

Management of Stage B Heart Failure

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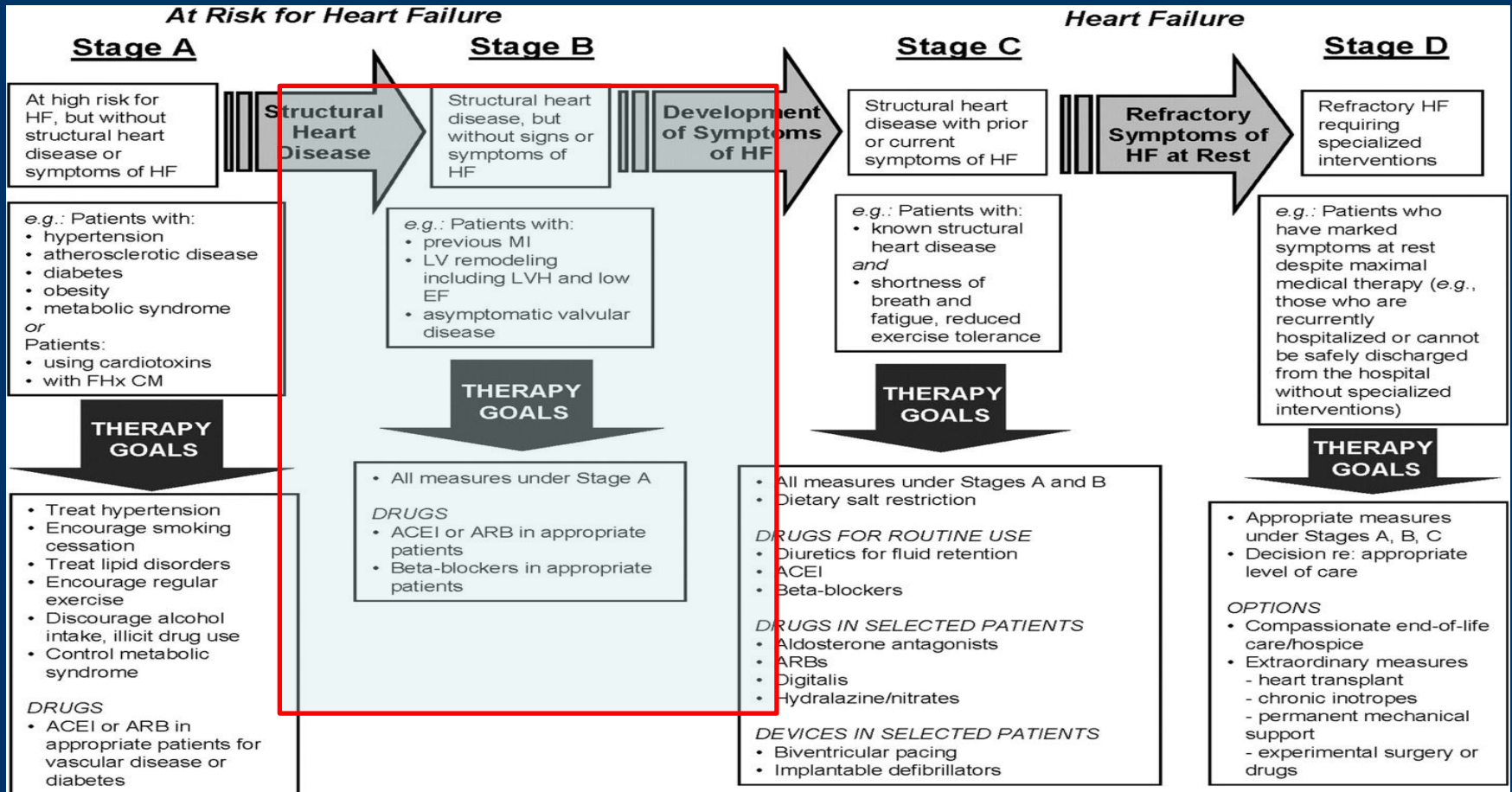
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Focused on ...

- **Symptom**
- **ASLVSD, ASLVDD**
- **LVH**
- **HF progression and Morbidities**
- **Medical Treatment**

HF stages



STAGE B CLINICAL DEFINITIONS

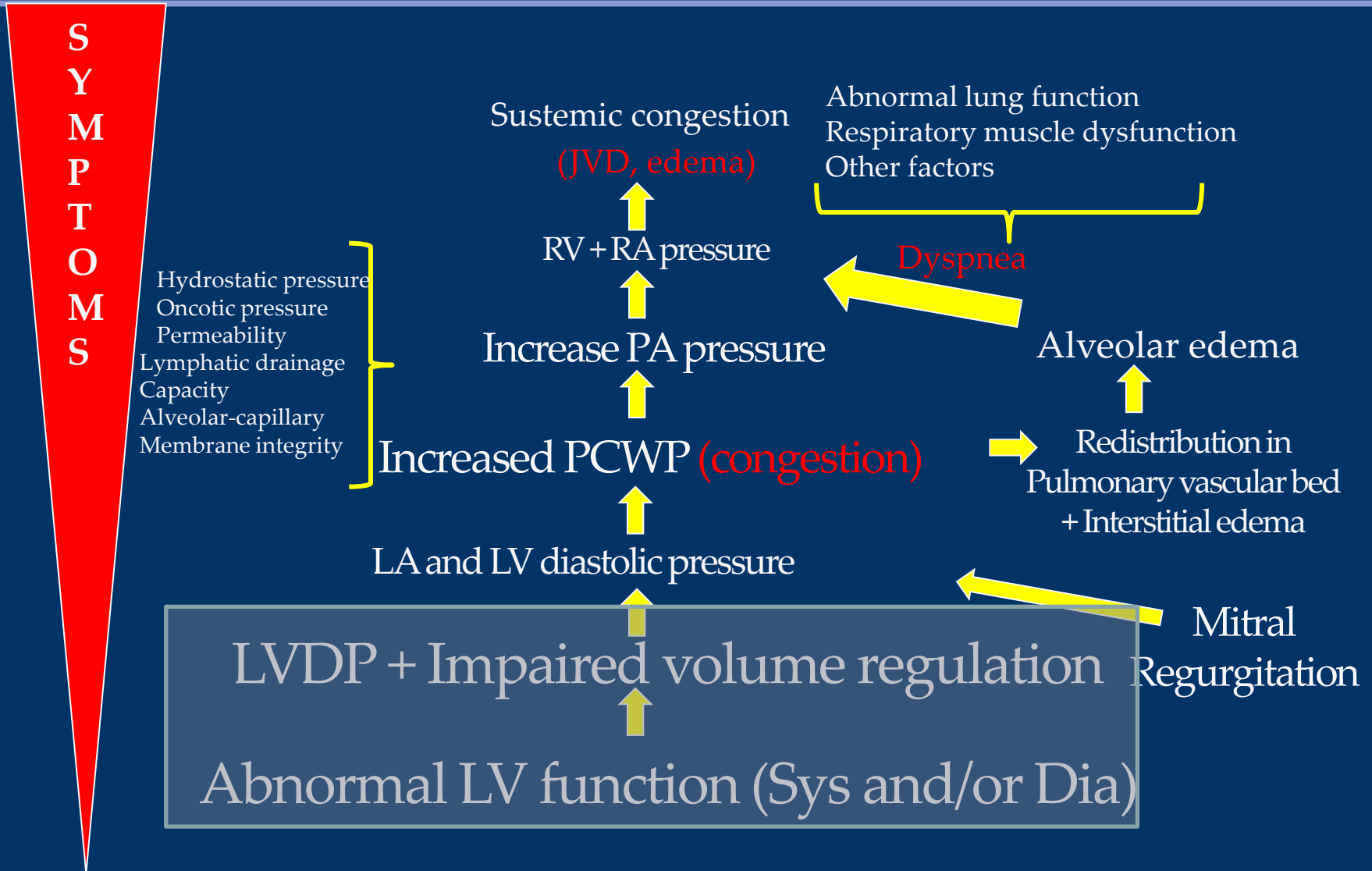
AHA/ACC Guidelines

- Patients with structural heart disease that is strongly associated with the development of heart failure (HF) but without HF signs or symptoms.

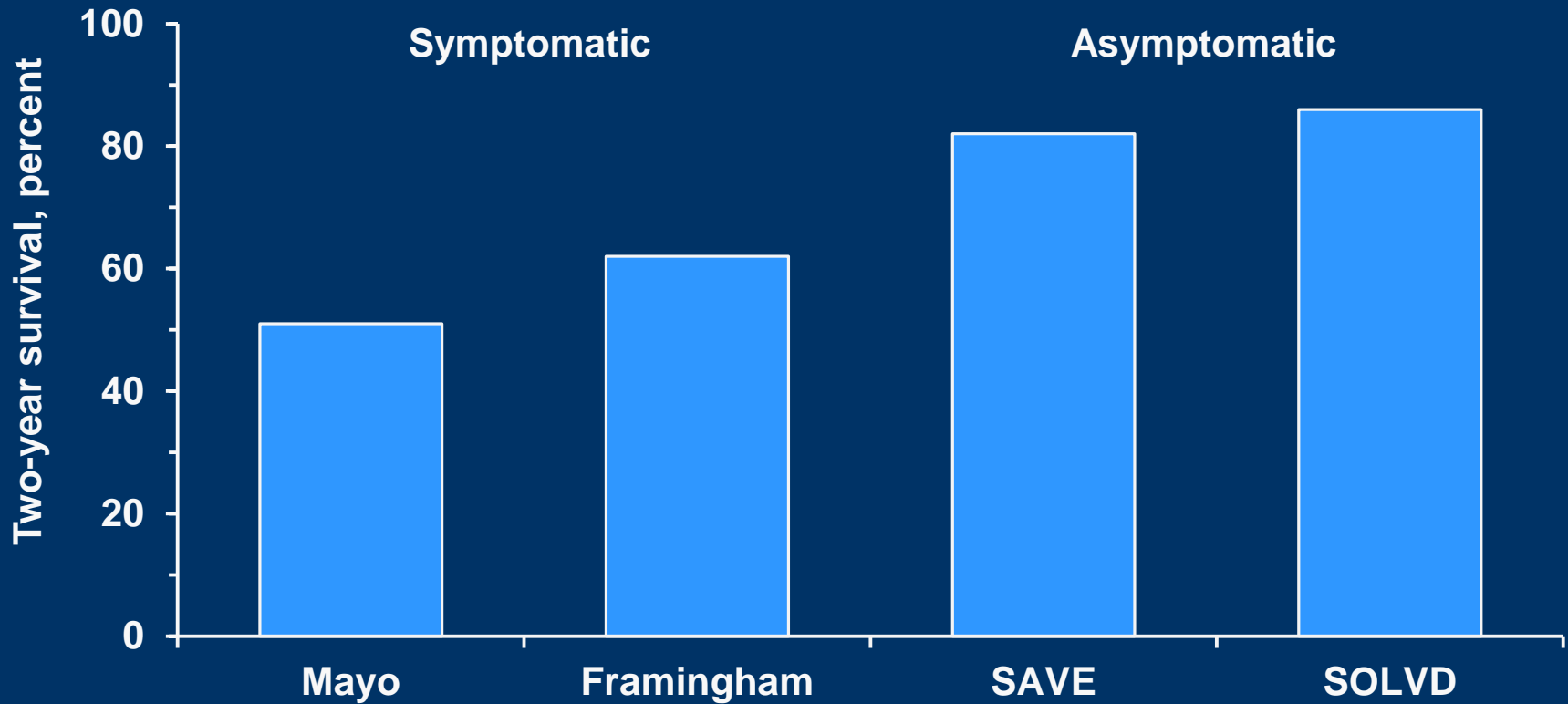
Mayo Clinic

- Previous myocardial infarction; left ventricular hypertrophy by echocardiogram or ECG; left ventricular dilatation or hypocontractility; moderate to severe valvular heart disease.
- Asymptomatic physical capacity of > 7 mets.

Symptoms: The Tip of the Congestion Iceberg in Heart Failure



Survival in HF and Sx



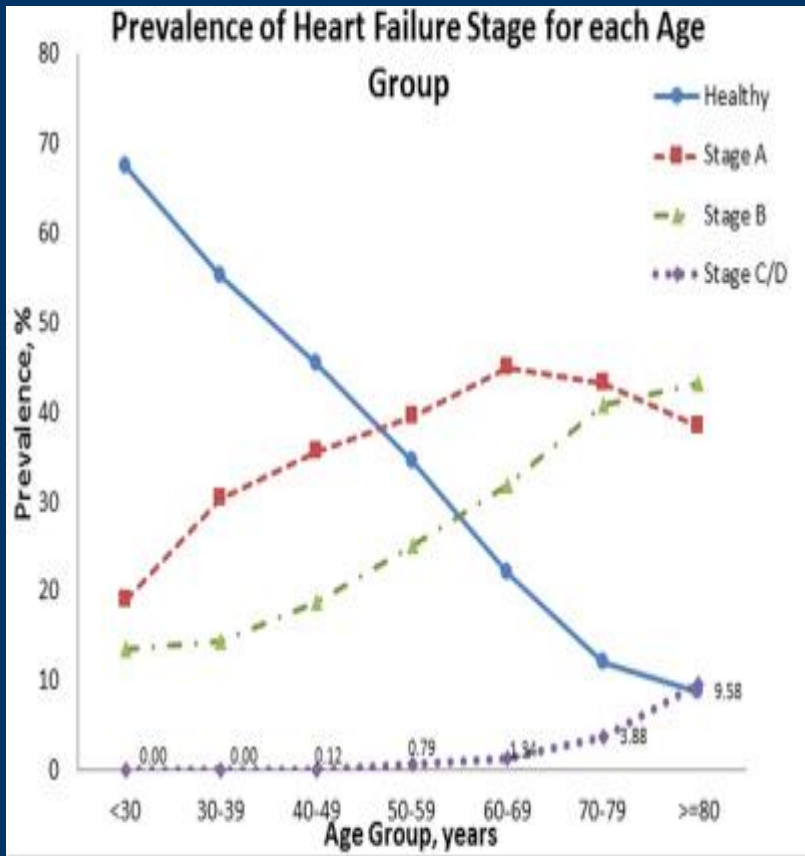
Rodeheffer RJ, Jacobsen SJ, Gersh BJ, et al. *Mayo Clinic Proc* 1993; 68:1143; Ho, KK, Anderson, KM, Kannel, WB, et al, *Circulation* 1993; 88:107; Pfeffer, MA, Braunwald, E, Moye, LA, et al, *N Engl J Med* 1992; 327:669; The SOLVD Investigators, *N Engl J Med* 1992; 327:685.

Focused on ...

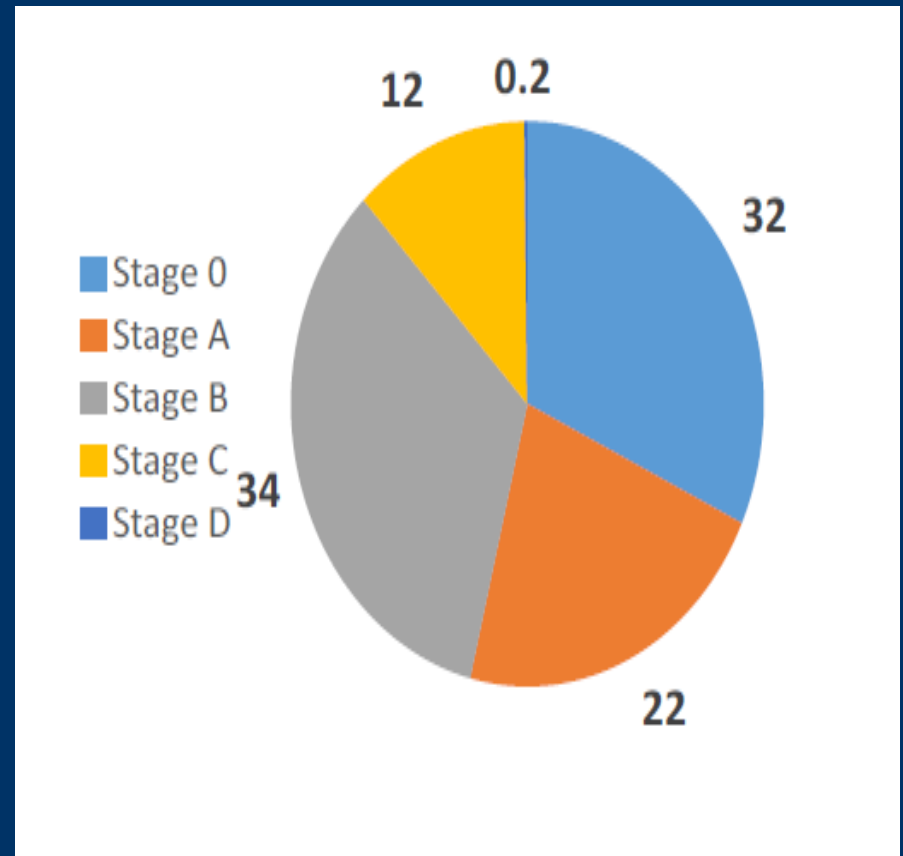
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Prevalence of Stage B HF

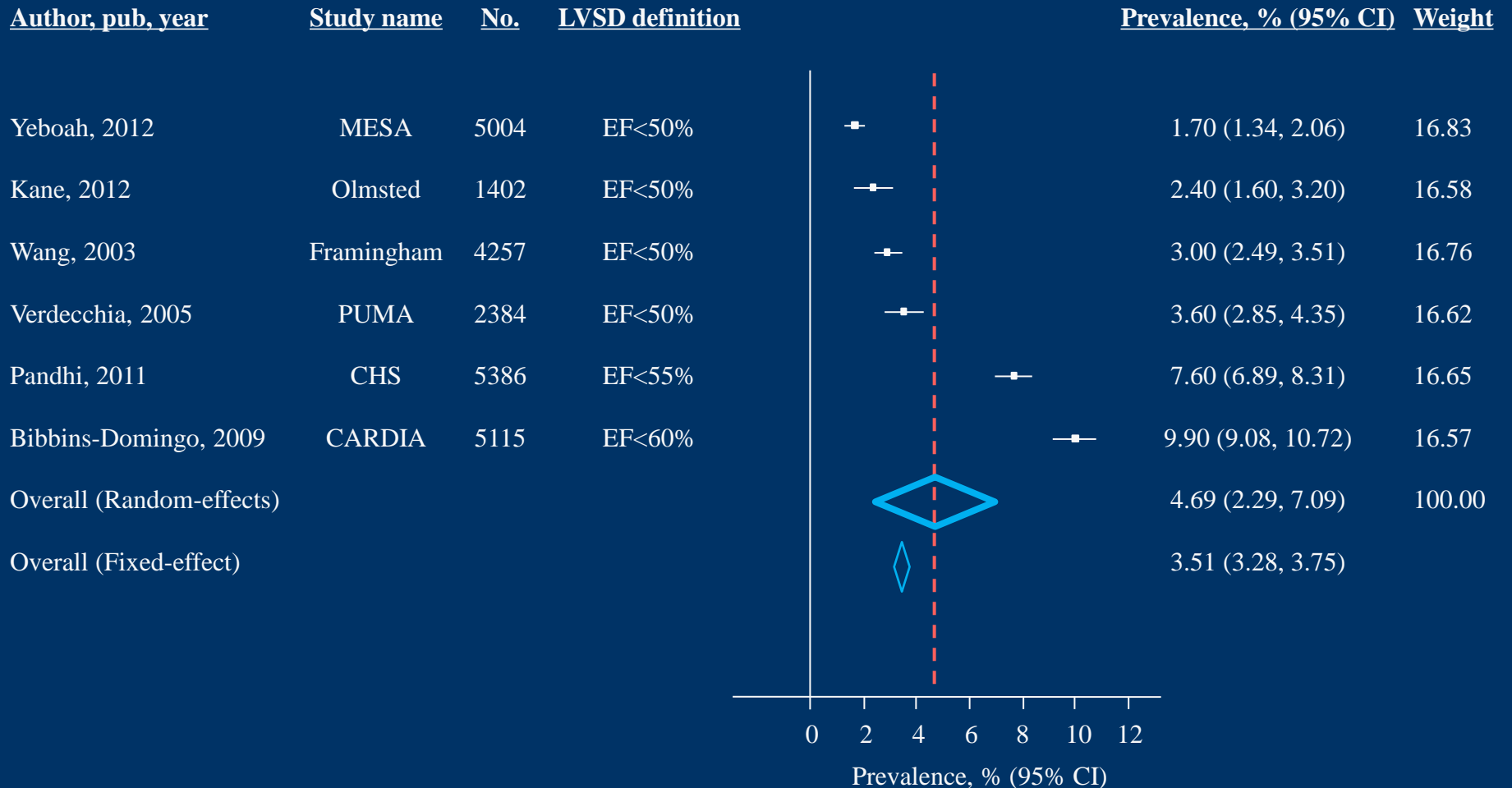
Framingham Study



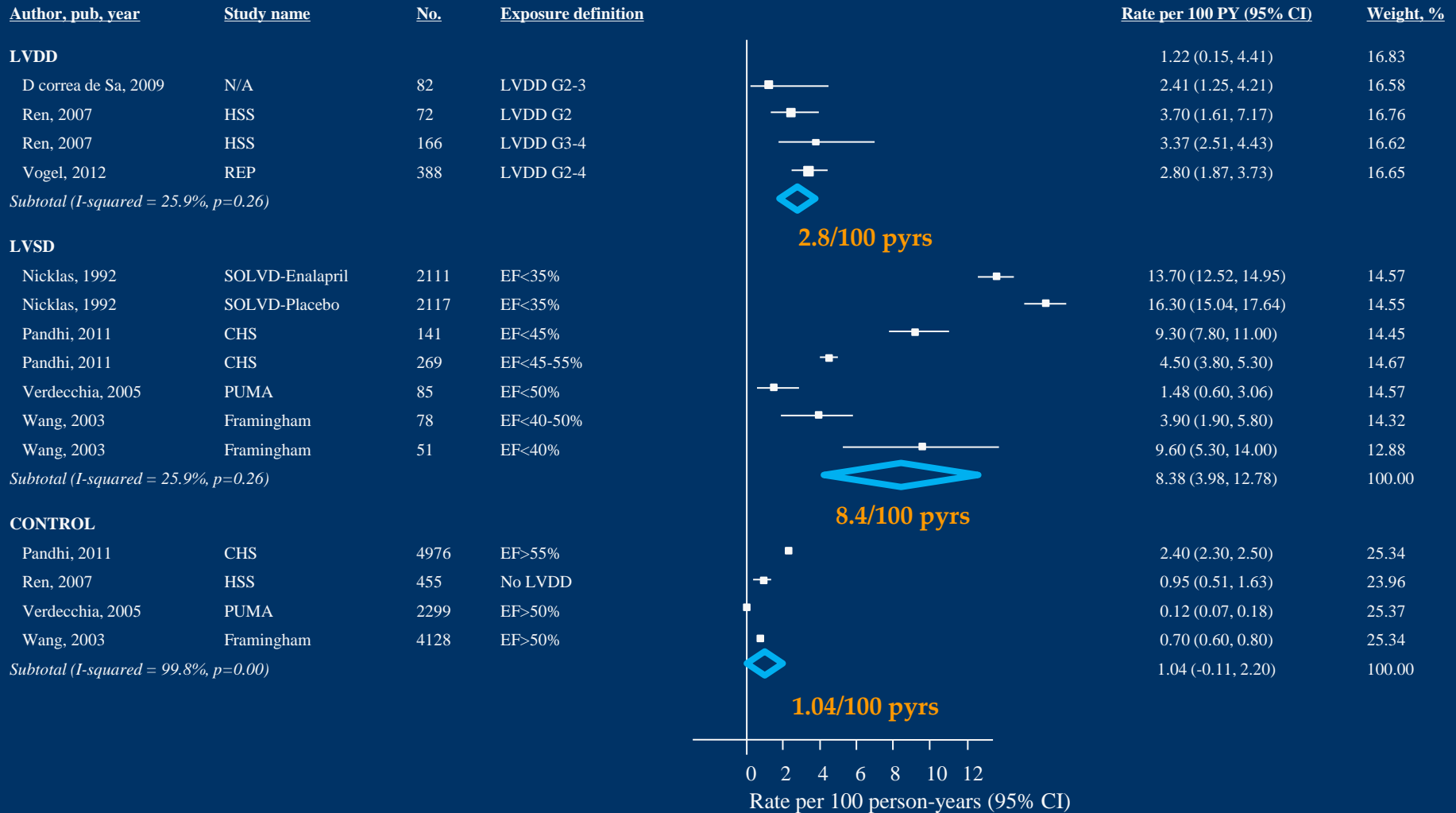
Olmsted Study



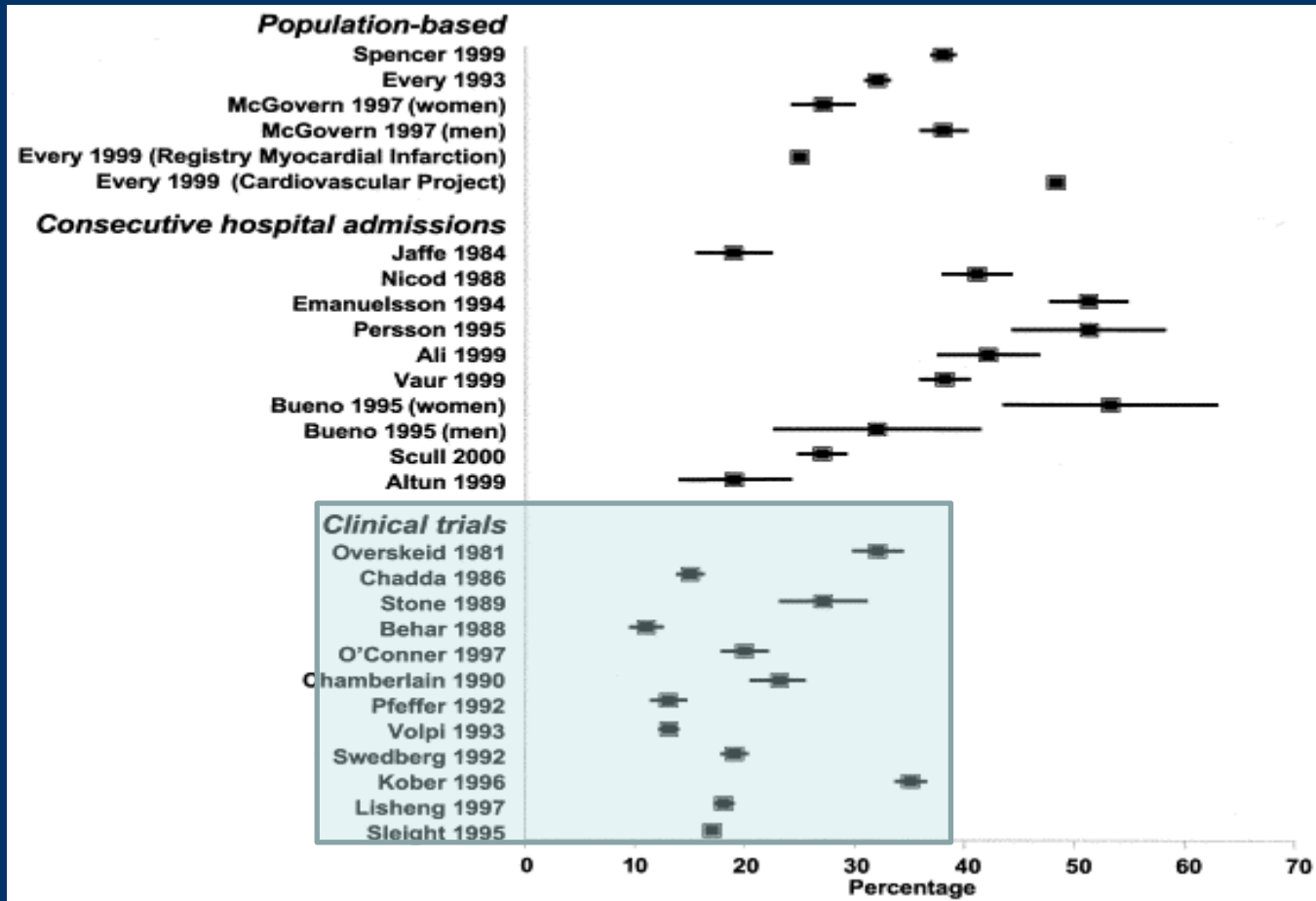
Prevalence of LVSD in 6 Cohorts



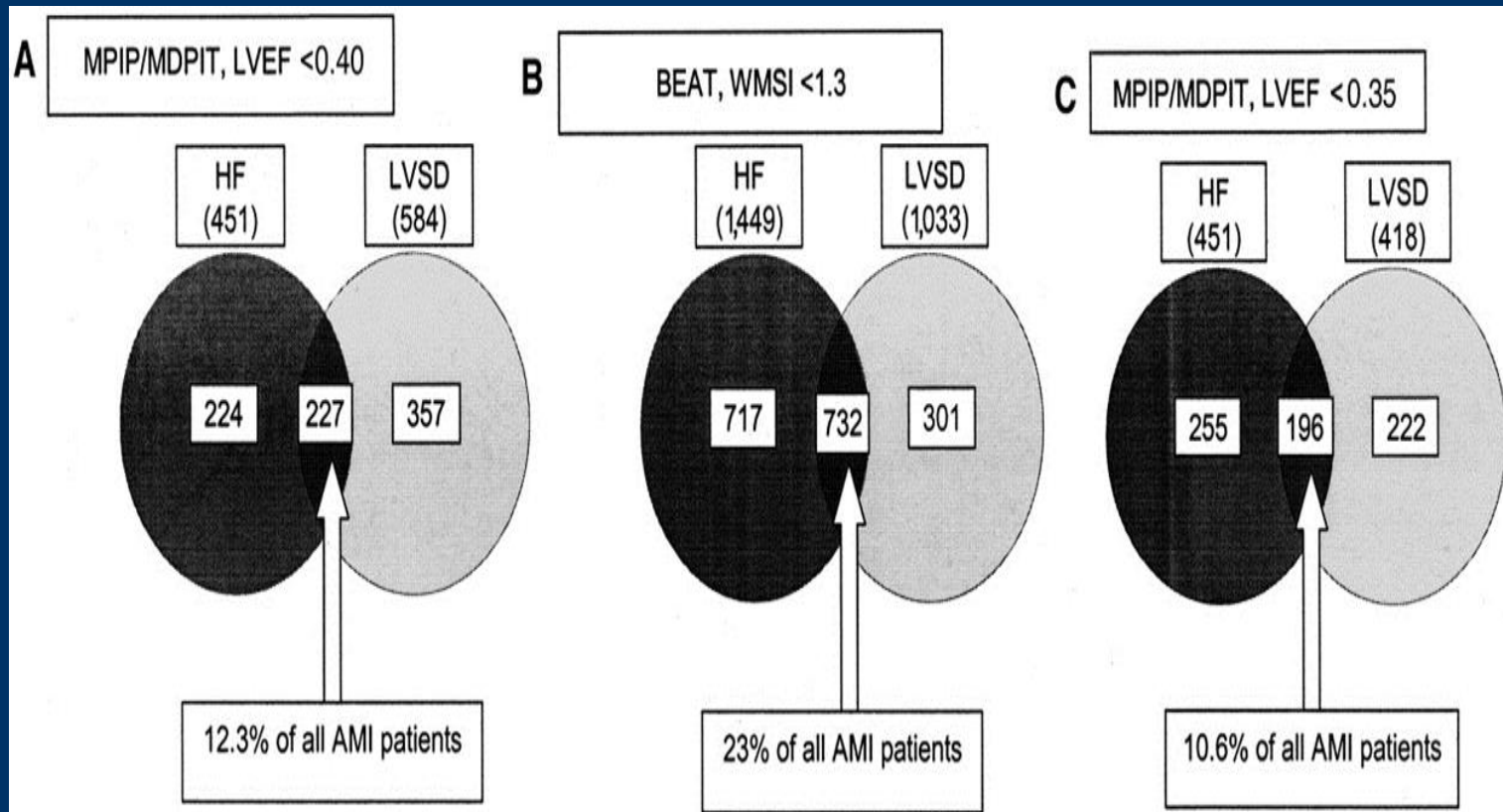
Incident CHF Event Rates



Heart failure after MI



Comparative interrelation between AMI heart failure and LVSD



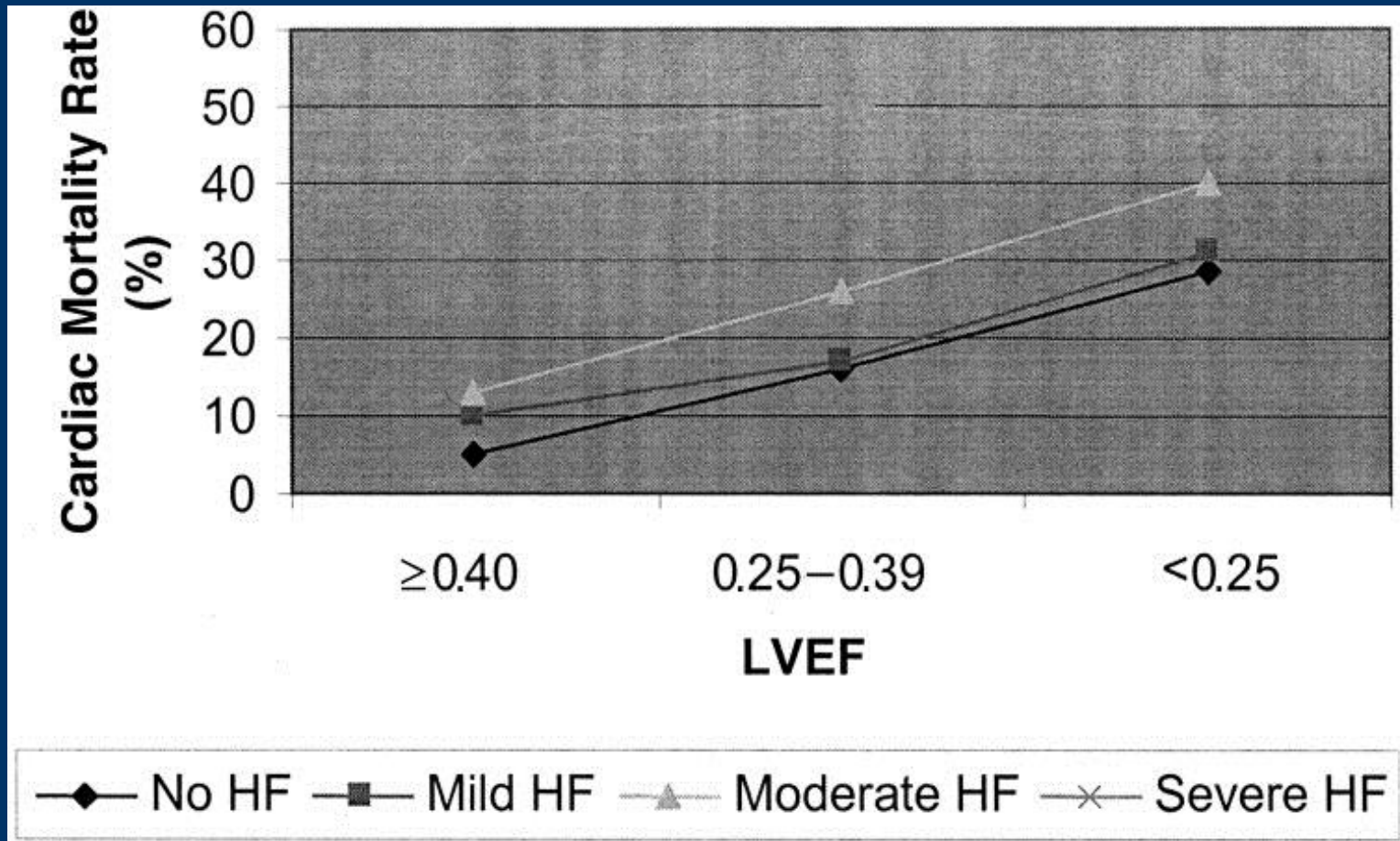
KAMIR data : ? ~ 20%

Table 1. Clinical characteristics of patients

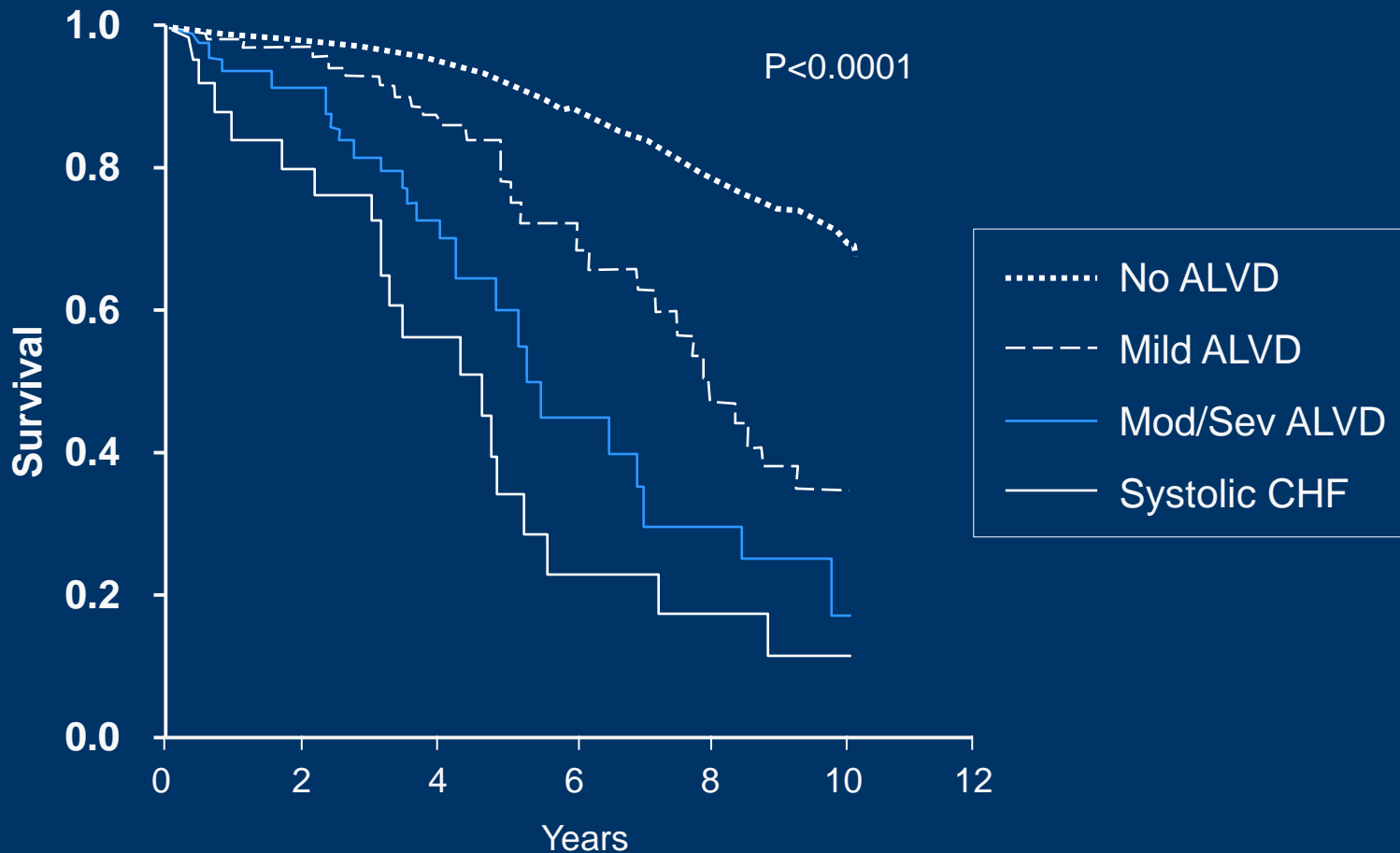
Clinical characteristics	MR Grades 0-2			MR Grades 3-4		
	EF ≤ 40% (n = 2,422)	EF > 40% (n = 12,252)	P value	EF ≤ 40% (n = 197)	EF > 40% (n = 226)	P value
Age (mean ± SD) (yr)	67.0 ± 12.2	63.4 ± 12.5	< 0.001	71.1 ± 11.7	72.6 ± 10.6	0.164
Men (%)	1,695 (70.1)	8,906 (72.6)	0.006	106 (54.1)	97 (42.9)	0.022
Body mass index, median (IQR)	23 (21-25.4)	24 (22-26)	< 0.001	23 (21-24)	23 (21-25)	0.791
Heart rate (beats/min)	83 (72-99.5)	74 (64-84)	< 0.001	90 (72-107)	78 (64-91)	< 0.001
Blood pressure (mmHg)						
Systolic	121 (110-140)	130 (110-150)	< 0.001	120 (100-146)	128 (105-140)	0.518
Diastolic	80 (69-90)	80 (70-90)	< 0.001	71 (60-87)	77 (63.5-89.5)	0.626
Killip class ≥ III	673 (28.7)	1,003 (8.5)	< 0.001	91 (46.4)	87 (38.7)	0.094
Risk factor (%)						
Hypertension	1,209 (50.2)	5,818 (47.8)	0.018	103 (53.1)	130 (61.3)	0.693
Diabetes mellitus	829 (34.2)	3,078 (25.3)	< 0.001	93 (47.2)	70 (31.4)	< 0.001
Currently smoking	1,169 (48.9)	6,552 (54.0)	< 0.001	74 (38.1)	67 (30.0)	0.081
Dyslipidemia*	224 (9.3)	1,407 (11.6)	0.001	27 (13.9)	37 (16.4)	0.459
Ischemic heart disease history	500 (20.8)	1,688 (13.9)	< 0.001	62 (31.5)	45 (20.4)	0.009
STEMI	1,535 (63.4)	6,927 (56.5)	< 0.001	77 (39.1)	81 (36.0)	0.546
NSTEMI	887 (36.6)	5,325 (43.5)	< 0.001	120 (60.9)	144 (64.0)	0.540
Q wave	473 (19.6)	1,547 (12.6)	< 0.001	43 (22.5)	19 (8.7)	< 0.001
Atrial fibrillation/ flutter	130 (5.4)	389 (3.2)	< 0.001	23 (11.8)	22 (10.0)	0.546

Data are expressed as the mean ± SD or number (%), or median (IQR) as appropriate. *Defined as patients who were previously diagnosed by a physician and/or patients receiving lipid-lowering drugs. NSTEMI, non-ST elevation myocardial infarction; STEMI, ST elevation myocardial infarction; MR, mitral regurgitation; EF, ejection fraction.

Combined effect of HF and LVSD of varying severity on cardiac mortality

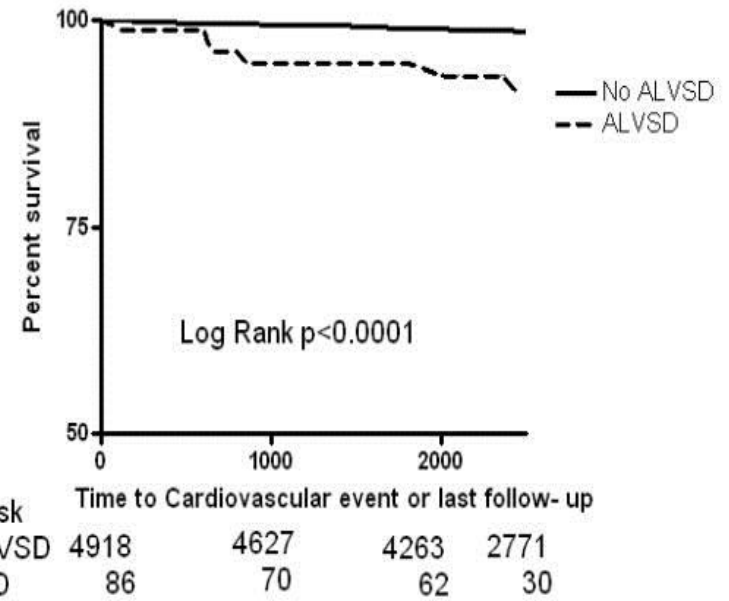
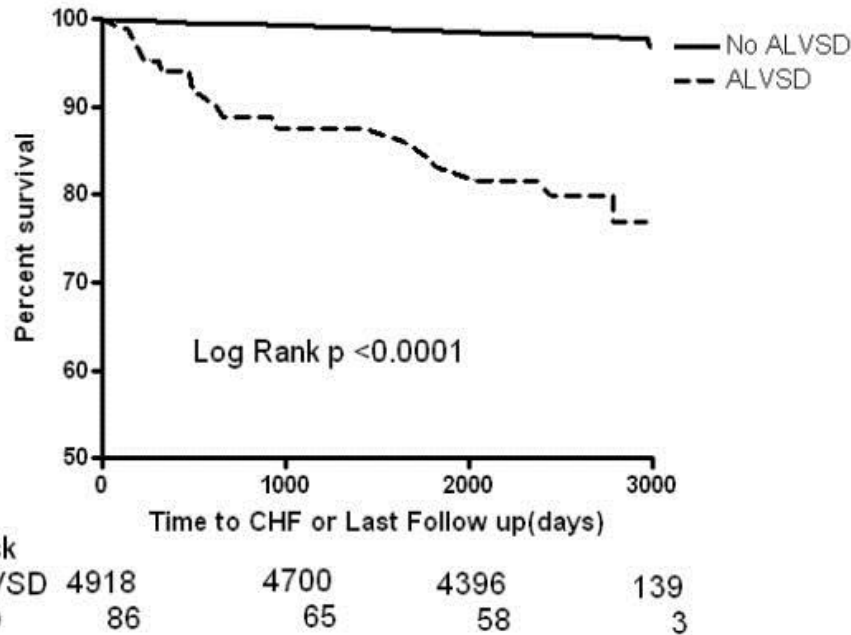


Asymptomatic left ventricular systolic dysfunction (ALVSD)



Kaplan-Meier curves for survival. Reference group (No ALVD) consists of subjects with normal LV systolic function (LVEF >50%) and no history of congestive HF. Mild ALVD indicates mild asymptomatic LVSD (LVEF 40% to 50%); Mod/Sev ALVD, moderate-to-severe asymptomatic LVSD (LVEF <40%); and Systolic CHF, congestive heart failure with LVEF ≤50%

Asymptomatic LV systolic dysfunction (ALVSD) from MESA, 1.7%



(Follow up truncated at 3000 days due to significantly reduced # at risk) (Follow up truncated at 2800 days due to significant reduction in # at risk)

During nine-year follow-up, these individuals were at increased risk for **incident HF** (adjusted hazard ratio [HR] 8.69; 4.89 to 15.45), **CV disease** (adjusted HR 2.21; 1.13 to 3.73), and **mortality** (adjusted HR 2; 1.13 to 3.54).

Progression of preclinical diastolic dysfunction (PDD) and HFpEF

Table 2 Natural History of PDD and Subsequent Progression to Symptomatic HF

First Author (Ref. #)	Year	Population	Incidence of Symptomatic HF Development
Correa de Sa et al. (50)	2010	PDD	2-yr incidence HF development: 1.9% (2-yr incidence of any HF symptom: 31.1%)
Vogel et al. (52)	2012	PDD	1-yr incidence HF development: 2.2% 2-yr incidence HF development: 5.7% 3-yr incidence HF development: 11.6%
From et al. (53)	2010	PDD + DM	1-yr incidence HF development: 13.1% 5-yr incidence HF development: 36.9%
Ren et al. (57)	2007	PDD + CAD	3-yr incidence HF hospitalization: 8.4%
Lam et al. (24)	2011	PDD + noncardiac	4-yr incidence HF development: 4%, 7%, 10% (0, 1, 2 noncardiac risk factors, respectively)
Kane et al. (8)	2011	PDD (moderate to severe diastolic dysfunction)	1-yr incidence HF development: 3% 3-yr incidence HF development: 7% 5-yr incidence HF development: 10%

Noncardiac includes renal, pulmonary, and hematologic factors.

CAD = coronary artery disease; DM = diabetes mellitus; HF = heart failure; PDD = pre-clinical diastolic dysfunction.

Echocardiographic Criteria

Signs (\pm symptoms) of HF

+

HFpEF: EF \geq 50%
HFmrEF: EF 40-49%

+

Structural abnormalities

LAVI
>34ml/m²

LVMi
>115g/m² (m)
>95 g/m²(f)

Functional abnormalities

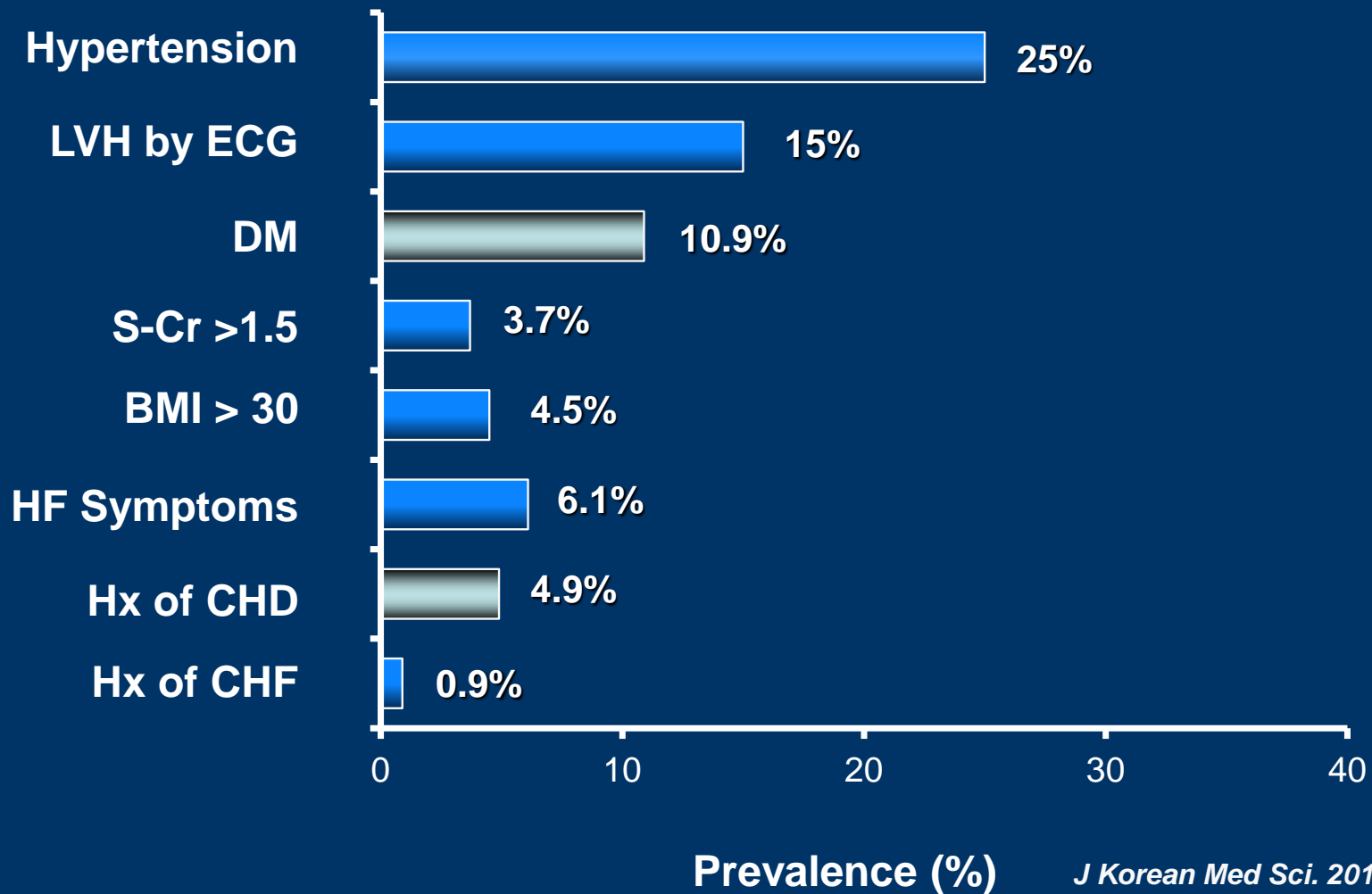
E/e'_{avg} \geq 13

e' average
(lateral-septal)
<9 cm/s

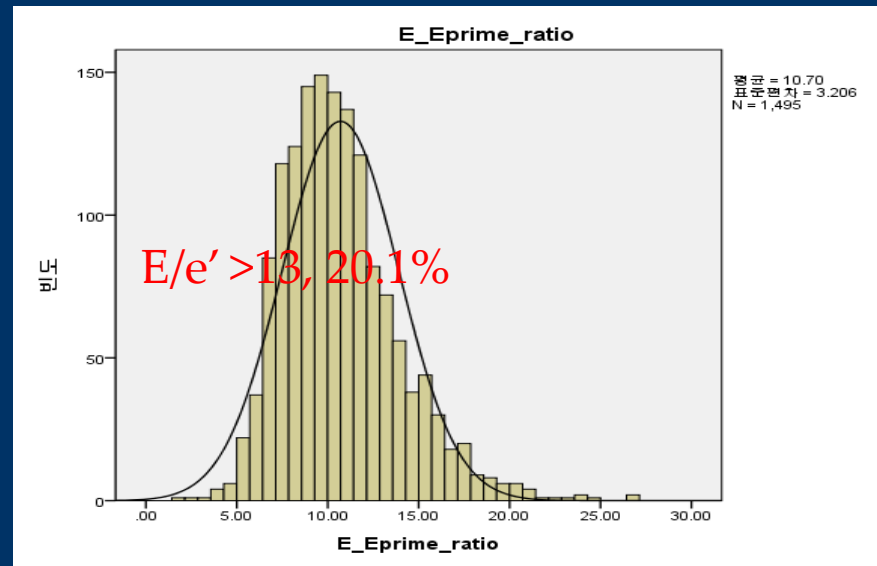
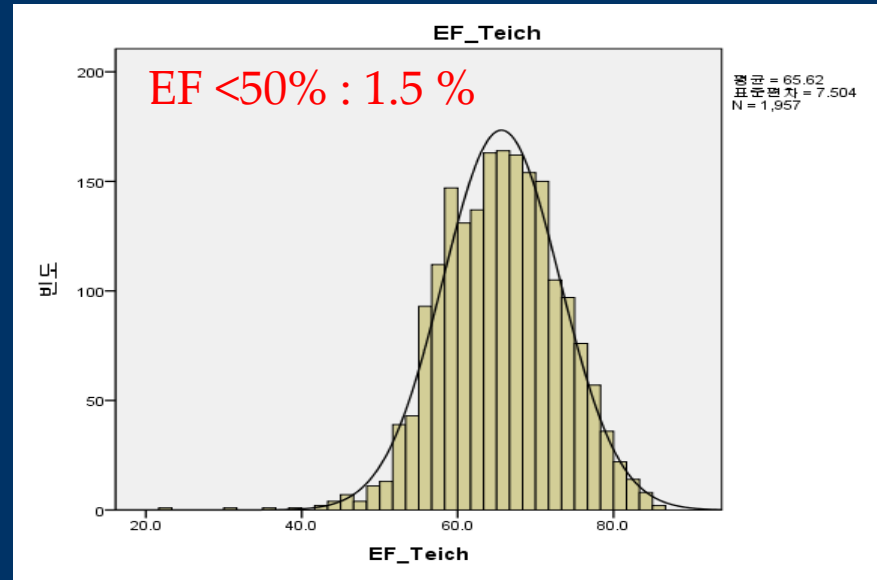
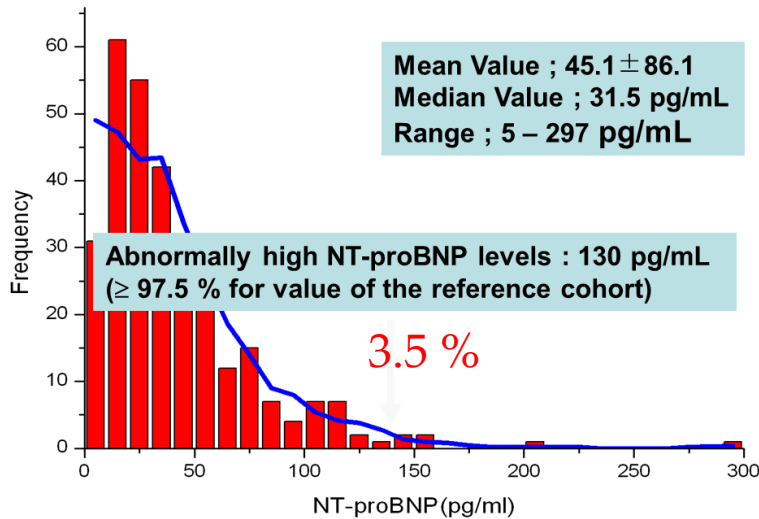
Diagnosis of HFpEF/HFmrEF

- Limited data (Unmet Need!)
- Cut-offs arbitrary
- More criteria; greater certainty of diagnosis
- Diastolic stress test?
- Invasive hemodynamic measurements?

Prevalence of CHF and Risk Factors in Adults With Cohort Study



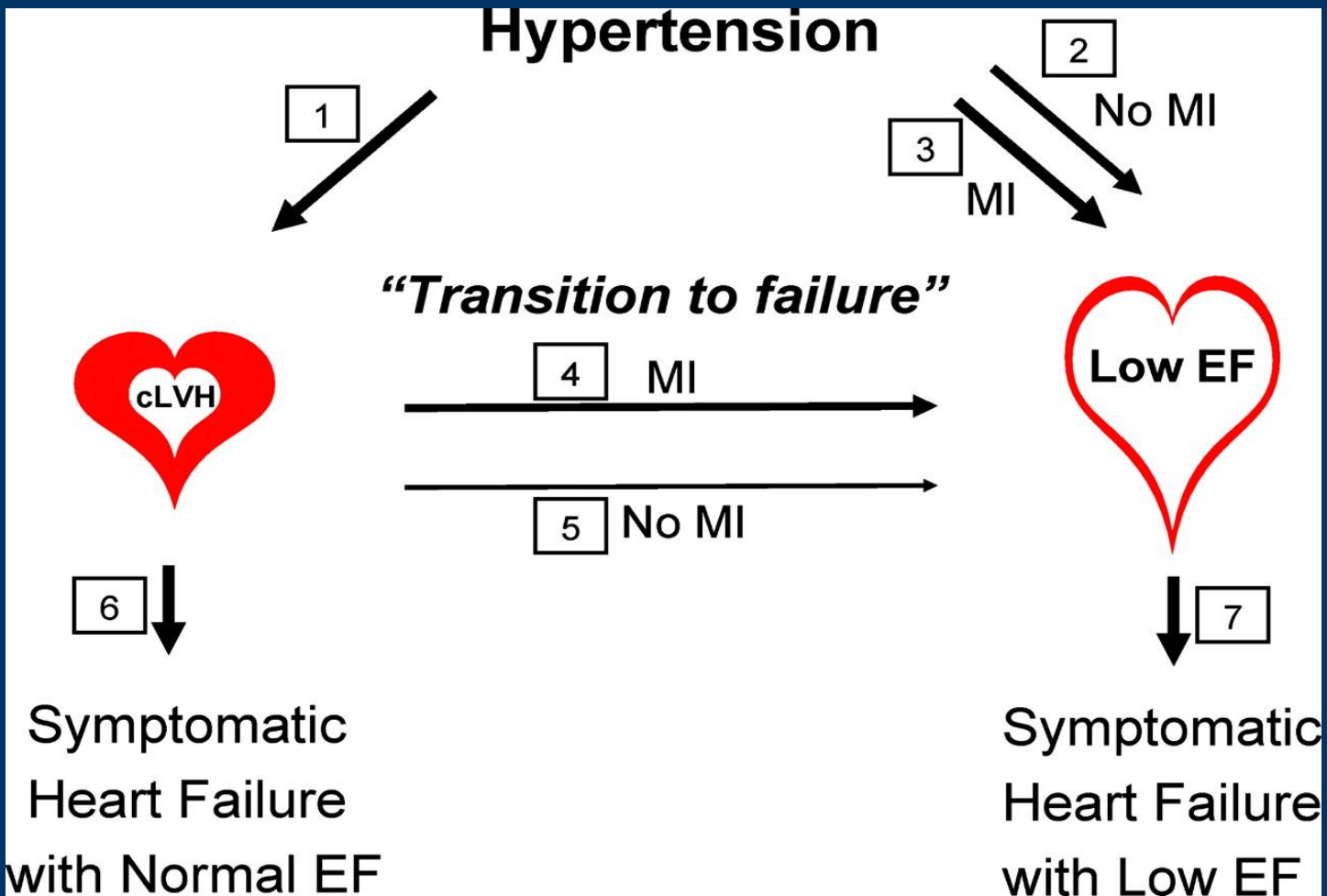
ASLVD in Korea



Focused on ...

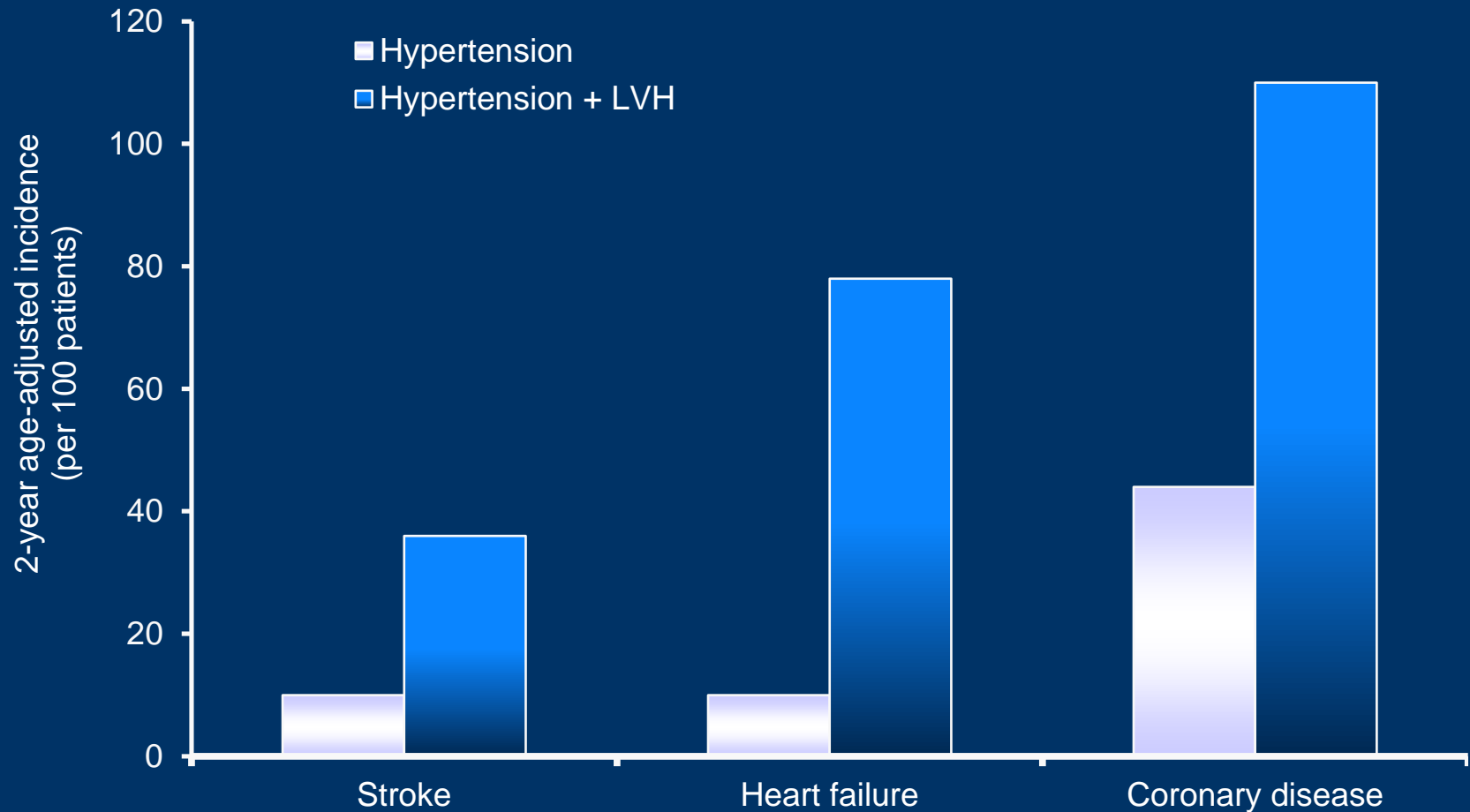
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The 7 pathways in the progression from hypertension to heart failure



LVH increases cardiovascular risk

; the 32-year Framingham Heart Study follow-up of men aged 32–64 years



LVH prevalence by ECG and echocardiography

Author	ECG LVH criteria	ECHO LVH criteria	Prevalence of LVH (%)	
			ECG	ECHO
Verdecchia [13]	Wilson	LVMi >125 g/m ²	0.6	27.2
	LV strain	LVMi >51 gm ^{2.7}	3.0	49.9
	Romhilt-Estes		4.8	
	Gubner Ungerleider		7.1	
	Sokolow -Lyon		11.1	
	Cornell voltage		11.9	
	Perugia score		18.4	
Salles [17]	Sokolow -Lyon, or Cornell voltage	LVM >294 g (M); >198 g (F)	18.9	50.0
Verdecchia [18]	Perugia score	LVMi >49.2 gm ^{2.7} (M); >46.7 gm ^{2.7} (F)	17.1	47.8
Martinez [19]	Cornell voltage	LVMi >134 gm ² (M); >110 gm ² (F)	9.0	32.0
Schneider [21]	Cornell voltage	LVMi >134 gm ² (M); >110 gm ² (F)	5.0	37.0
	Cornell voltage-duration product		9.5	
Cuspidi [29]	Sokolow-Lyon	LVMi >125 gm ² (M); >110 gm ² (F)	10.4	36.5
Radulescu [32]	Sokolow-Lyon or Cornell voltage-duration product	LVMi >125 gm ²	40.0	41.4
Salles [38]	Sokolow-Lyon	LVMi >125 gm ² (M)	20.5	75.7
	Cornell voltage	>110 gm ² i(F)	21.9	
	Cornell voltage-duration product		25.4	

Journal of Hypertension, 2012, p 2066–2073

The median prevalence of LVH was 33% (interquartile range 23-41%) in primary care settings (10 studies) and 65% (37-81%) In secondary care settings (11 studies): from systemic review in BMJ 2012.

LVH by ECG and Echocardiography

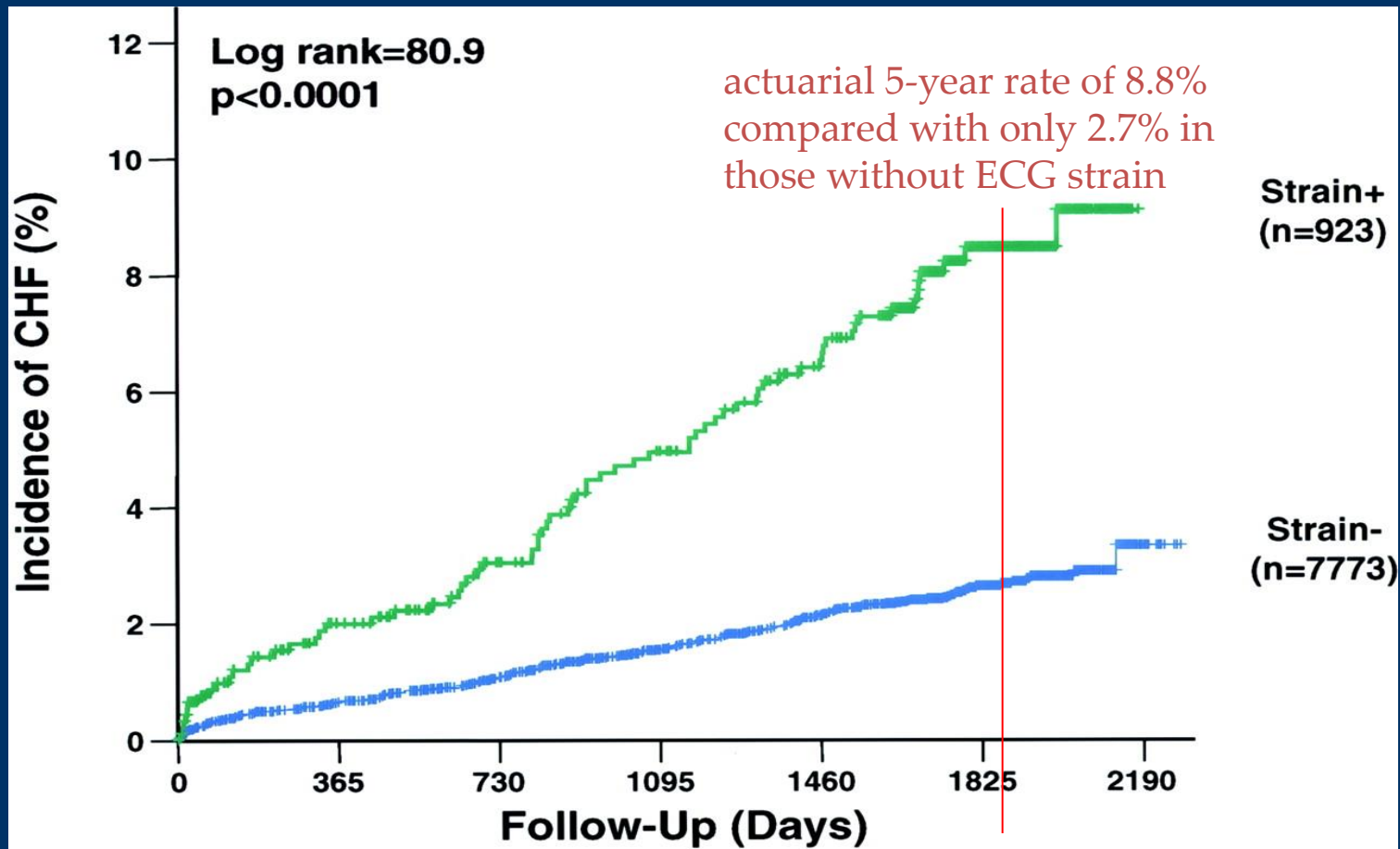
Diagnostic performance of electrocardiographic left ventricular hypertrophy criteria

Diagnostic values	Sokolow-Lyon criteria	Cornell voltage criteria
Sensitivity (%)	3.3	6.6
Specificity (%)	95.6	96.0
Positive predictive value (%)	21.4	37.5
Negative predictable value (%)	73.3	74.0
Accuracy (%)	71.1	72.3

Demographic and clinical characteristics

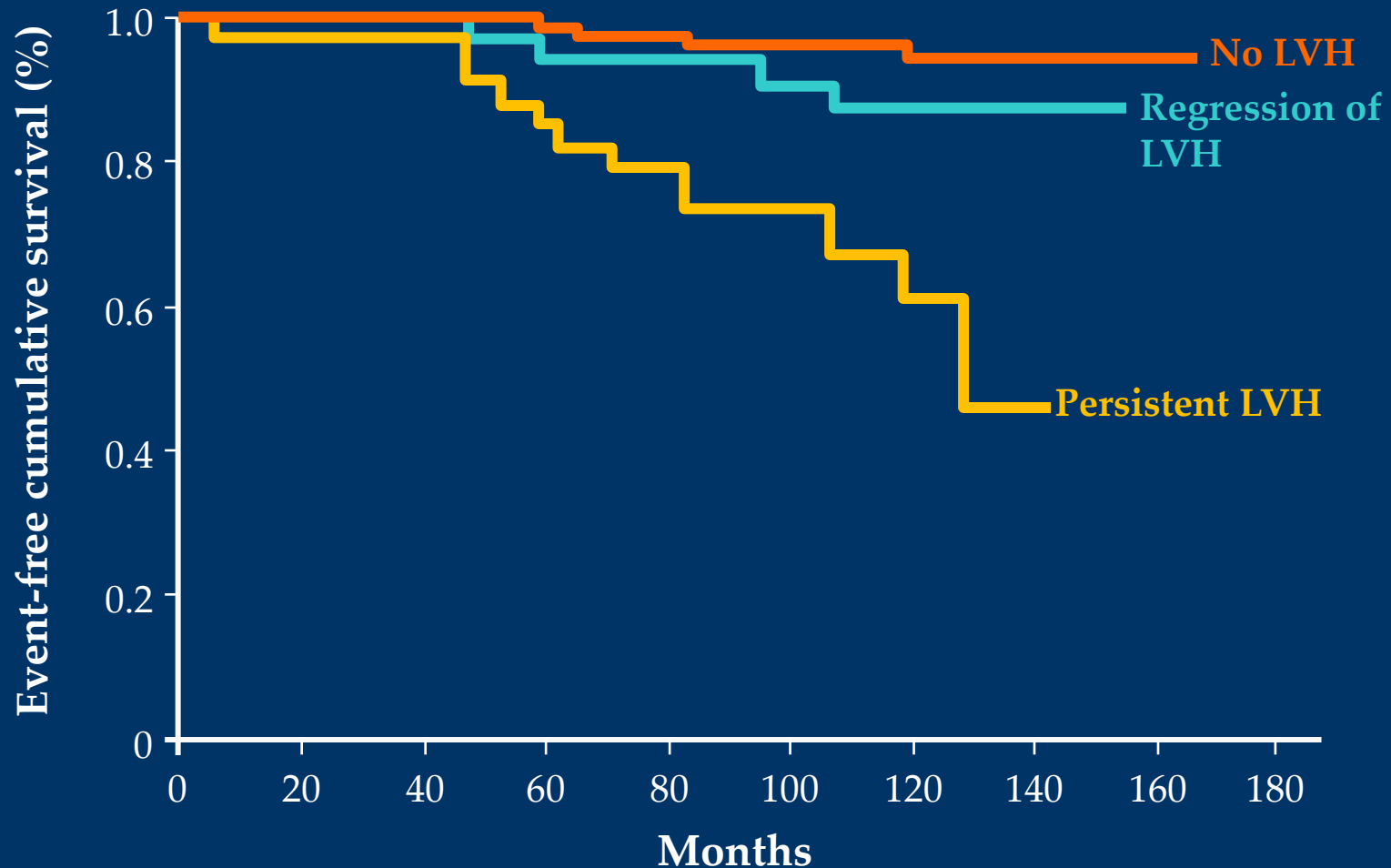
Parameters	Without LVH (n = 252)	With LVH (n = 91)	P
Male, No. (%)	113 (44.8)	22 (24.2)	0.001
Age (yr)	51.2 ± 7.3	57.3 ± 7.8	< 0.001
Height (cm)	160.8 ± 8.6	156.0 ± 8.0	< 0.001
Weight (kg)	64.0 ± 10.2	62.6 ± 10.4	0.26
Waist circumference (cm)	85.5 ± 10.0	86.9 ± 11.0	0.26
Hip circumference (cm)	96.3 ± 8.4	97.7 ± 6.2	0.15
Body mass index (kg/m ²)	24.7 ± 3.1	25.7 ± 3.5	0.02
History of hypertension, No. (%)	38 (15.1)	22 (24.2)	0.050
History of diabetes mellitus, No. (%)	18 (7.1)	7 (7.7)	0.86
History of dyslipidemia, No. (%)	18 (7.1)	2 (2.2)	0.08
Systolic blood pressure (mmHg)	130.9 ± 15.6	134.7 ± 19.5	0.11
Diastolic blood pressure (mmHg)	81.6 ± 12.2	82.0 ± 11.5	0.80
Glucose (mg/dL)	97.8 ± 20.2	93.6 ± 13.1	0.02
Total cholesterol (mg/dL)	196.8 ± 35.1	200.8 ± 41.2	0.38
HDL-cholesterol (mg/dL)	45.2 ± 11.4	45.3 ± 10.2	0.96
LDL-cholesterol (mg/dL)	113.3 ± 30.0	120.9 ± 33.7	0.045
Triglyceride (mg/dL)	158.7 ± 133.1	133.4 ± 68.9	0.02
Creatinine (mg/dL)	0.95 ± 0.15	0.88 ± 0.12	< 0.001
NT-proBNP (pg/mL)	39.6 ± 48.7	58.4 ± 51.1	< 0.01

Event rates according to LV strain for the development of CHF (LIFE).



ECG strain identifies hypertensive patients at increased risk of developing CHF and dying as a result of CHF, even in the setting of aggressive blood pressure lowering.

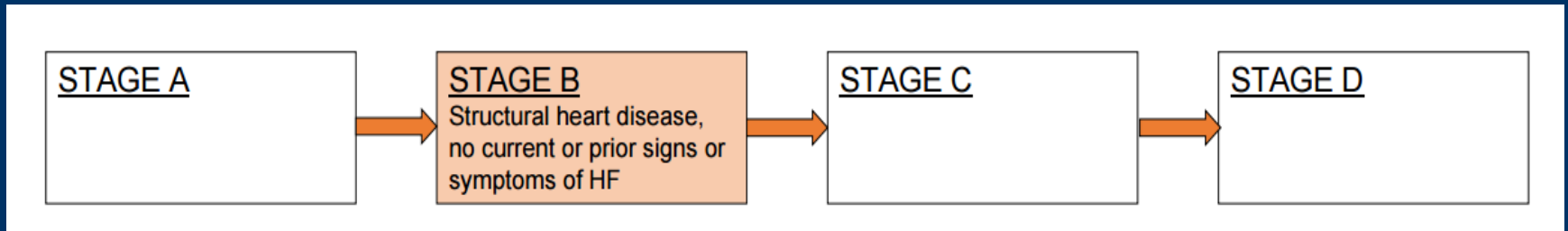
Association of Change in LV Mass with Prognosis during Long-term Antihypertensive Treatment



Focused on ...

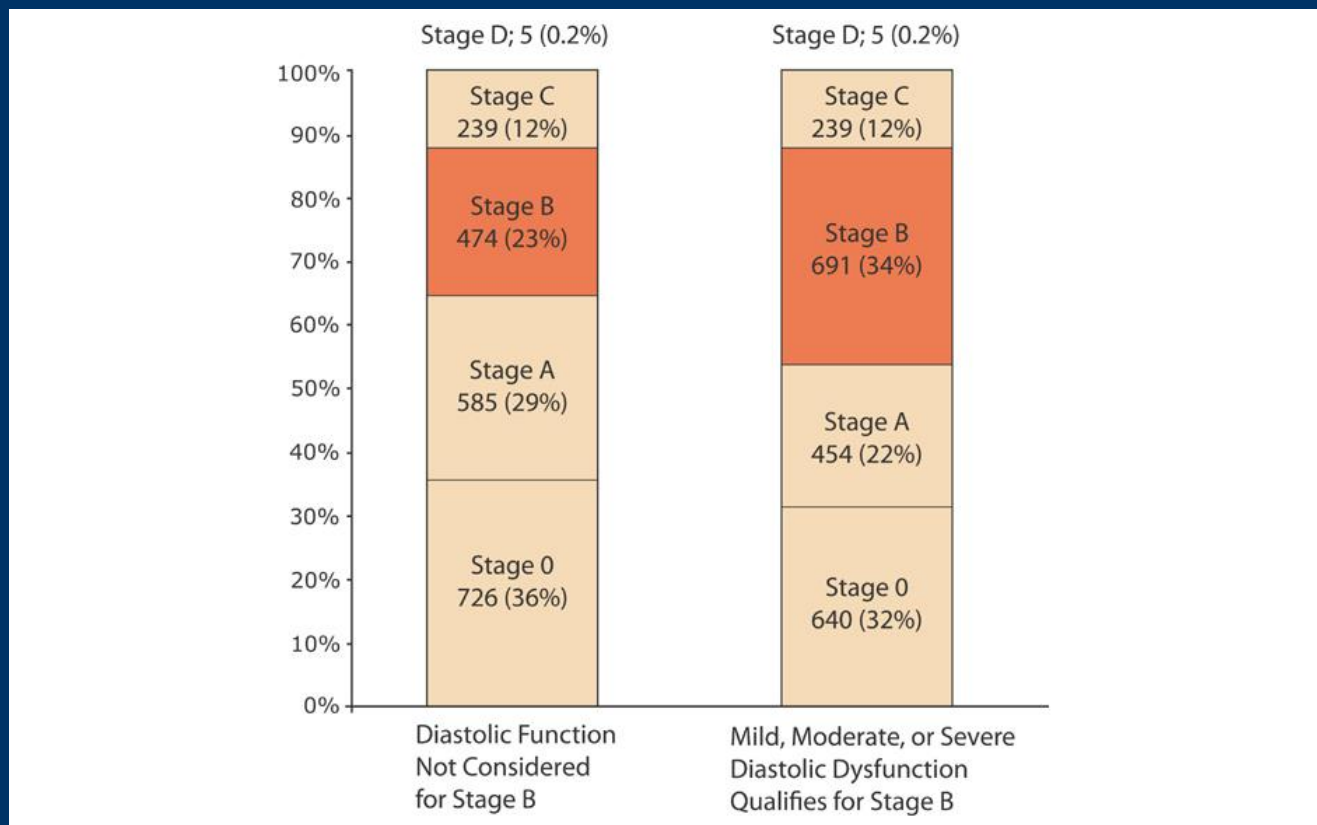
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From Stage B to Stage C

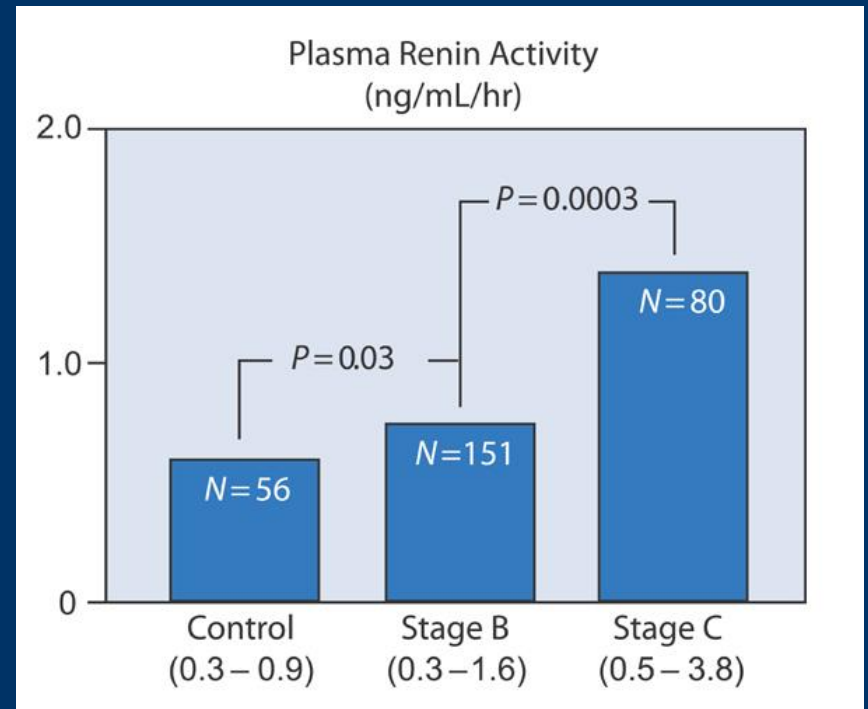
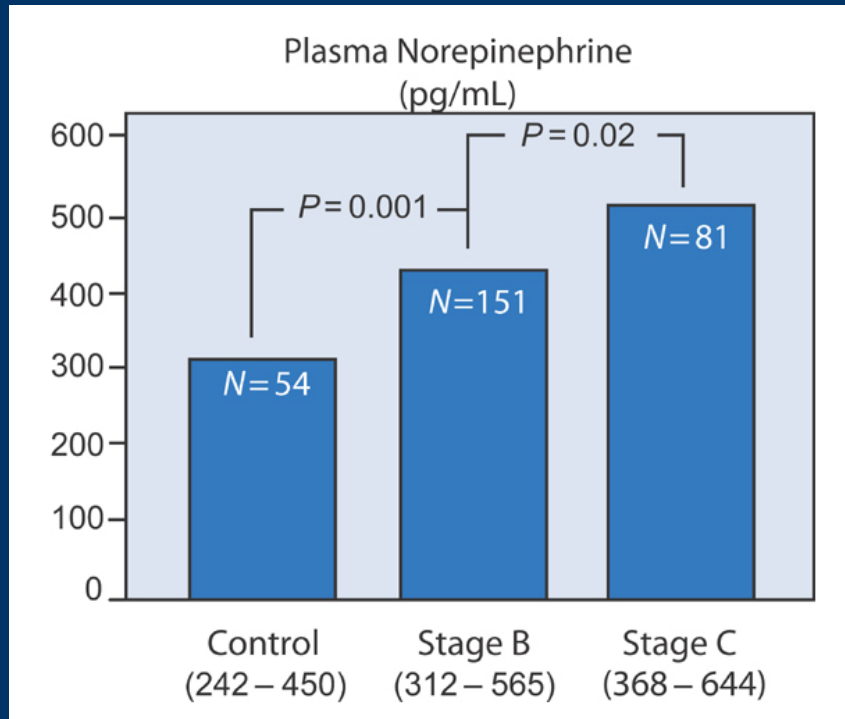


*Progression of LV dysfunction
or Other Factors*

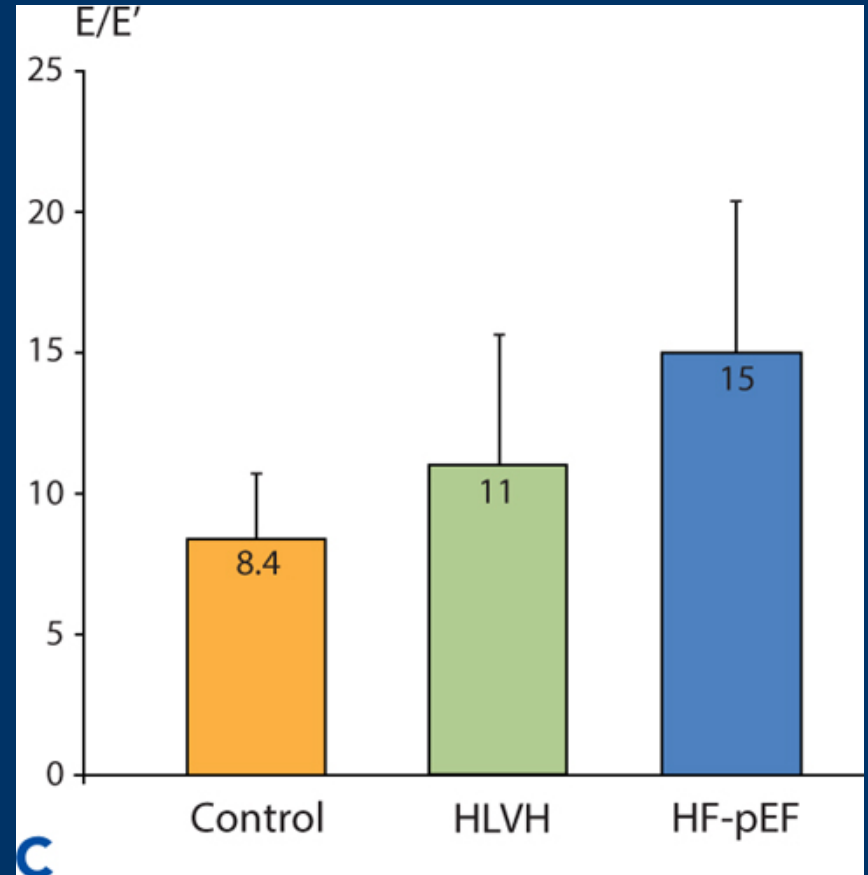
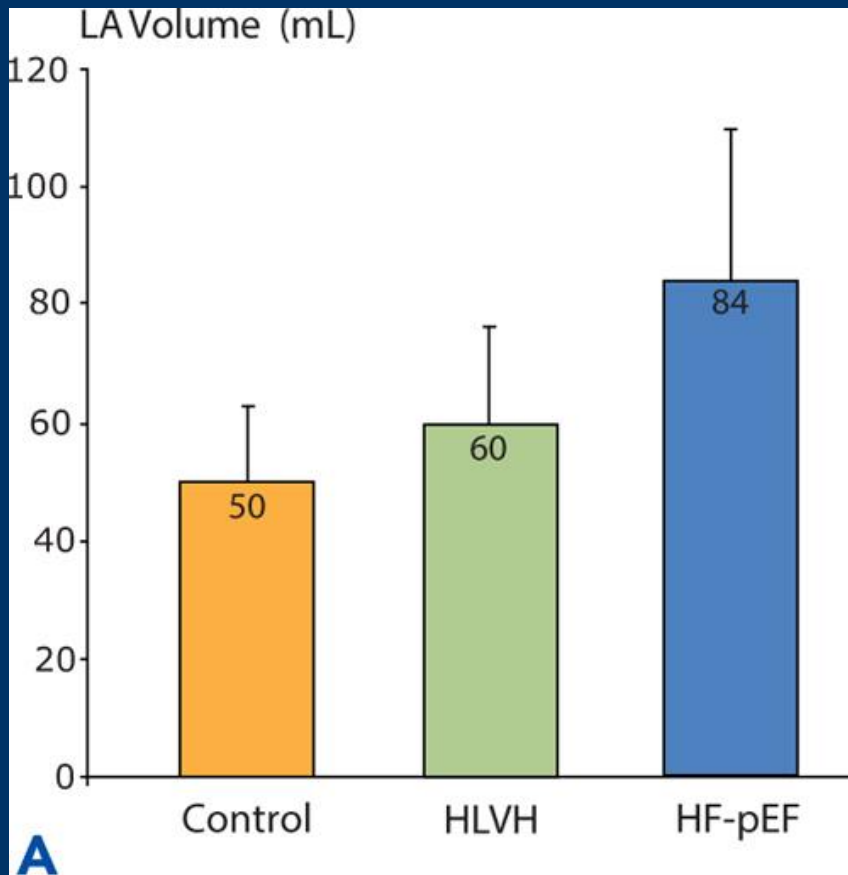
Prevalence of heart failure by stages with and without diastolic dysfunction as criteria for Stage B



Neurohumoral Continuum from Stage B to Stage C Systolic Dysfunction

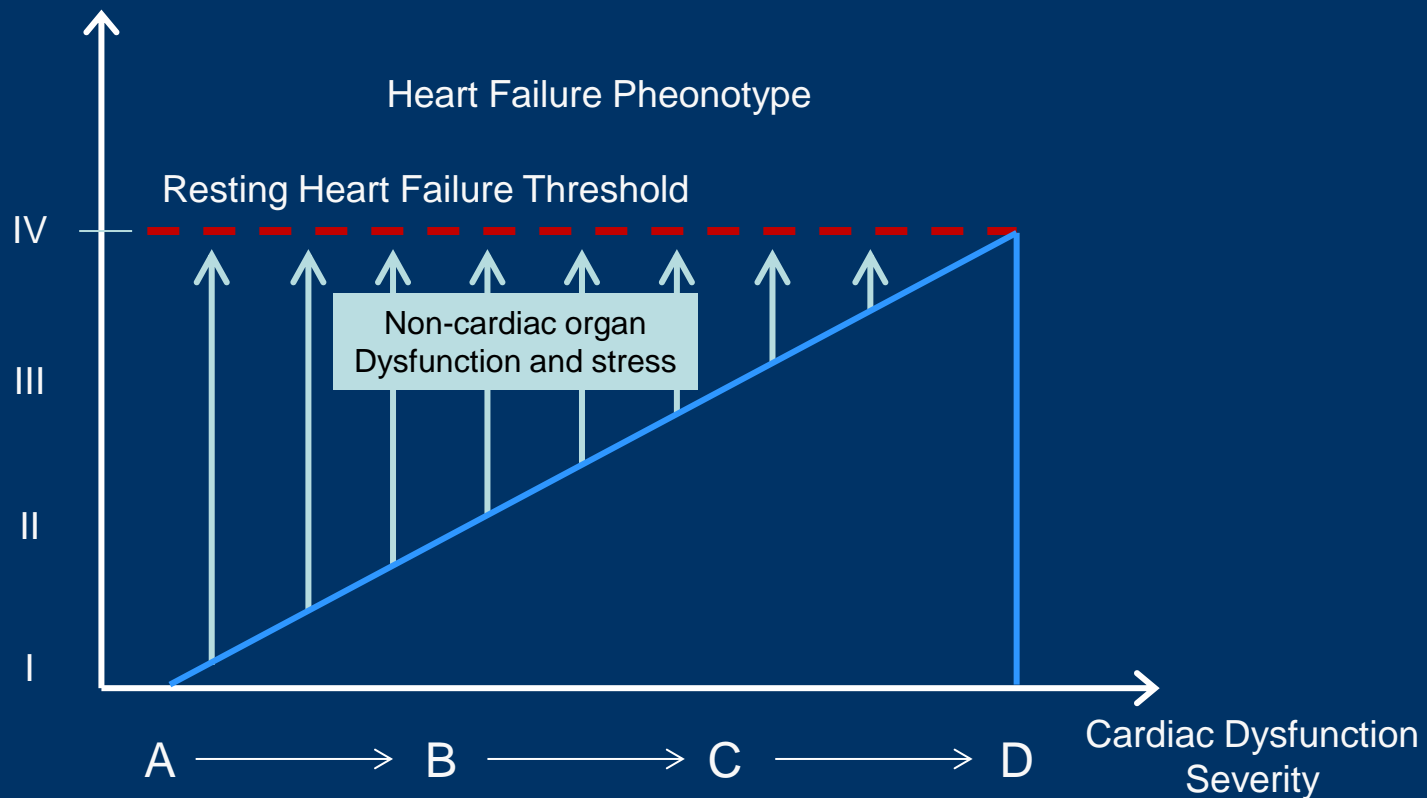


Diastolic dysfunction from Stage B to Stage C Systolic Dysfunction

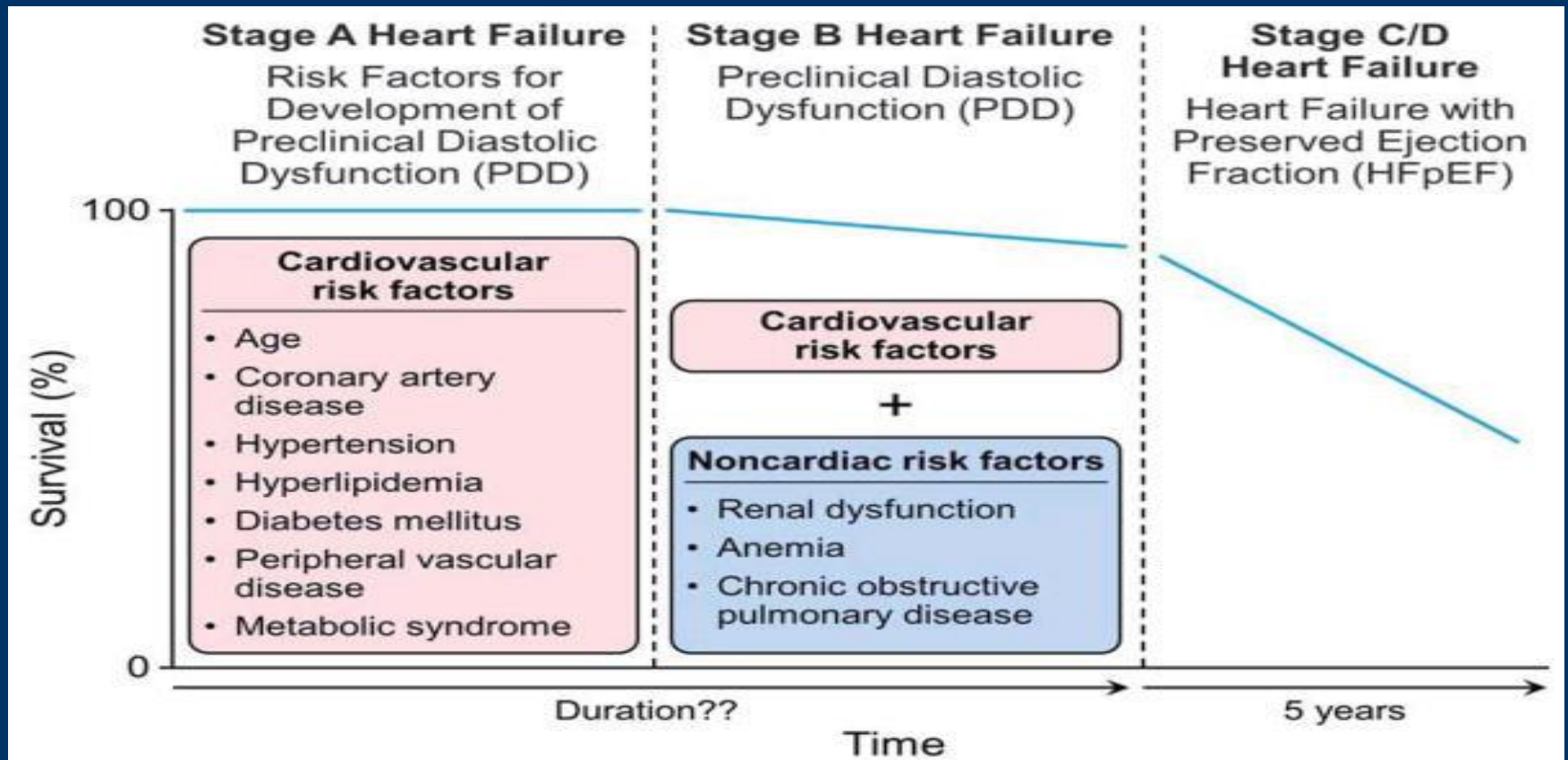


Significant noncardiac organ dysfunction can induce NYHA symptoms (class II and higher)

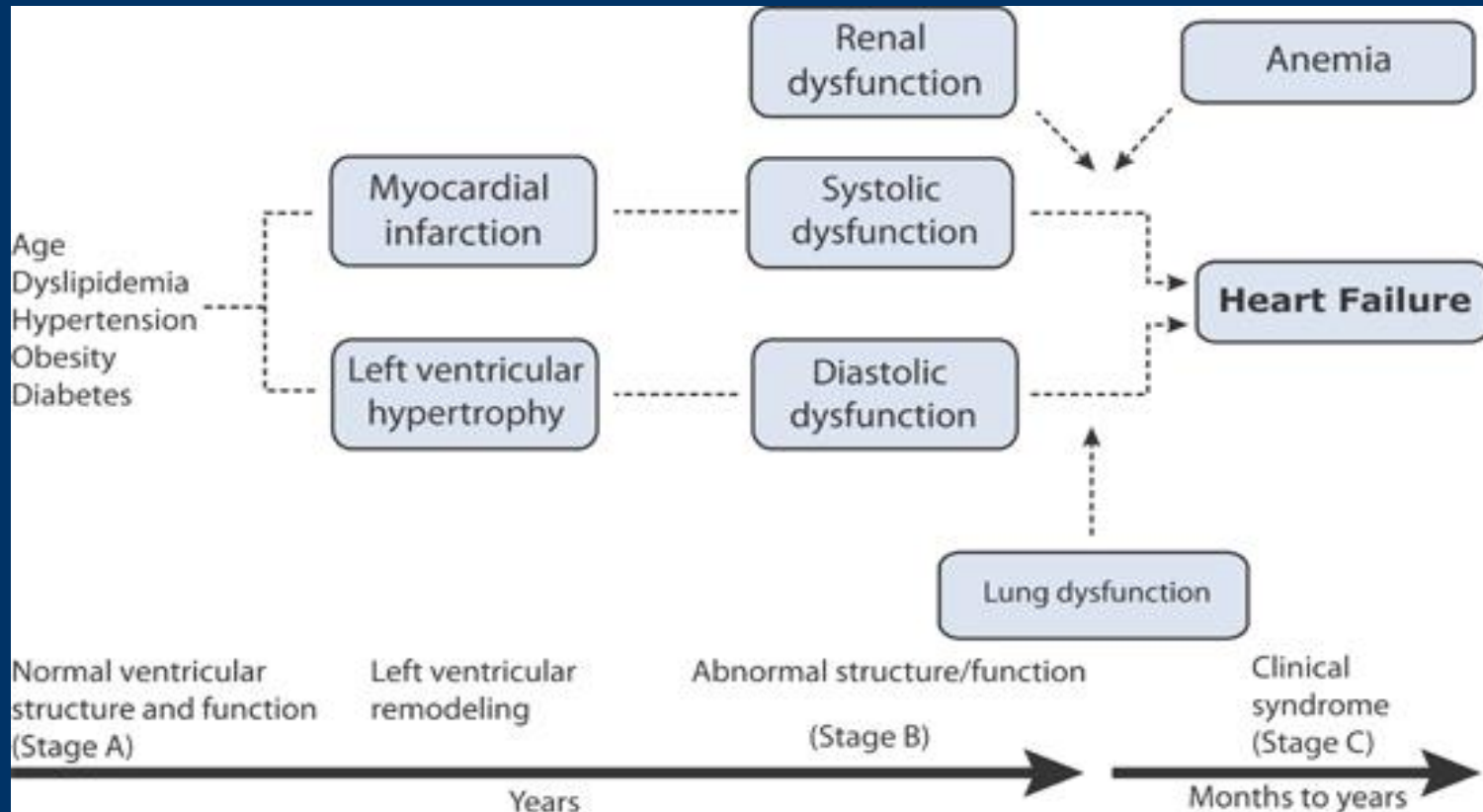
NYHA
Heart Failure Symptoms



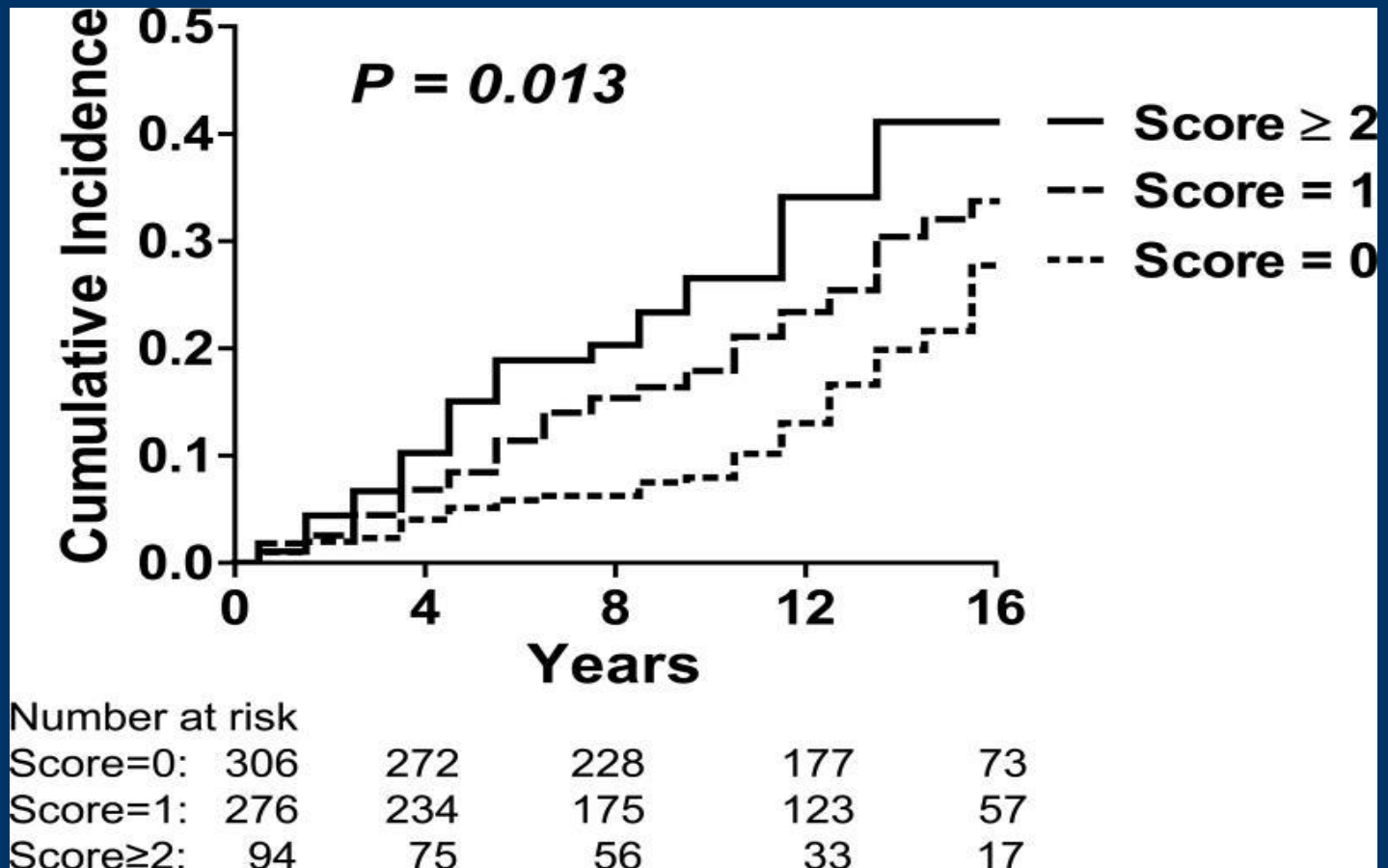
Cardiovascular and noncardiac risk factors in the development and progression of preclinical diastolic dysfunction (PDD) and HFpEF



Interaction of cardiac and noncardiac dysfunctions and progression to HF



Noncardiac Risk Score and cumulative incidence of symptomatic heart failure

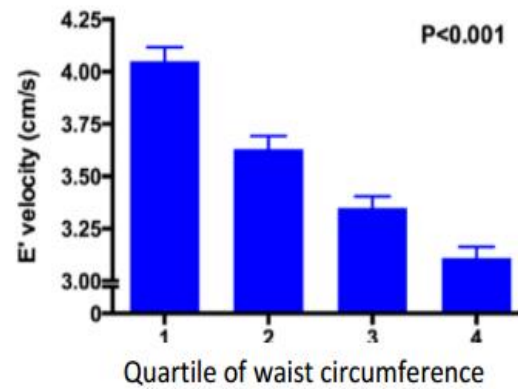


Circulation. 2011;124(1):24-30.

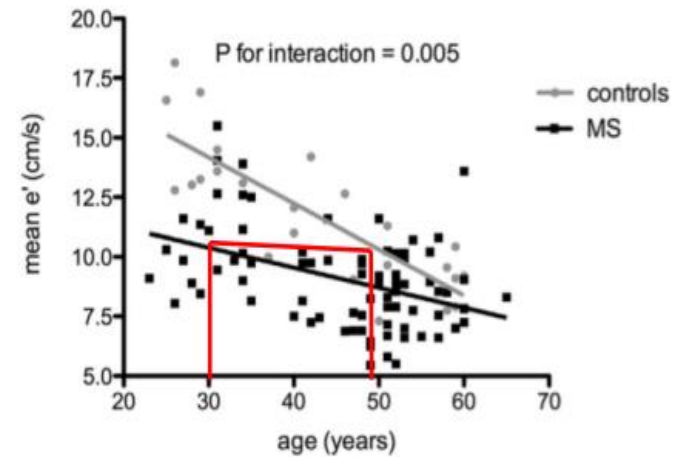
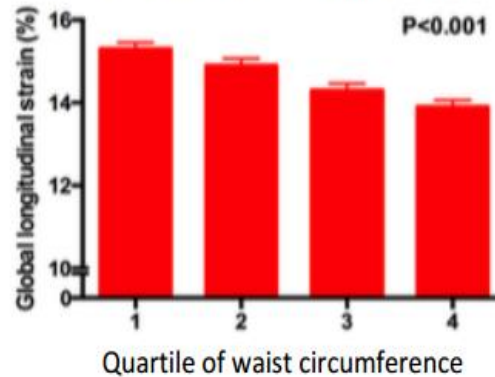
Risk score ranges from 0 to 3. One point each was awarded for the presence of the following three parameters: serum creatinine > 1.05 mg/dL (92.8 μmol/L), FEV₁ : FVC < 91% predicted, and hemoglobin concentration < 13 g/dL.

Obesity and Subclinical Cardiac Remodeling

- Diastolic Dysfunction



- Abnormal Strain



Subclinical PH is prominent in metabolic disease

	Nonobese n=45	Obese n=45	MetS n=156	P ANOVA
Age, years	44±12	38±10	44±11	0.006
Women, n (%)	33 (73)	40 (89)	111 (71)	0.05
BMI, kg/m ²	24±3	40±11	40±9	<0.001
Diabetes, n (%)	0	0	66 (44)	<0.001
Hypertension	0	9 (20)	98 (63)	<0.001
PASP, mmHg	32±10	32±9	42±10	<0.001
PCWP, mmHg	10±2	11±2	13±2	<0.001
PVR, wu	2.1±1.0	2.0±0.7	2.7±0.9	<0.001
TAPSE, mm	23±4	24±4	23±4	0.15
TV e', cm/s	12±2	13±2	11±3	<0.001

Focused on ...

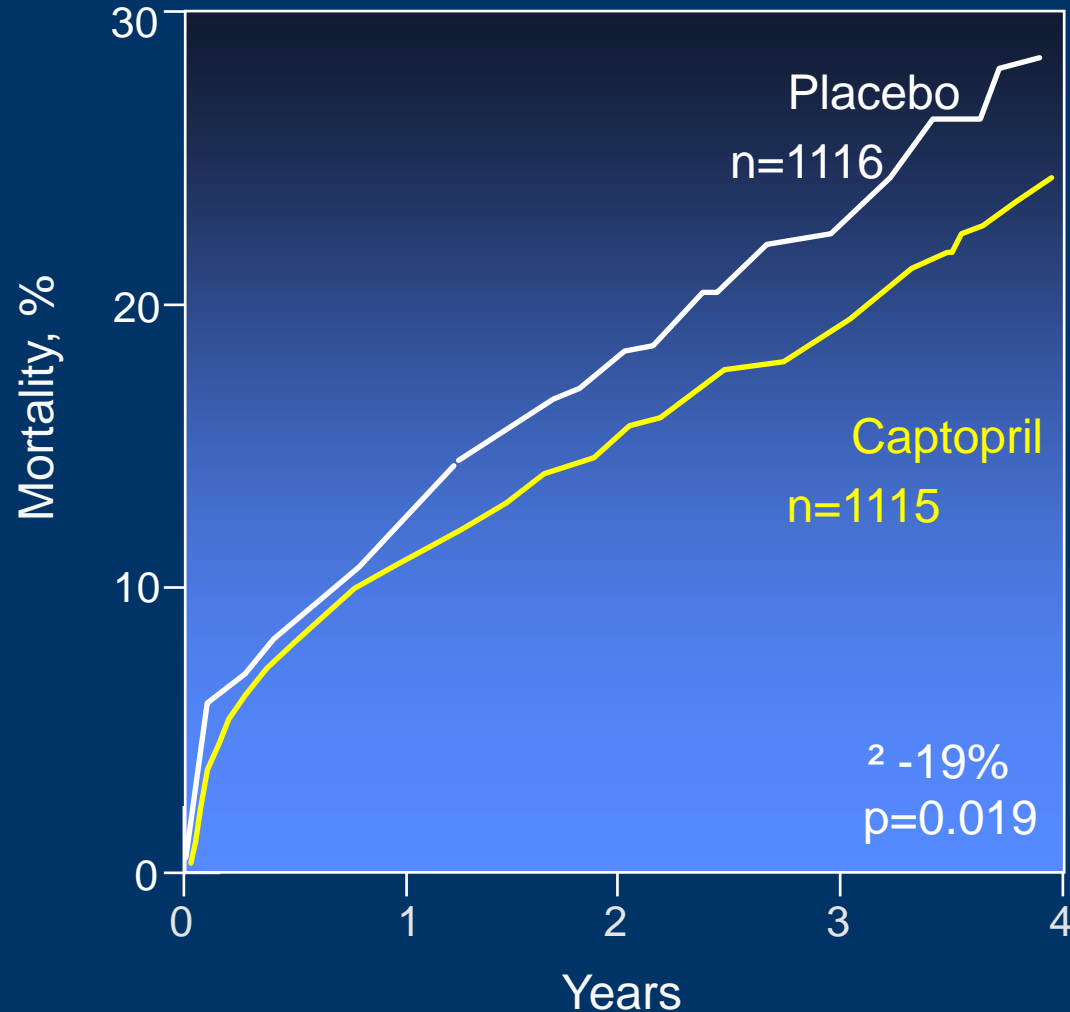
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Clinical trials with asymptomatic LVSD

Study	Population of patients (N)	Treatment	Average duration, months	Risk reduction, %		
				Relative mortality	Sudden death	Death due to worsening heart failure
ACE inhibitors						
SAVE	Acute myocardial infarction and asymptomatic LVSD (2231)	Captopril vs placebo	42	19 ($P = .02$)	No difference ($P = NS$)	36 ($P = .032$)
SOLVD prevention	Asymptomatic LVSD (4228)	Enalapril vs placebo	37.4	8 ($P = NS$)	No difference ($P = NS$)	20 ^a ($P < .001$)
TRACE	Myocardial infarction and LVSD (6676; 1749 randomized); asymptomatic LVSD (542)	Trandolapril vs placebo	24-50	22 ($P = .001$)	24 ($P = .03$)	29 ^b ($P = .003$)
β-Blockers						
Retrospective analysis of SOLVD prevention	Asymptomatic LVSD (4228; 1015 patients taking β -blockers)	β -Blockers vs no β -blockers plus enalapril	37.4	23 ($P < .01$)	28 ^c ($P < .05$)	29 ($P < .05$)
Post hoc analysis of SAVE	Asymptomatic LVSD (2231; 789 patients taking β -blockers)	β -Blockers vs no β -blockers plus captopril	42	43 ($P < .001$)	NR	32 ^b ($P < .001$)
ANZ	Heart failure (415); asymptomatic LVSD (124)	Carvedilol vs placebo	19	36 ^a ($P = .02$)	10 ($P = NS$)	8 ($P = NS$)
CAPRICORN	LVSD after acute myocardial infarction (1959); asymptomatic LVSD (1023)	Carvedilol vs placebo (including ACE inhibitor)	15.6	23 ($P = .03$)	26 ($P = .098$)	40 ($P = .08$)

ACEI SURVIVAL

Asymptomatic ventricular dysfunction post MI



n = 2231
3 - 16 days post AMI
EF < 40
12.5 --- 150 mg / day

SAVE

N Engl J Med 1992;327:669

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Post hoc analysis of SAVE	Asymptomatic LVSD (2231; 789 patients taking β -blockers)	β -Blockers vs no β -blockers plus captopril	42	43 ($P < .001$)	NR	32 ^b ($P < .001$)
ANZ	Heart failure (415); asymptomatic LVSD (124)	Carvedilol vs placebo	19	36 ^a ($P = .02$)	10 ($P = NS$)	8 ($P = NS$)
CAPRICORN	LVSD after acute myocardial infarction (1959); asymptomatic LVSD (1023)	Carvedilol vs placebo (including ACE inhibitor)	15.6	23 ($P = .03$)	26 ($P = .098$)	40 ($P = .08$)

β BLOCKERS Mortality

		β BLOCKER	
		YES	No
ACEI	Yes	13.3%	24.3%
	No	19.5%	27.7%

n=2231

SAVE

Circulation 1995;92:3132

ESC guideline for stage B

Recommendations to prevent or delay the development of overt heart failure or prevent death before the onset of symptoms

Recommendations	Class ^a	Level ^b	Ref ^c
Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life.	I	A	126, 129, 150, 151
Treatment with statins is recommended in patients with or at high-risk of CAD whether or not they have LV systolic dysfunction, in order to prevent or delay the onset of HF and prolong life.	I	A	137–140, 152
Counselling and treatment for smoking cessation and alcohol intake reduction is recommended for people who smoke or who consume excess alcohol in order to prevent or delay the onset of HF.	I	C	131–134
Treating other risk factors of HF (e.g. obesity, dysglycaemia) should be considered in order to prevent or delay the onset of HF.	IIa	C	130, 141, 153–155
Empagliflozin should be considered in patients with type 2 diabetes in order to prevent or delay the onset of HF and prolong life.	IIa	B	130
ACE-I is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction in order to prevent or delay the onset of HF and prolong life.	I	A	5, 144, 145
ACE-I is recommended in patients with asymptomatic LV systolic dysfunction without a history of myocardial infarction, in order to prevent or delay the onset of HF.	I	B	5
ACE-I should be considered in patients with stable CAD even if they do not have LV systolic dysfunction, in order to prevent or delay the onset of HF.	IIa	A	142
Beta-blocker is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction, in order to prevent or delay the onset of HF or prolong life.	I	B	146
ICD is recommended in patients: <ul style="list-style-type: none"> a) with asymptomatic LV systolic dysfunction (LVEF ≤30%) of ischaemic origin, who are at least 40 days after acute myocardial infarction, b) with asymptomatic non-ischaemic dilated cardiomyopathy (LVEF ≤30%), who receive OMT therapy, in order to prevent sudden death and prolong life.	I	B	149, 156–158

HFSA guidelines

- 5.5 **ACE inhibitor therapy** is recommended for asymptomatic patients with reduced LVEF (<40%). (**Strength of Evidence = A**)
- 5.7 **Beta blocker therapy** should be considered in asymptomatic patients with reduced LVEF. (**post-MI, Strength of Evidence = B; non post-MI, Strength of Evidence = C**)

Clinical trials with asymptomatic LVSD

Angiotensin-receptor blockers

VALIANT	Myocardial infarction and LVSD, heart failure, or both (14 703); asymptomatic LVSD (4099)	Valsartan, captopril, or both	24.7	No difference ($P = \text{NS}$)	NR	No difference ($P = \text{NS}$)
OPTIMAAL	Acute myocardial infarction and symptomatic heart failure (5477); asymptomatic LVSD (1735)	Losartan vs captopril	32.4	13% increase in risk with losartan ($P = .07$)	19% increase in risk with losartan ($P = .07$)	NR

Implantable cardioverter defibrillators

MADIT-II	Myocardial infarction and LVEF $\leq 30\%$ (1232); Asymptomatic LVSD (461)	ICD vs CMT	20	31 ($P = .02$)	NR	NR
DEFINITE	Nonischemic dilated cardiomyopathy, LVEF $< 36\%$ (458); Asymptomatic LVSD (99)	ICD vs CMT	29	35 ($P = \text{NS}$)	80 ^d ($P = .006$)	NR

Abbreviations: ACE, angiotensin-converting enzyme; CMT, conventional medical therapy; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; NR, not reported; NS, not significant.

^a Death or hospitalization for heart failure.

^b Severe heart failure.

^c Arrhythmic death.

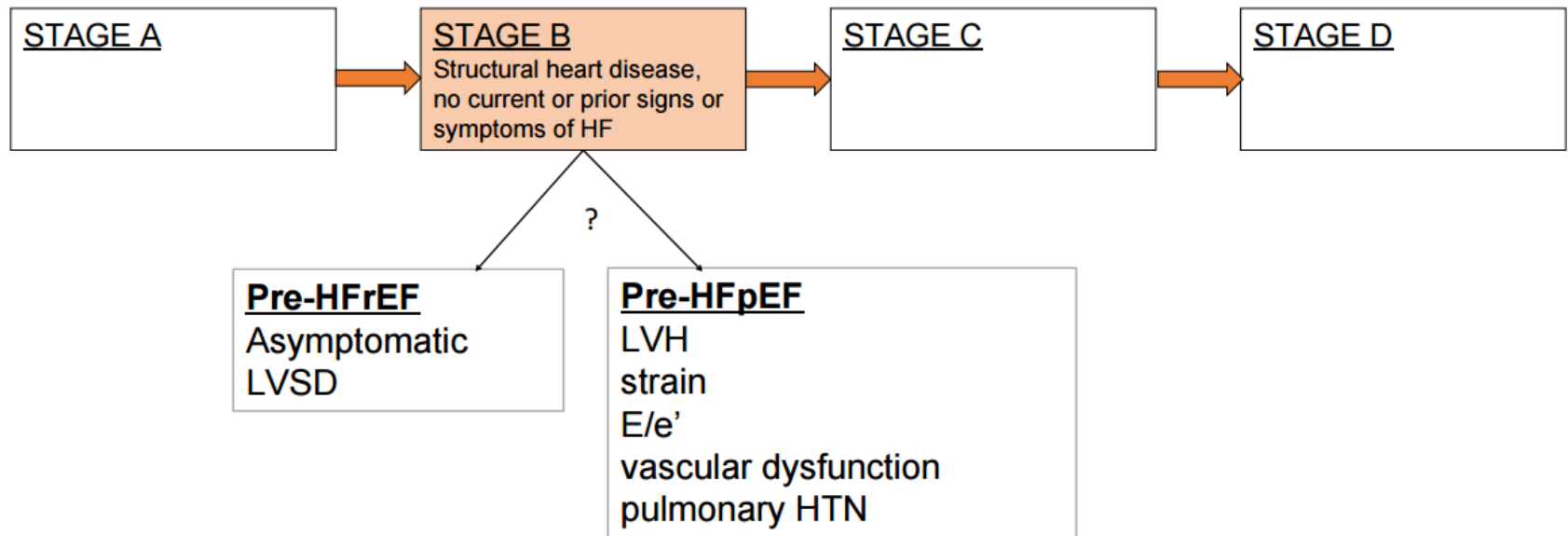
^d Sudden death from arrhythmia.

Reprinted from Goldberg and Jessup,⁵⁵ with permission.

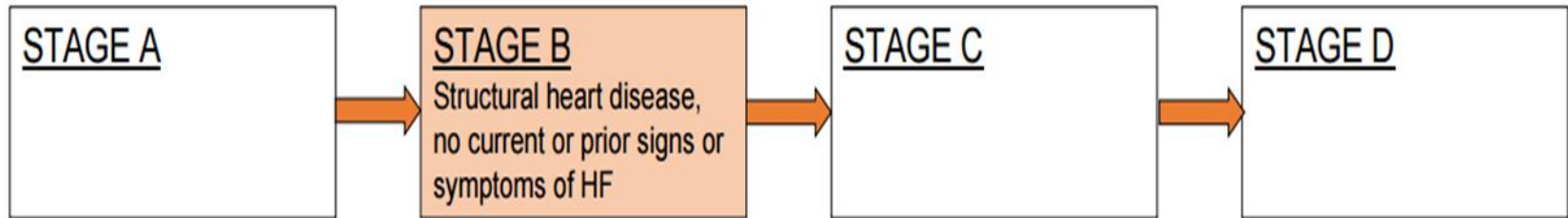
Aldosterone Antagonists in Patients With ALVD

- Although aldosterone antagonists have been demonstrated to decrease morbidity and mortality in patients with moderate to severe symptoms of HF and reduced LVEF, **there are currently no substantial data** to suggest that these agents should be recommended as treatment for patients with ALVD.

Can we re-imagine stage B HF phenotyping?



Conclusion : Management of Stage B Heart Failure



- Prevalence : 2~9% in general population, 10~20% in AMI population, 3 to 4 X greater than those at stages C and D
- Risk Modification, especially co-morbidities
- Gold standard Tx : ACEI + BB
- New Targeted Therapies for Prevention

감사합니다.

