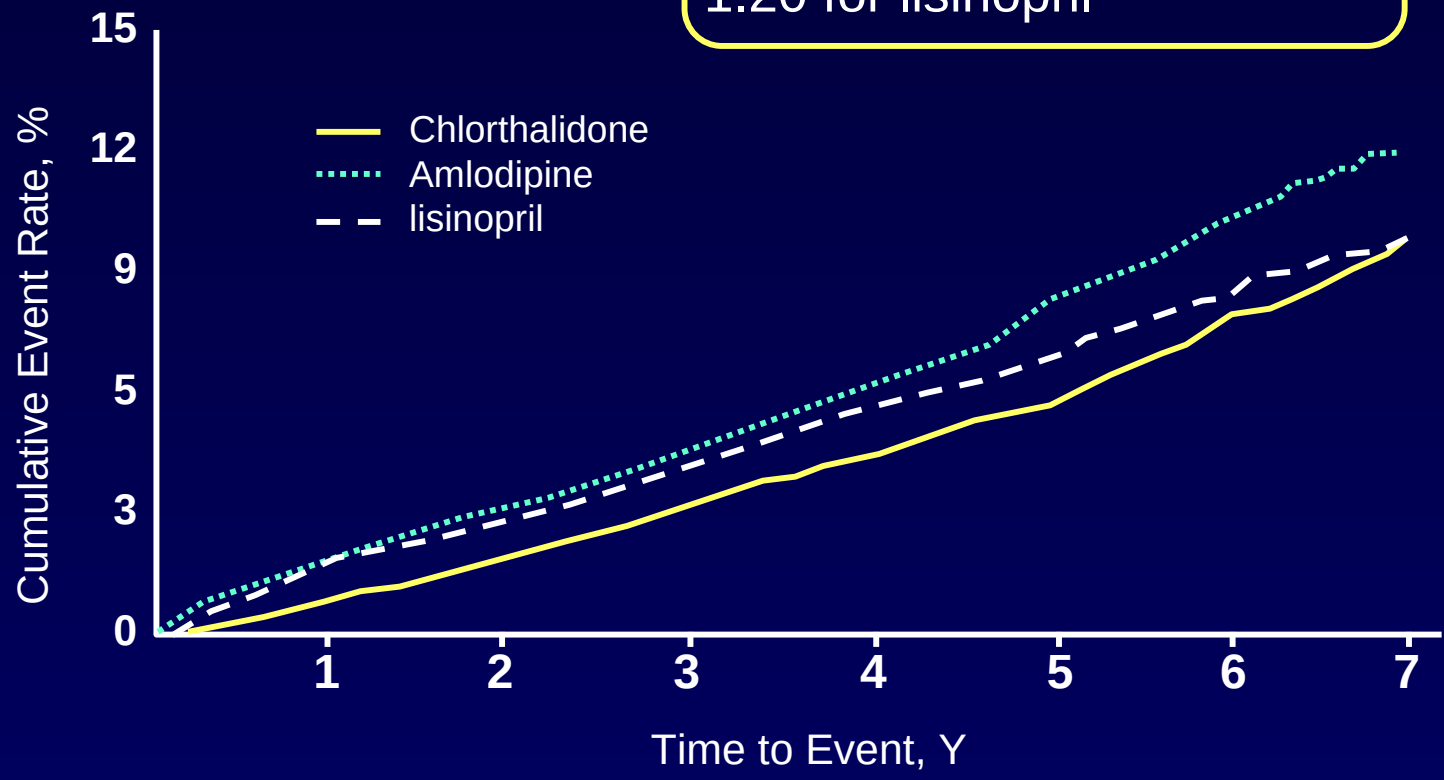
- 33,357 age over 55 + at least 1 CHD risk
- Chlorthalidone 12.5-25mg : 15,255
- Amlodipine 2.5-10mg : 9,048
- Lisinopril 10-40mg : 9,054

ALLHAT trial

- Primary outcome (fatal CHD or non-fatal MI) : no difference
- All cause mortality : no difference
- 6-yr rate of HF : chlorthalidone(7.7%) < amlodipine(10.2%)
- Combined CVD : chlorthalidone(30.9%) < lisinopril(33.3%)

Heart Failure in ALLHAT trial

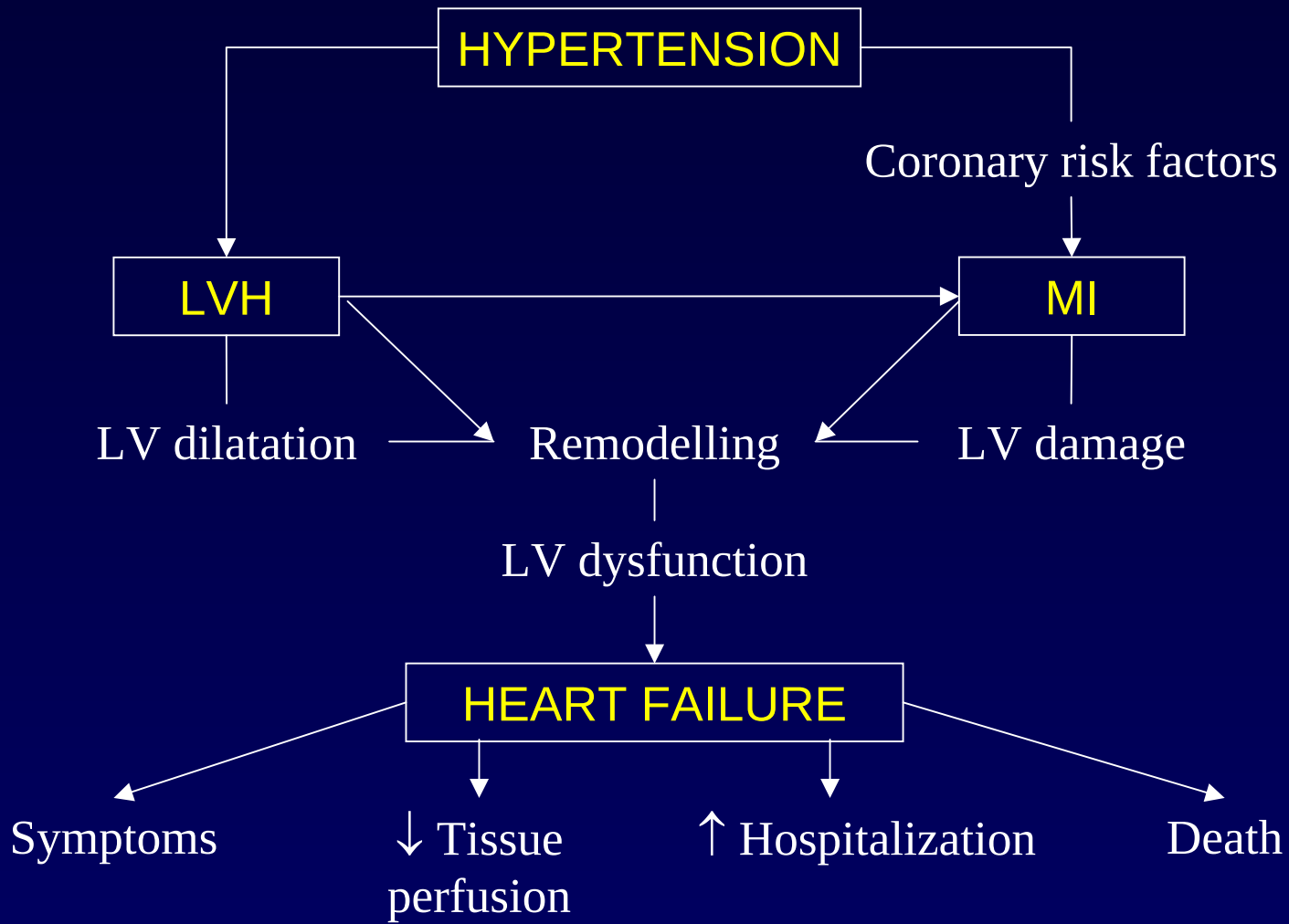
RR for heart failure
1.38 for amlodipine(p<0.05)
1.20 for lisinopril



Regression of LVH (Stage B)

Stage	Description	Examples
A	Untreated of inappropriately treated hypertnsion	Control of blood pressure Modification of risk factors of atherosclerotic vascular disease
B	Concentric or eccentric LVH without Sx Asymptomatic LV dysfunction	Regression of LVH Preventing progression to symptomatic HF
C	Symptomatic LV systolic dysfunction HF with preserved systolic function	Relieve symptom of heart failure & improve survival
D	End stage heart failure	Relieve Sx and improve quality of life

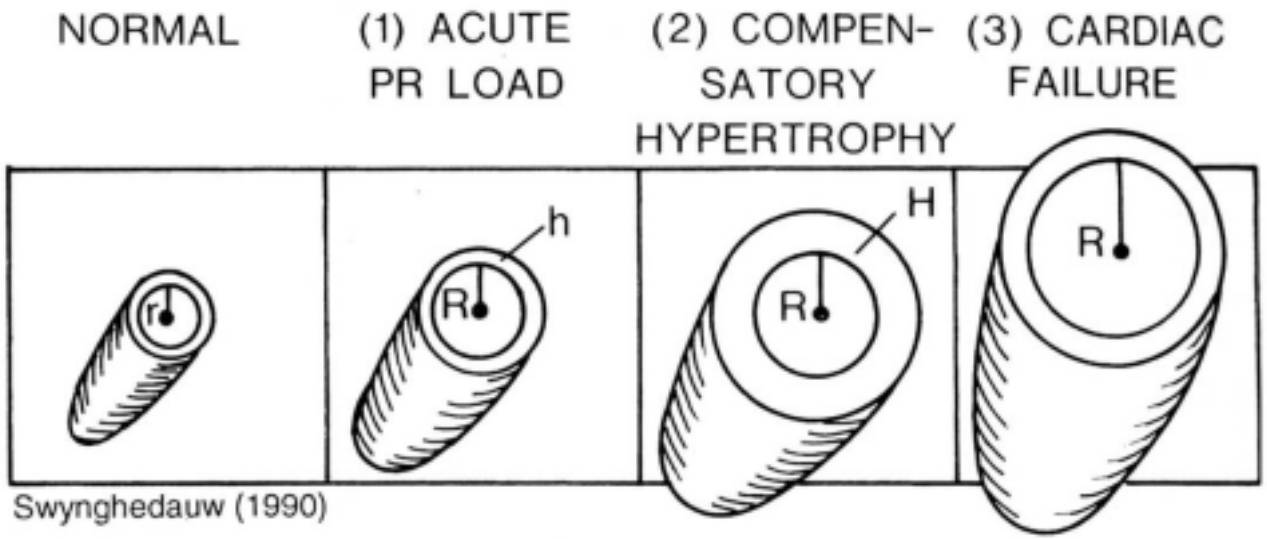
Practical Clinical Situation



3 Phases of Myocardial Hypertrophy

- Developing hypertrophy
- Compensatory hypertrophy
- Heart failure

3 Phases of Myocardial Hypertrophy



Swynghedauw (1990)

LV systolic pressure	N	+	+	+
LV radius	N	+	+	+
LV wall thickness	N	N	+	+
LV diastolic volume	N	+	N	+
Systolic wall stress	N	+	N	+
Diastolic wall stress	N	+	N	+
Diastolic dysfunction	N	±	+	+
Systolic dysfunction	N	±	O	+

Left Ventricular Hypertrophy

Concentric LVH
wall thickness ↑
LV mass ↑

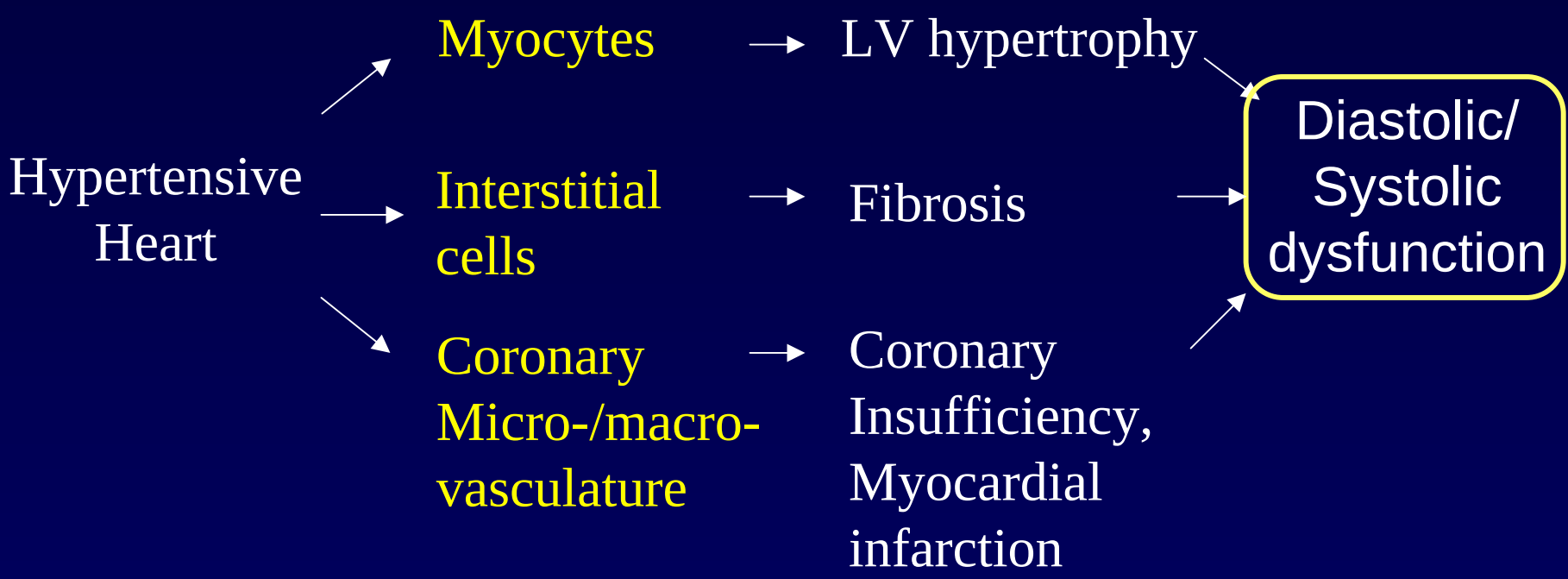
Concentric remodeling
wall thickness ↑
but LV mass →

Eccentric LVH
wall thickness →
LV mass(volume) ↑

Mixed up Form
Eccentric LVH
+
wall thickness ↑

Common in
HT with HF

Components of Cardiac Remodeling in Hypertensive Heart Disease



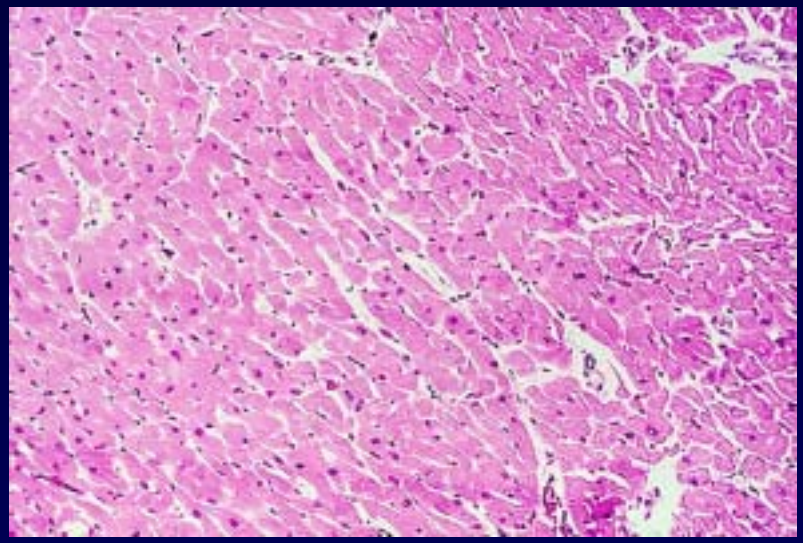
Morphological Aspect

- Cardiomyocyte
- Interstitium
- Vasculature

Structural Change of Myocardium

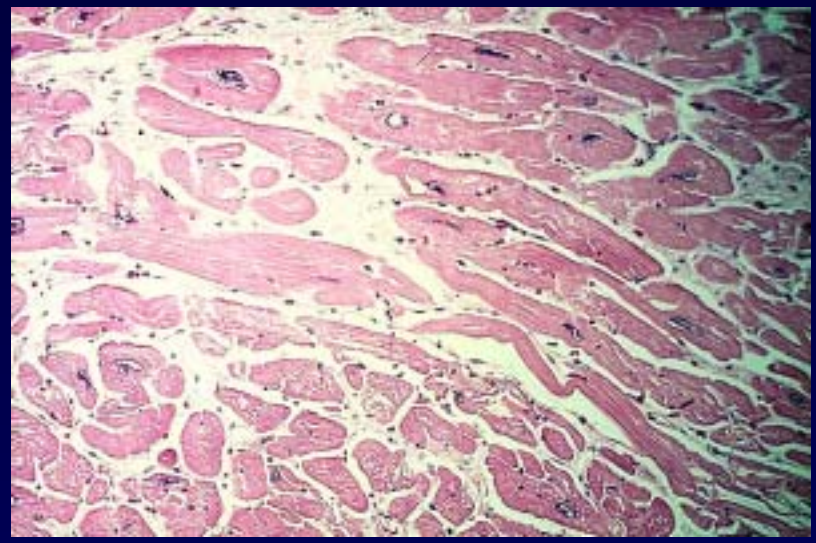
Morphological Change of Cardiac Hypertrophy

Normal Heart



- Modest size ratio of nucleus and cytoplasm.
- Delicate interstitial supporting stroma
- Rich vascularity.

Hypertrophied Heart

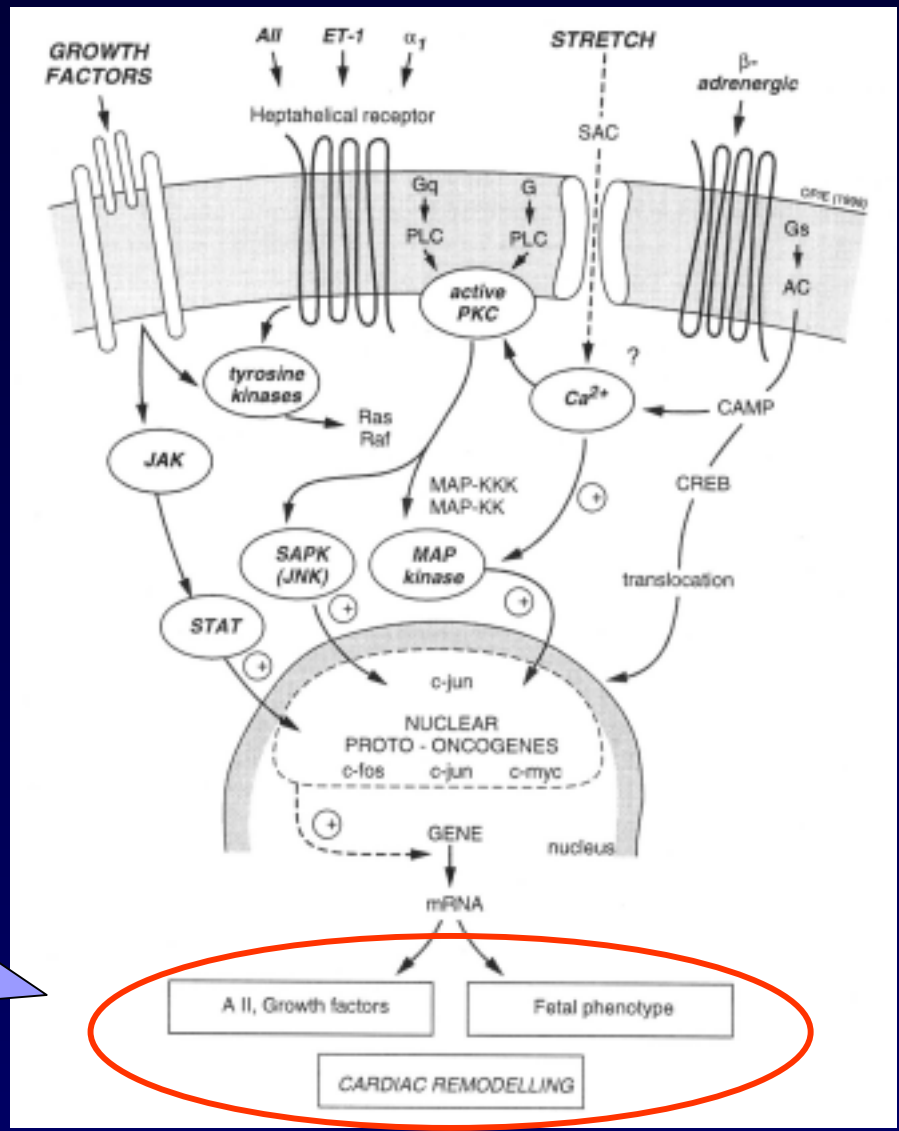


- Enlarged myocardial cells
- Large hyperchromatic nuclei
- Increased amount of interstitial tissue
- Relatively scanty vascularity

Molecular Basis of Cardiac Hypertrophy

Outline of Alterations of Protein Synthesis to Chronic Load

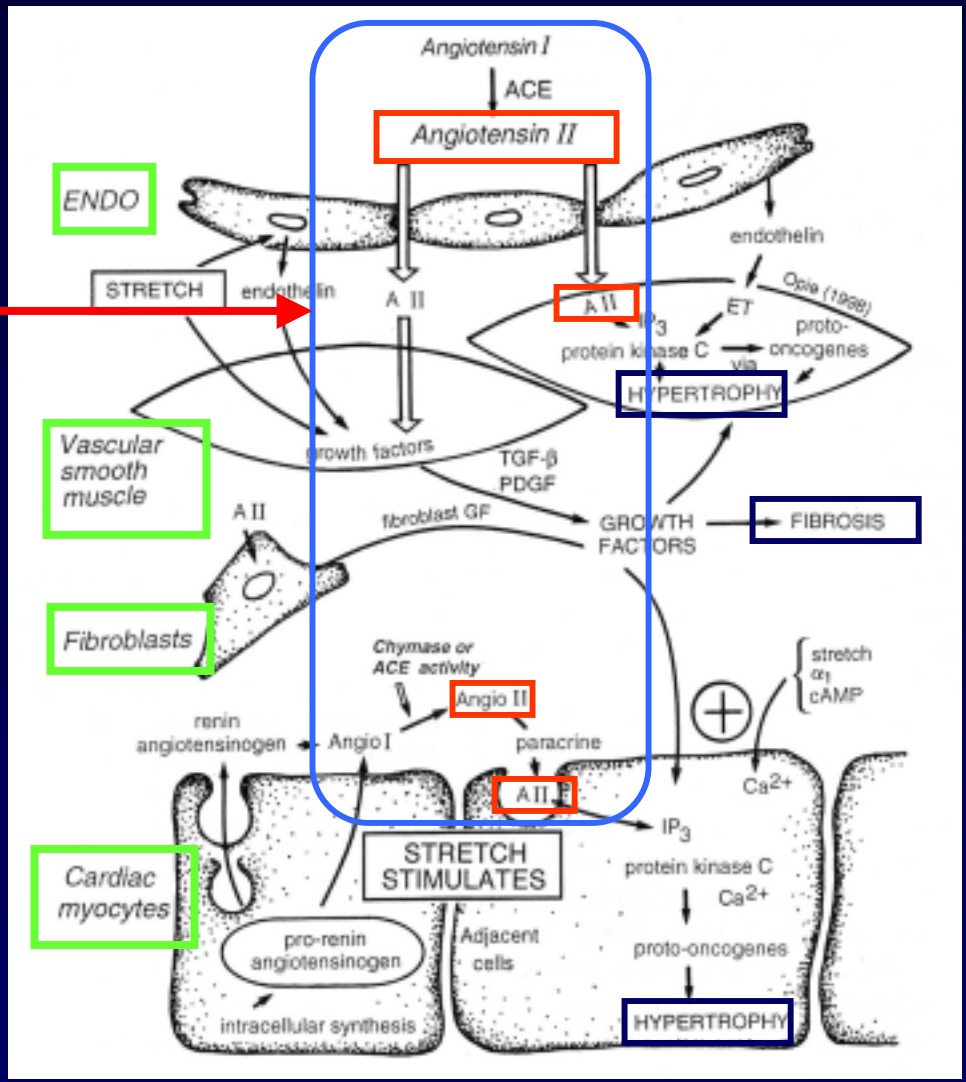
1) Stretch activated ion channels
   - PKC via phospholipase C
   - → stimulate proto-oncogenes
   - Tyrosine kinase
   - Ca influx
2) Agonist for heptahellical receptor
   - ANG II
   - α1-catecholamines
   - Eendothelin-1
3) Growth factors
   - IGF
   - TGF



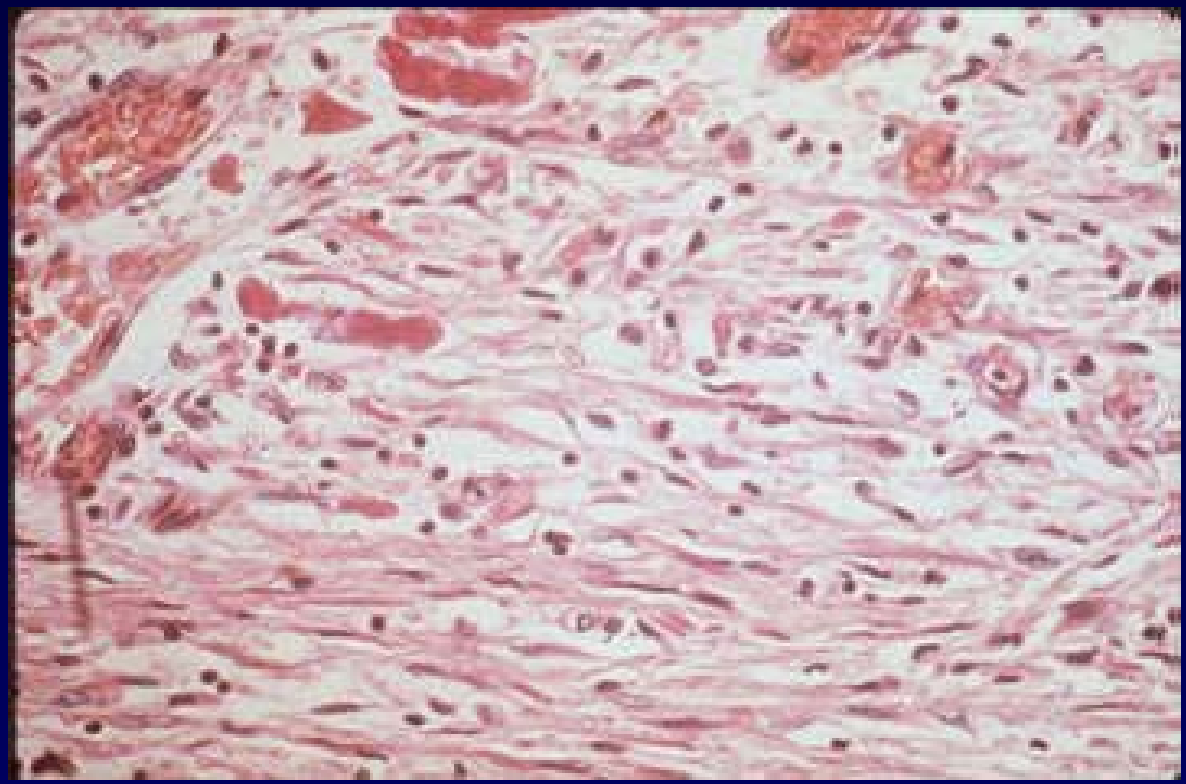
Molecular Basis of Cardiac Hypertrophy

Stretch and Cardiac Growth (Role of Angiotensin II & Endothelin)

RAAS

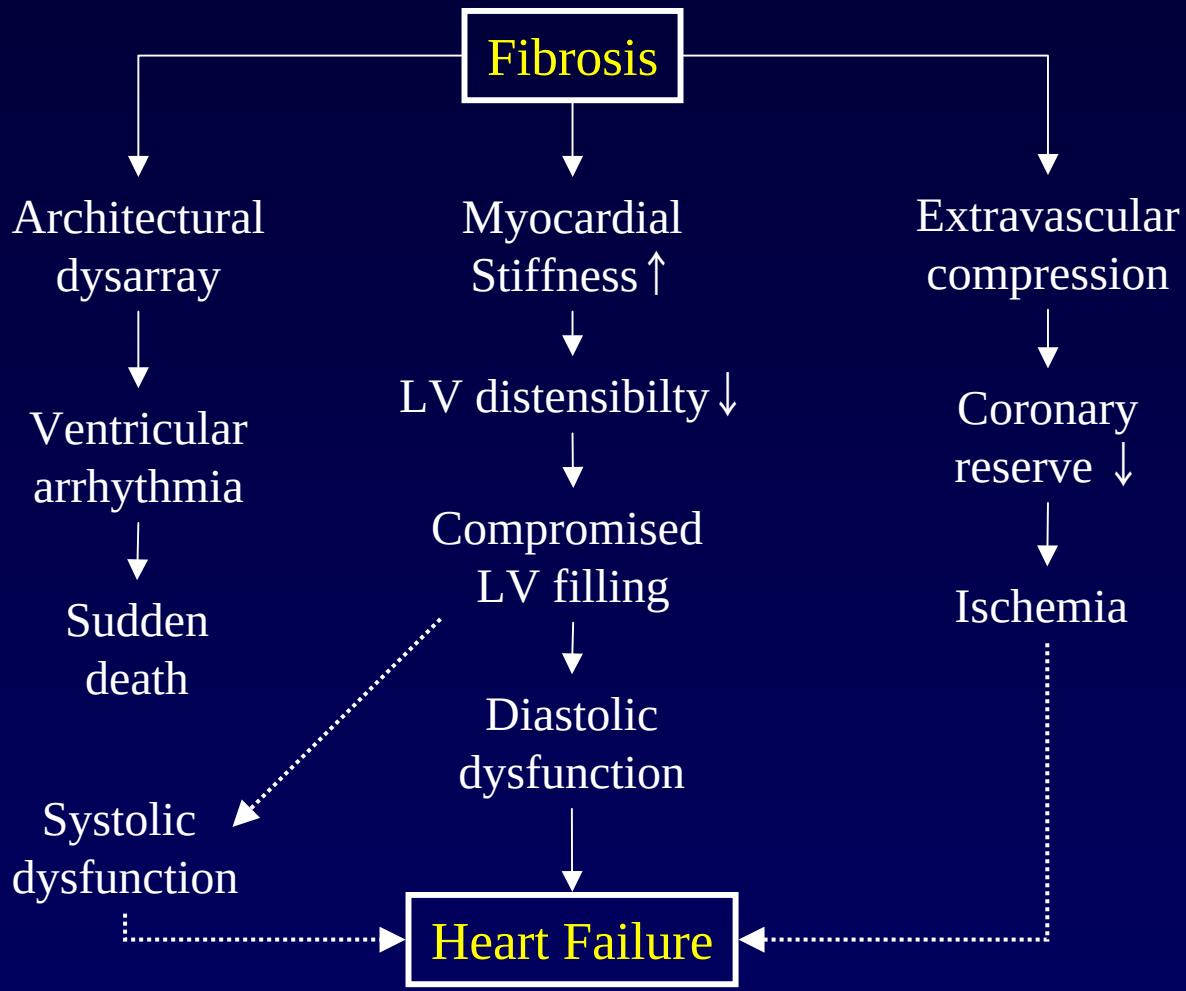


Interstitium

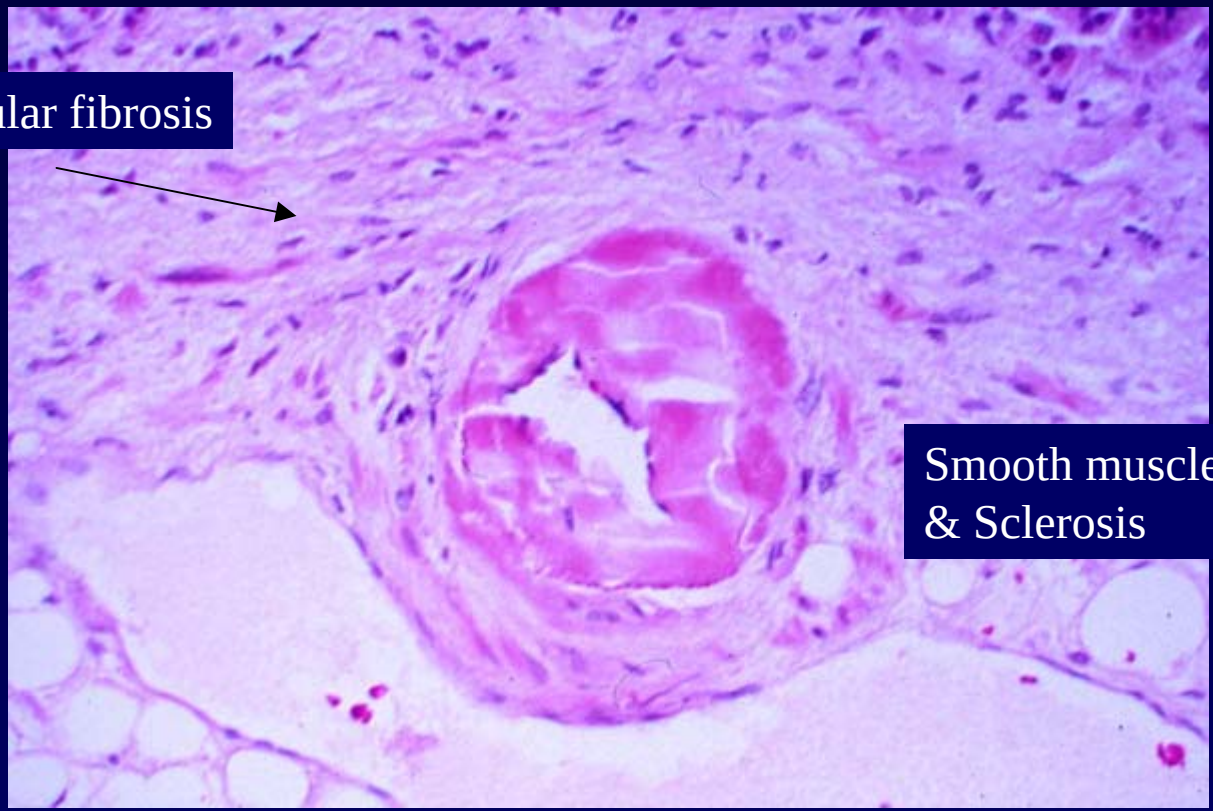


Interstitium

Detremental Consequence of Myocardial Fibrosis

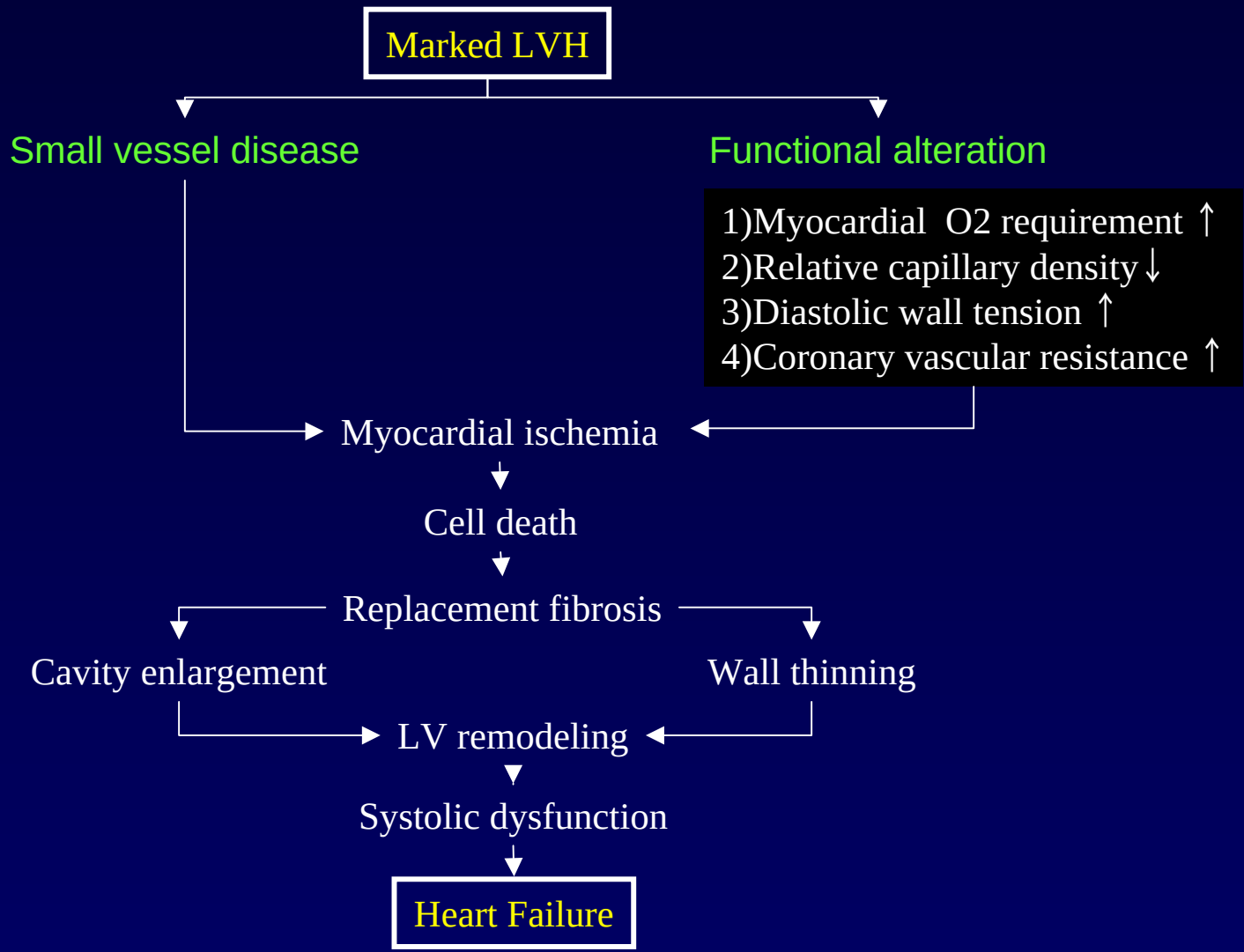


Vasculature



Vasculature

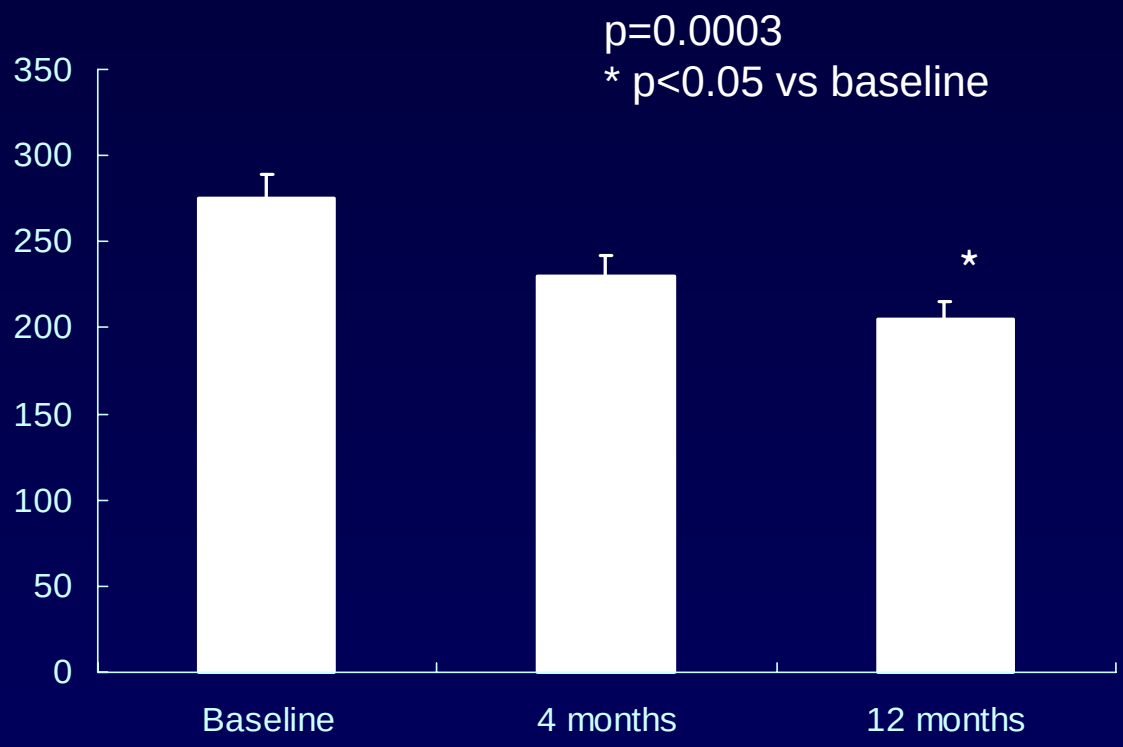
Microangiopathy in Hypertensive Hypertrophy



Regression of LVH

Effect of Carvedilol on LV Mass

Lowes BD. Am J Cardiol 1999



Regression of LVH

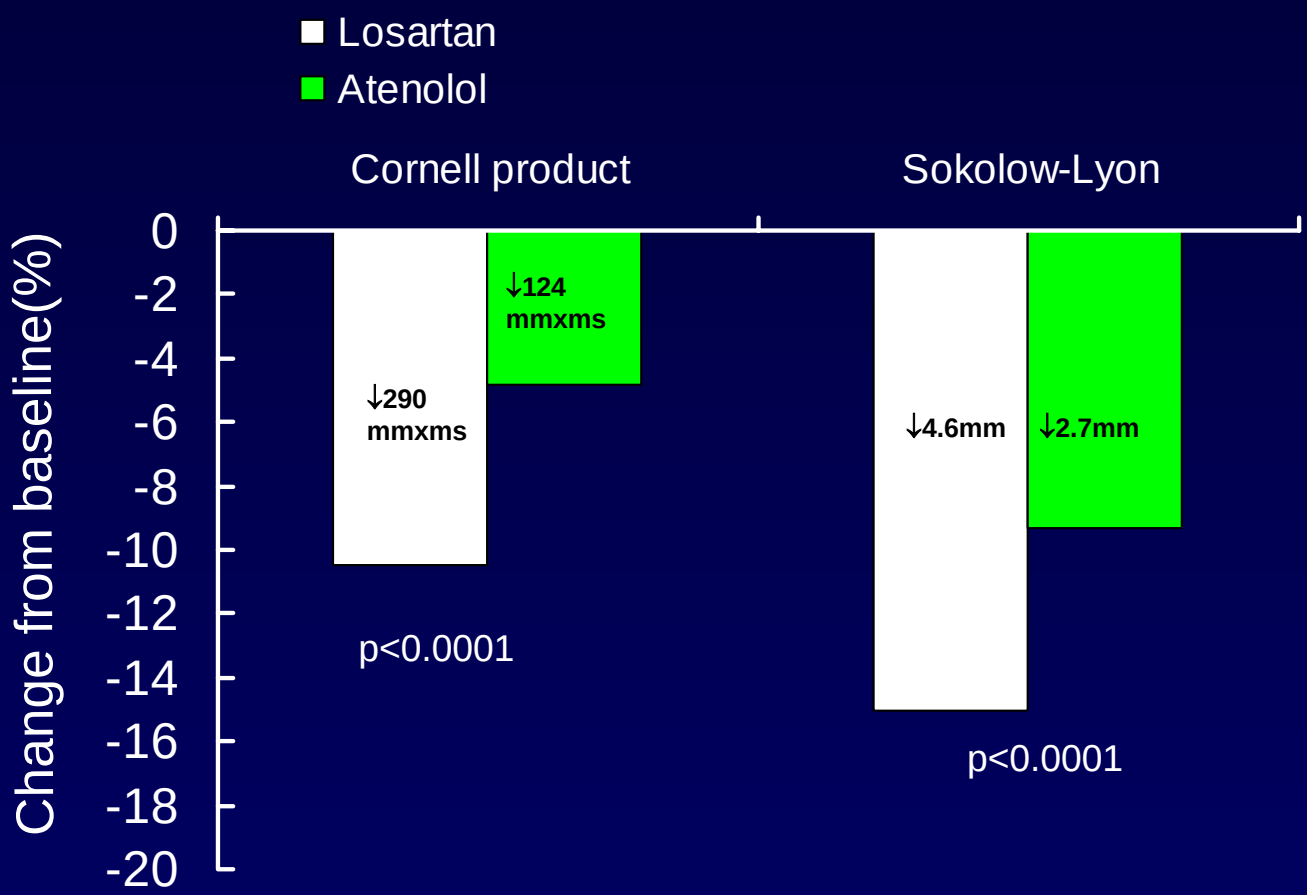
Comparisons of anti-adrenergic properities of β-blockers & ACE inhibitors

	Metoprolol	Bucindolol	Carvedilol	ACEIs
β1-blockade	++	++	++	0
β2-blockade	0	+	+	0
α1-blockade	0	0	+	0
Down regulates β1-receptors	-	+	+	-
Cardiac NE↓	0	+	+	+
Systemic NE ↓	0	+	0	+
ANG II ↓	+	+	+	+
Total score	+3	+7	+7	+3

LIFE

Dahlöf B et al *Lancet* 2002

Regression of LVH



Symptomatic LV dysfunction (Stage C)
systolic / diastolic dysfunction

Stage	Description	Examples
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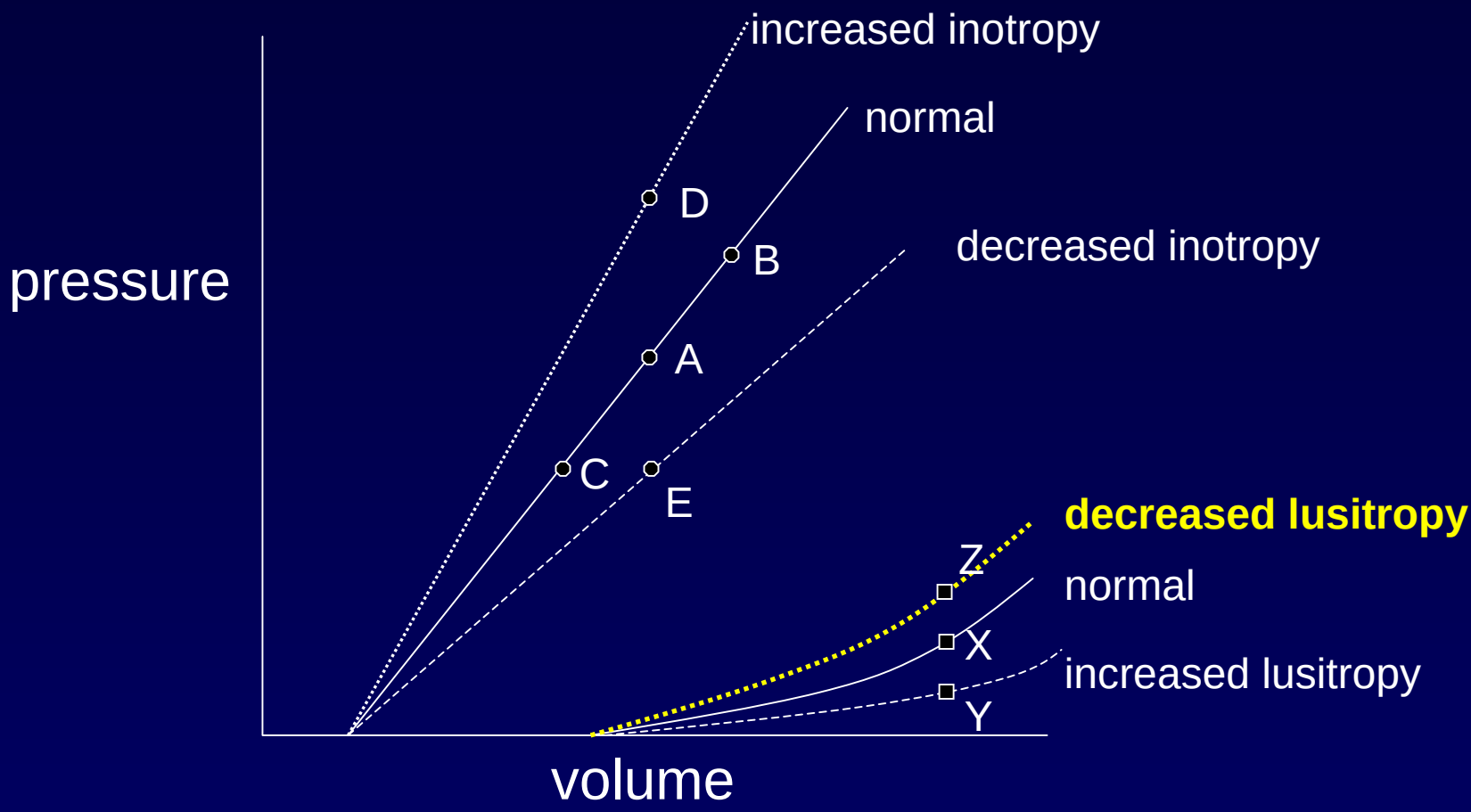
Diastolic Dysfunction

Prerequisites

- Diastolic heart failure (property of myocardium?)
- HF with preserved systolic function (composite mechanism?)

Diastolic dysfunction

Starling's curves & filling curves



ORIGINAL ARTICLE

Diastolic Heart Failure — Abnormalities in Active Relaxation and Passive Stiffness of the Left Ventricle

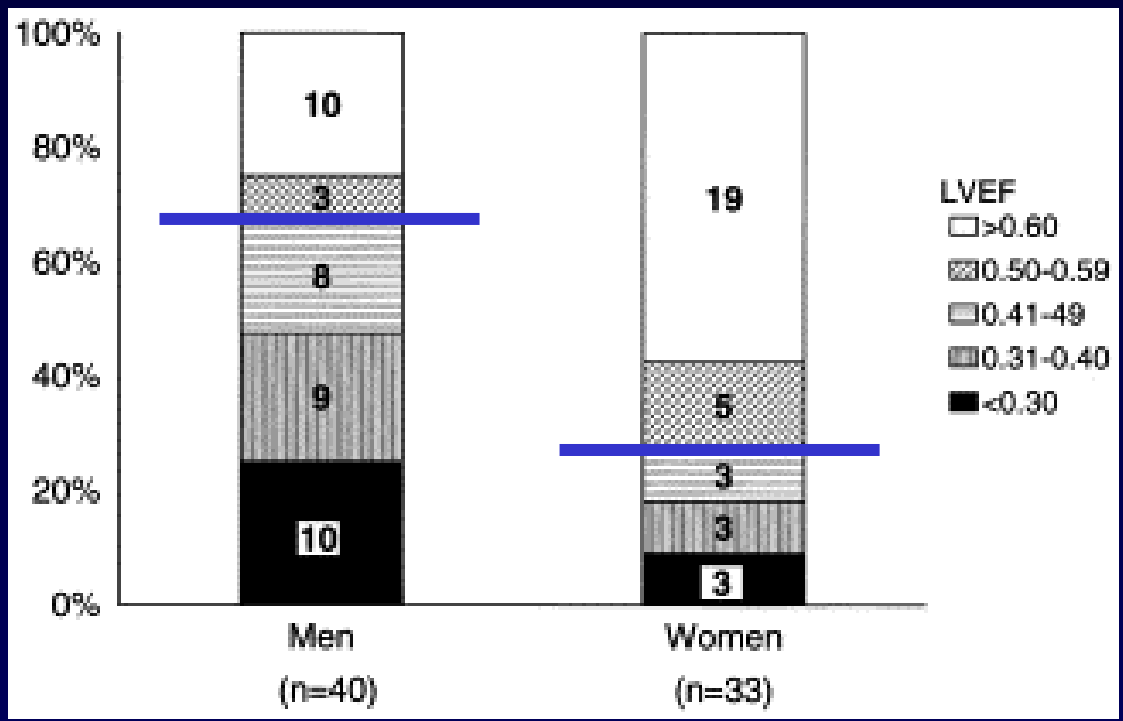
Michael R. Zile, M.D., Catalin F. Baicu, Ph.D., and William H. Gaasch, M.D.

A problem of myocardium?

CHF in subjects with normal vs reduced LVEF

Framingham Heart Study

Vasan RS et al. JACC 1999;33:1948



37/73 (51%) had normal LVEF

33 of women 9(27%); 40 of men 27(67.5%) had reduced LVEF

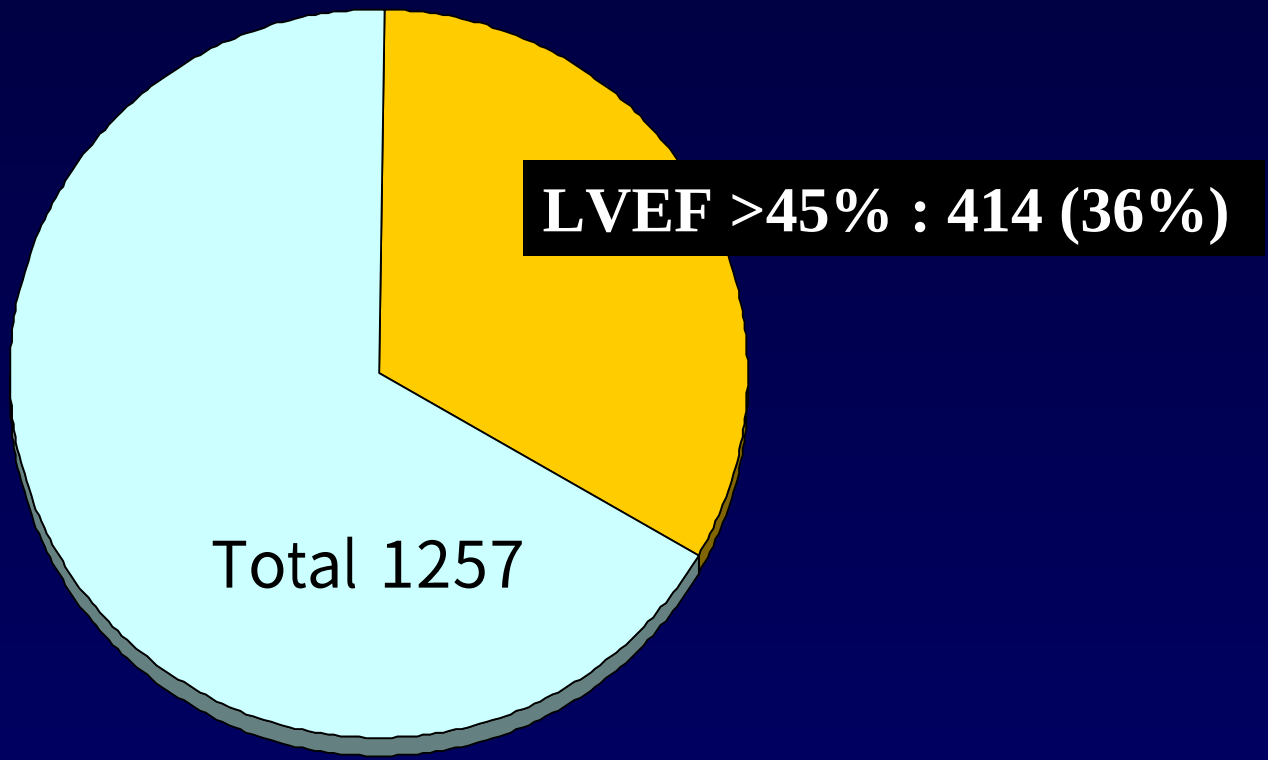
Summary of epidemiology and outcomes in patients with CHF and preserved systolic function

Dauterman KW, Am H J 1998;135:S310

Study	Setting	Criteria of LV function	Number	prevalence	Mortality
Gardin	Community	Echo, unclear	79	47%	
McDermoff	Ref Hosp	Echo, LVEF>50%	298	31%	
Madsen	Comm Hosp	Echo, LVEF>53%	190	14%	
Takarada	Ref Hosp	Echo, LVFS >30%	172	24%	
Ghali	Ref Hosp	Echo, LVFS >24%	78	28%	
McDermoff	Ref Hosp	Echo, LVEF >50%	413	28%	35%/69%
Dauterman	Random	Echo, RI, LVFS >40%	498	30%	
Vasan	Community	Echo, LVEF > 50%	77	51%	17.9/8.9/3.7
Cohn	Ref Hosp	Echo or CXR, CT<0.55 or LVEF >45%	623	13.3%	19%/8%
Setaro	Ref Hosp	RI, LVEF > 45%	52		56% at 7yrs
Gahli	Ref Hosp	Echo, LVFS > 24%	78		64/36%
Kinney	Ref Hosp	Echo, LVFS > 17%	91		11mo/26mo
Warnowicz	Ref Hosp	RI, LVEF > 45%	39		30/25%
Judge	CABG	Echo, LVEF > 45%	284		

Survival Rate & Prognostic Factors of Patients with Heart Failure in Korea
Multicenter Survey

HF with Preserved LV systolic function



Diastolic heart failure:
Effects of age on prevalence and prognosis

parameter	<50	50-70	>70
prevalence	15	33	50
Mortality	15	33	50
Morbidity	25	50	50

Data from 14 epidemiologic study
Mortality: 5-yr mortality rate
Morbidity: 1-yr rate of admission

Characteristics of HF with preserved LV systolic function

Older age and female

Systolic hypertension

Exacerbated hypetensive response

Coronary artery disease

Diabetes

Abrupt pulmonary edema

Ventricular stiffening

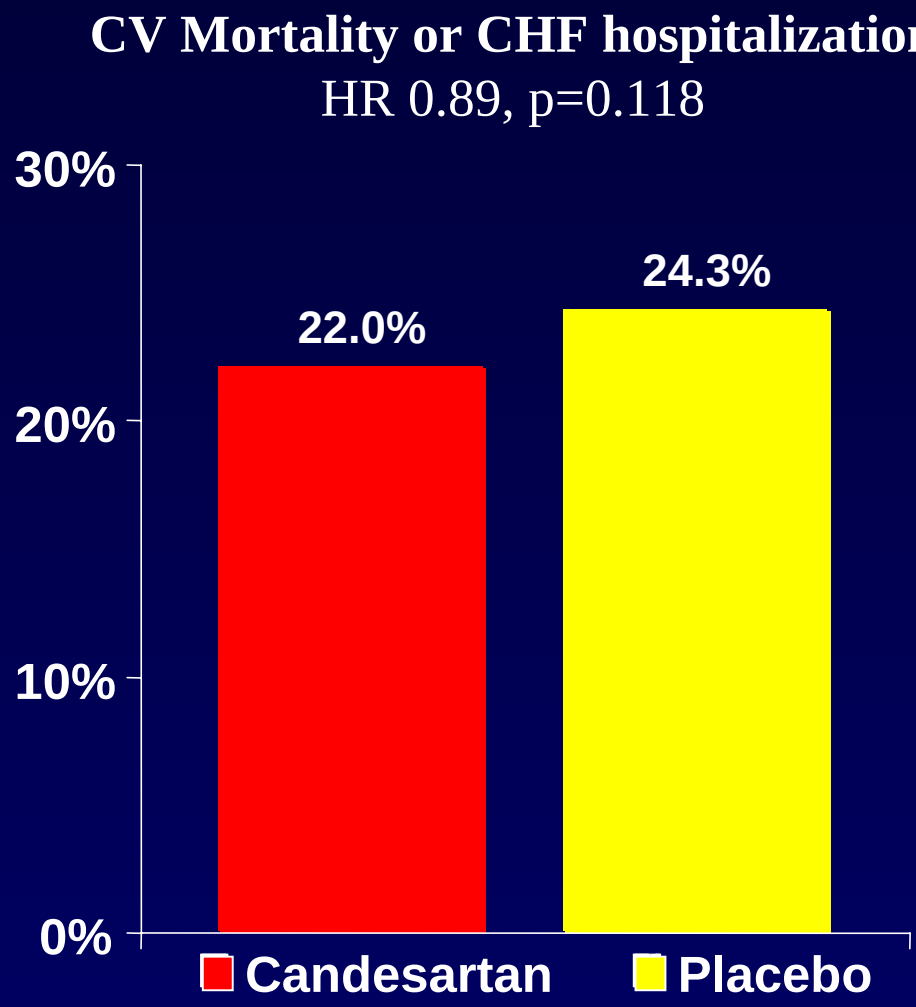
Arterial stiffening

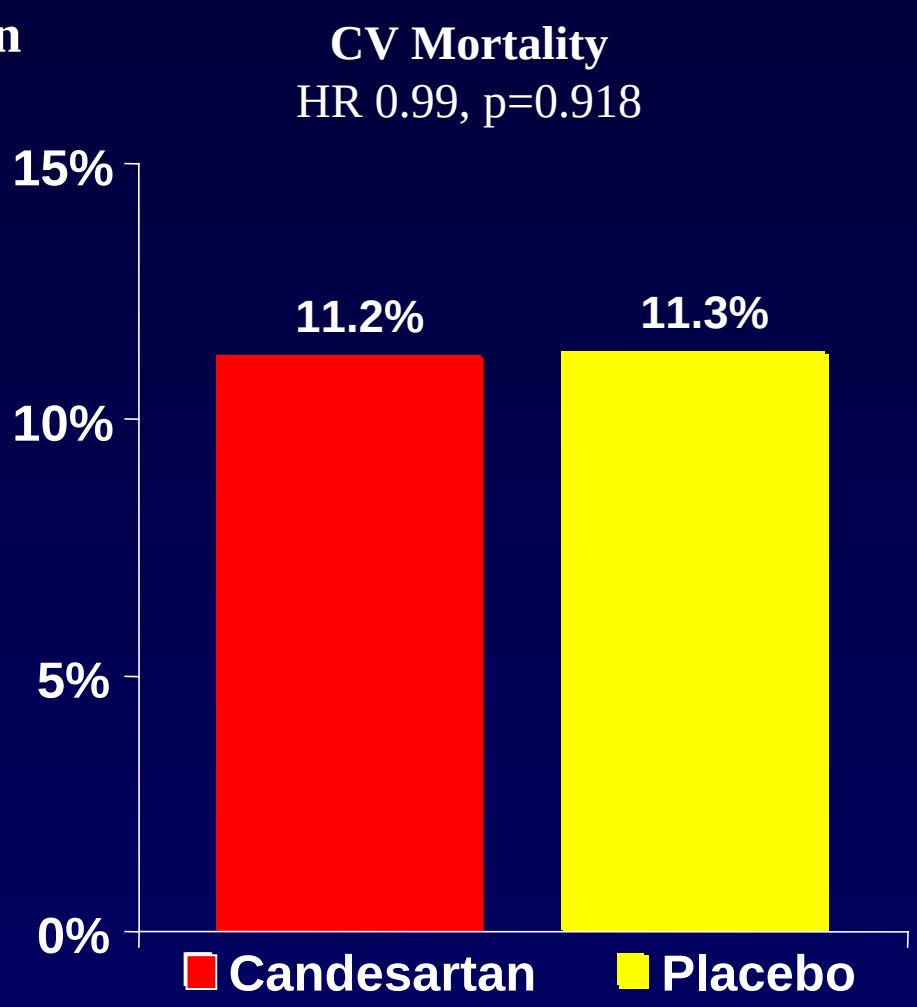
Impaired diastolic properties (-dp/dt..)

Treatment of Diastolic Heart Failure

- Control of blood pressure
- Prevention and control of tachycardia
- Maintain atrial contraction
- Control of volume
- Control of ischemia

CHARM Preserved Trial



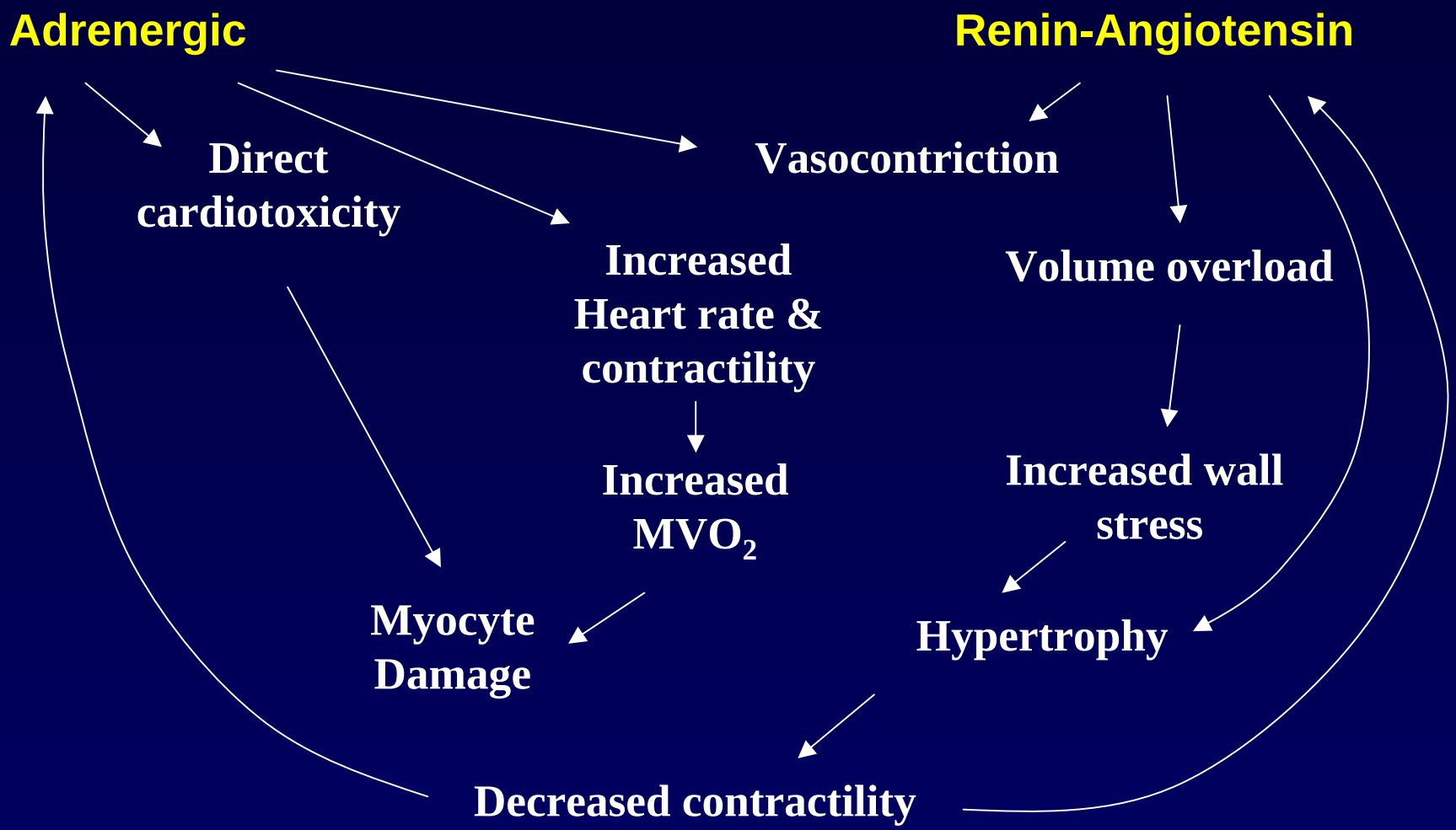


Ongoing Trials in Diastolic Heart Failure/diastolic dysfunction

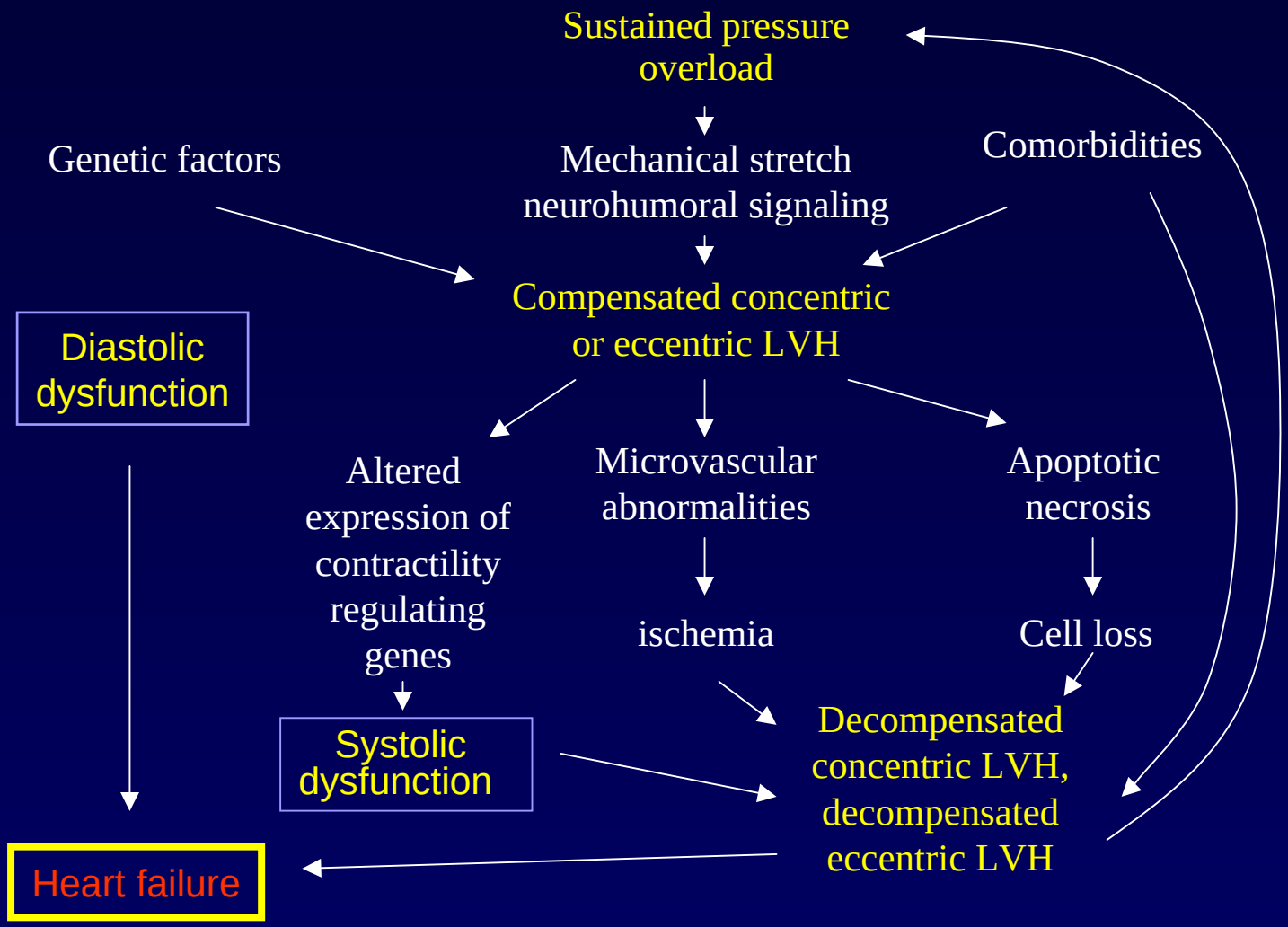
Trial	Agent	Sample, Duration	Inclusion Criteria	Principal Outcomes
SWEDIC	Carvedilol vs. Placebo	140,9 mths	DD by doppler	Regression of DD
Wake-Forest	Losartan vs. HCTZ	NA, 6 mths.	Exercise induced HTN and DD	Exercise tolerance , VO2 max
MCC-135	MCC-135 (SR Ca2+ uptake)	NA, 6 mths	CHF, EF<40%	Exercise tolerance, VO2 max.
PEP-CHF	Perindopril vs. Placebo	1000, 1.5 yrs	CHF, EF>40%, WMI >1.5	Death or hospitalization for HF.
SENIORS (diastolic subset)	Nebivolol vs. Placebo	NA	EF>35%	Death or hospitalization for HF.
I-PRESERVE	Irbesartan vs. Placebo	3600, 2 years	CHF, EF >45%	Death or hospitalization for HF.
Hong Kong Trial	Irbesartan vs. Ramipril vs. Placebo	450, 1 year	CHF, Doppler criteria	Death or hospitalization for HF; quality of life; 6-min walk test.

Systolic Dysfunction

HF Compensatory Mechanisms



Development of HF in Hypertensive Patients



ACE inhibitors
-Comparison of large scaled ACE inhibitor trials-

Trial	Agent	Subjects	Results
CONSENSUS (n=253,1987)	Enalapril vs placebo	NYHA IV	Mortality (36% vs 52%)
SOLVD-T (n=2569,1991)	Enalapril vs placebo	NYHA II-III	26% mortality ↓
SOLVD-P (n=4228, 1992)	Enalapril vs placebo	NYHA I-II	20% mortality ↓
SAVE (n=2231,1992)	Csptopril vs placebo	AMI	21% mortality ↓
AIRE (n=2006,1993)	Ramipril vs placebo	Post MI	25% mortality ↓

Muticenter Placebo-Controlled Trials with Beta-blockers in Chronic Heart Failure

Trial	Agent	Primary End point	Achieved End Point	Other Outcomes
MDC	Metoprolol	M+M	P=0.058	Decreased hsp
Bucindolol MC	Bucindolol	EF dose response	Yes	Prevention of LVEF ↓
CIBIS-1	Bisoprolol	Mortality	No	IDC increased mortaility
CIBIS-2	Bisoprolol	Mortality	Yes	Decreased hsp
MERIT-HF	Metoprolol*	Mortality	Yes	Decreased hsp

M+M: mortaliry and morbidity, hsp: hospitalization
EF: ejection fraction
* Metoprolol succinate(slow releasing form)

Muticenter Placebo-Controlled Trials with Carvedilol in Chronic Heart Failure

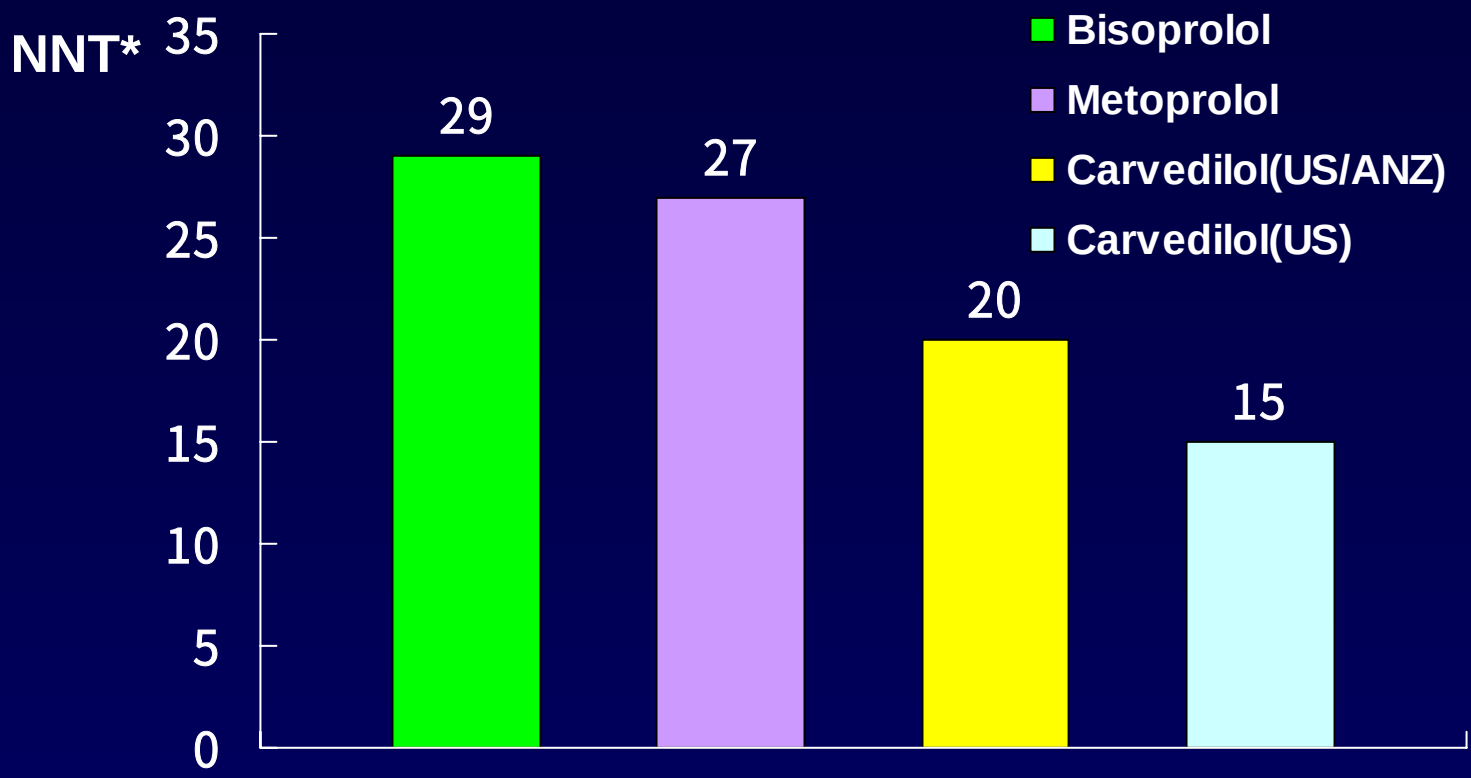
Trial	Primary End point	Achieved End Point	Other Outcomes
MOCHA	Submax Ex	No	Decreased mortality and hsp
PRECISE	Submax Ex	No	Decreased hsp and Sx
Mild carvedilol	HF progression	Yes	Decreased hsp
Severe carvedilol	QOL	No	Decreased hsp
ANZ carvedilol-1	Submax Ex	No	Decreased remodelling
ANZ carvedilol-2	M+M	Yes	Decreased hsp

Submax Ex: Submaxiam exercise, hsp: hospitalization, HF: heart failure
QOL: quality of life, M+M: mortaliry and morbidity

Beta-blockers in heart failure
-Annualized mortality rate from major clinical trials-

	Placebo mortality rate (annualized %)	β-blocker mortality rate (annualized %)
US carvedilol	15.0*	6.0*
CIBIS-2	13.2	8.8
MERIT-HF	11.0	7.2

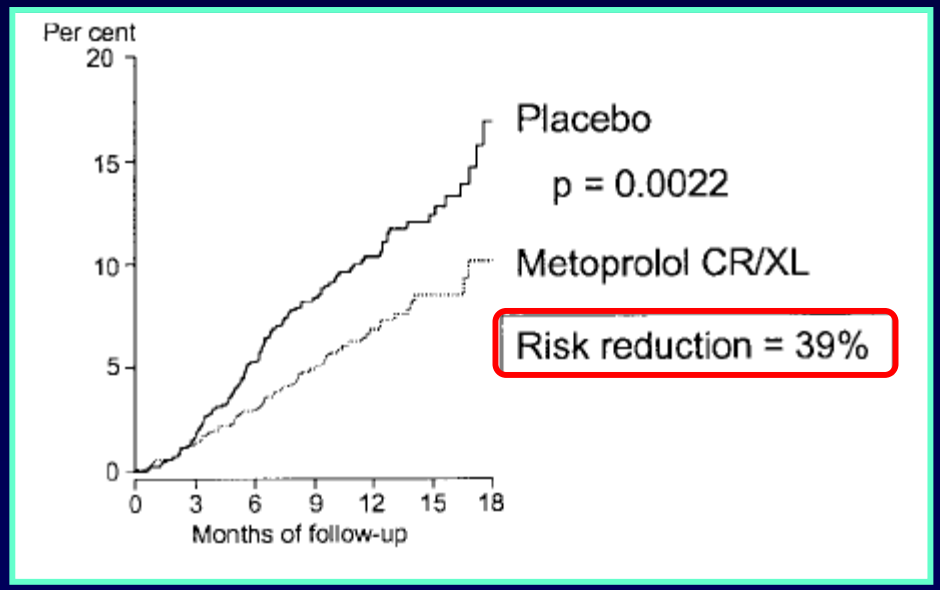
Anti-adrenergic therapy in heart failure
Number needed to treat for one year to save one life*



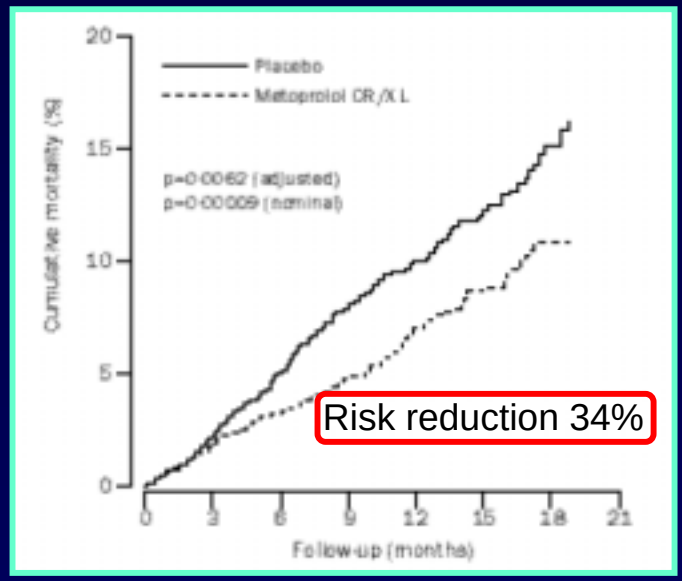
Metoprolol CR/XL on HF with Hypertension

Herlitz J et al. J Card Fail 2002

Subgroup of HT



Overall in MERIT-HF



Recovery pattern and term of reversal of left ventricular remodeling in patients with congestive heart failure

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Wo Seok Cheon,MD, Eung Joo Kim,MD, Yung Lee,MD.
Department of cardiovascular medicine,
Hallym Univ. Hospital

Results Recovery Pattern

	I-CMP (n=18)	HT-CMP (n=29)	T-CMP (n=24)	D-CMP (N=11)
Age (yr)	68±5.3	58 ± 13.6	66 ± 10.3	51 ± 15.8
Male (%)	11.1	75.9	54.2	63.6
LVEF at Adm(%)	22.8 ±6.6	22.8 ± 6.1	21.9 ± 6.0	19 ± 6.3
Partial recovery	12 (67%)	16 (55%)	9 (38%)	8 (73%)
Complete recovery	6 (33%)	13 (45%)	15 (62%)	3 (27%)

* LVER >40% and LVED >54mm, ** LVEF >50% and LVED ≤ 53mm

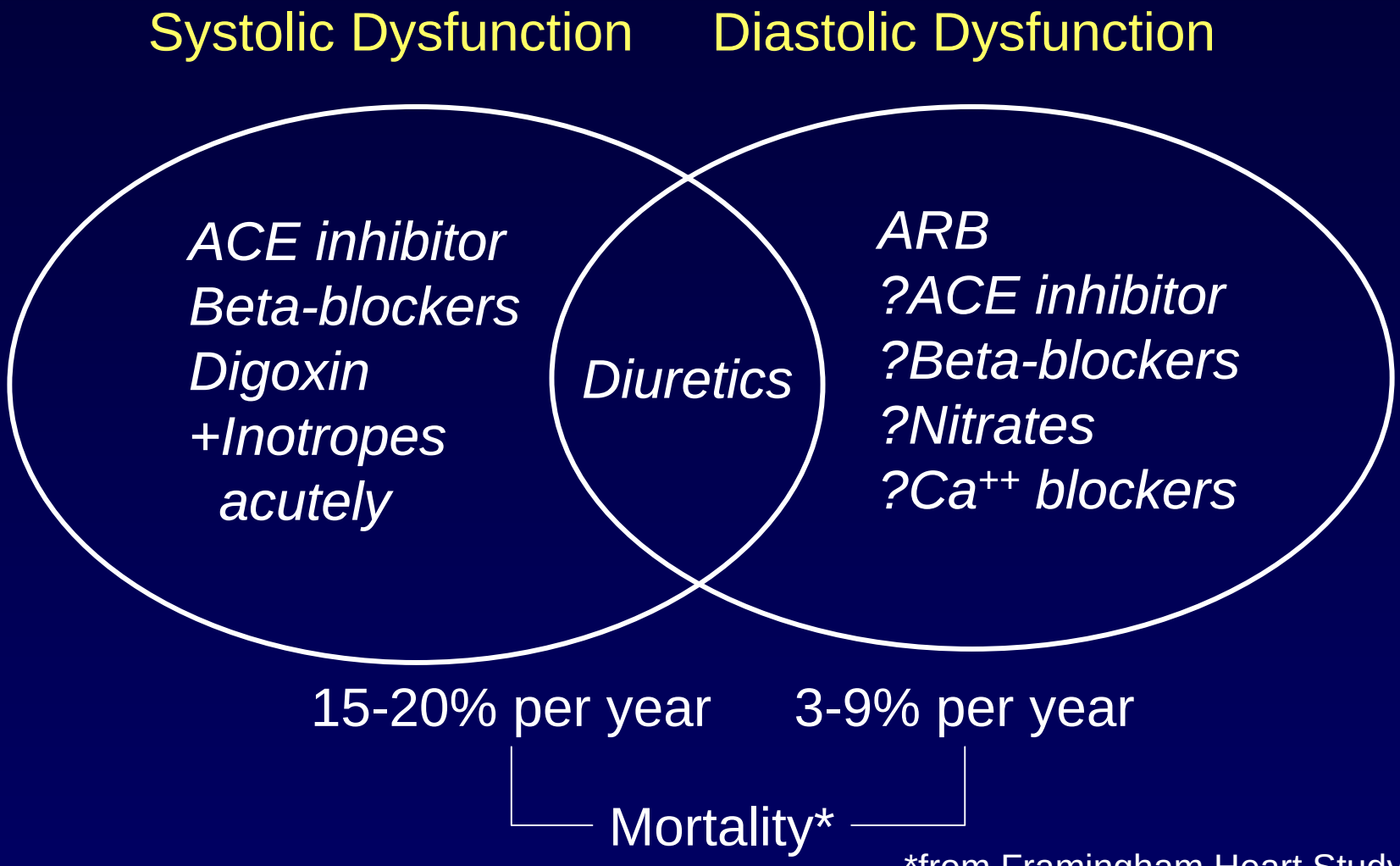
Results Recovery Term

	I-CMP (n=18)	HT-CMP (n=29)	T-CMP (n=24)	D-CMP (N=11)
<1 month	4(22%)	8(28%)	18(75%)	0
1-3months	7(39%)	9(31%)	5(21%)	0
3-6months	5(28%)	9(31%)	1(4%)	2(19%)
6-12months	2 (11%)	3 (10%)	0	9 (81%)

Summary
Management of Hypertensive Heart Failure

- Control of blood pressure
- Modification of risk factors for CVD
- Concern for diastolic heart failure
- Aggressive medical treatment
- Regarding as reversible condition

Drug therapy of diastolic and systolic dysfunction



*from Framingham Heart Study

Thanks for your attention !