



Heart Failure

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Round Up Centre, Calgary

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Objectives

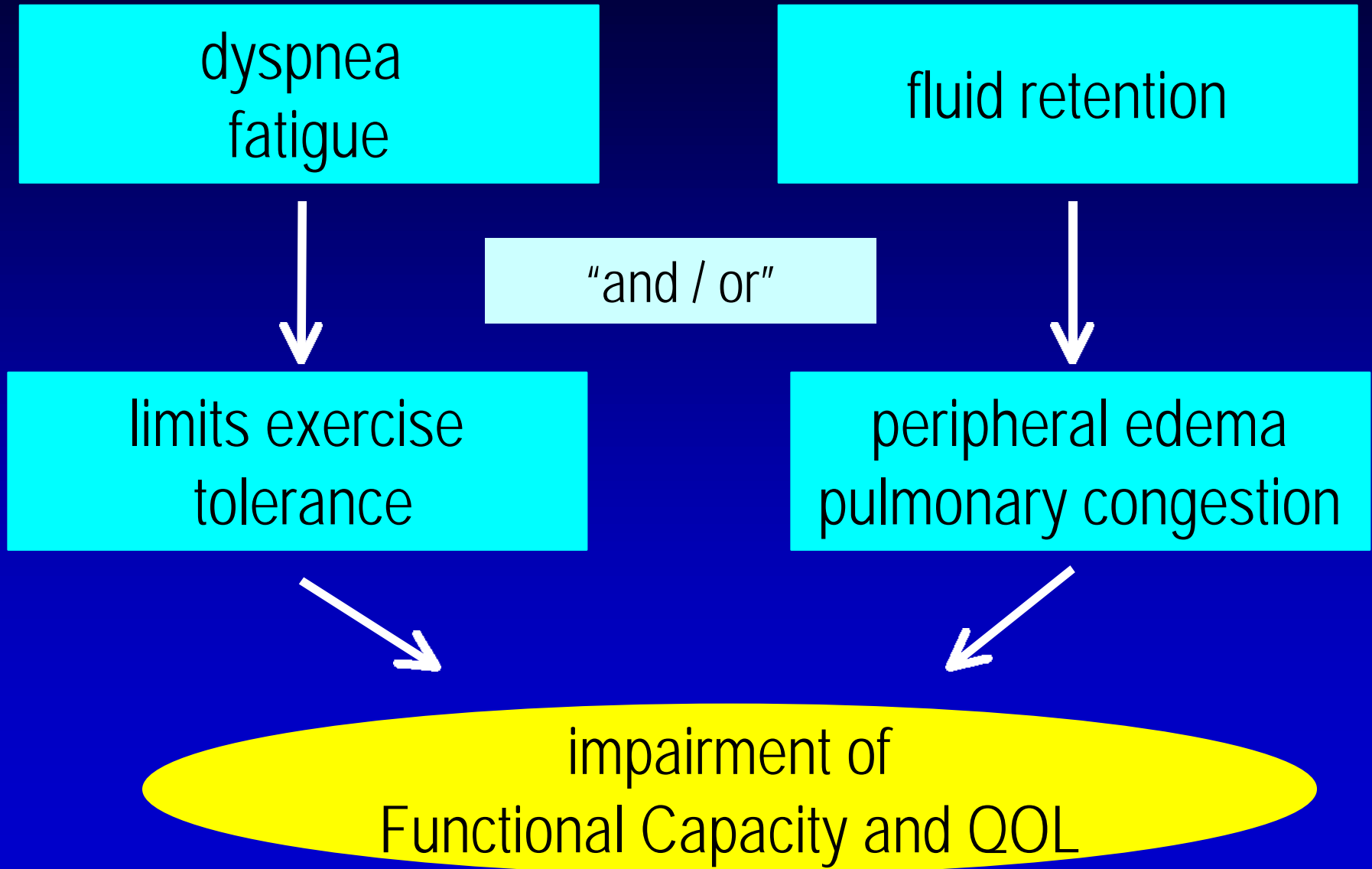
- Heart Failure
 - definition
 - epidemiology
 - prognosis
 - diagnosis
 - management

What is Heart Failure?

A complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.

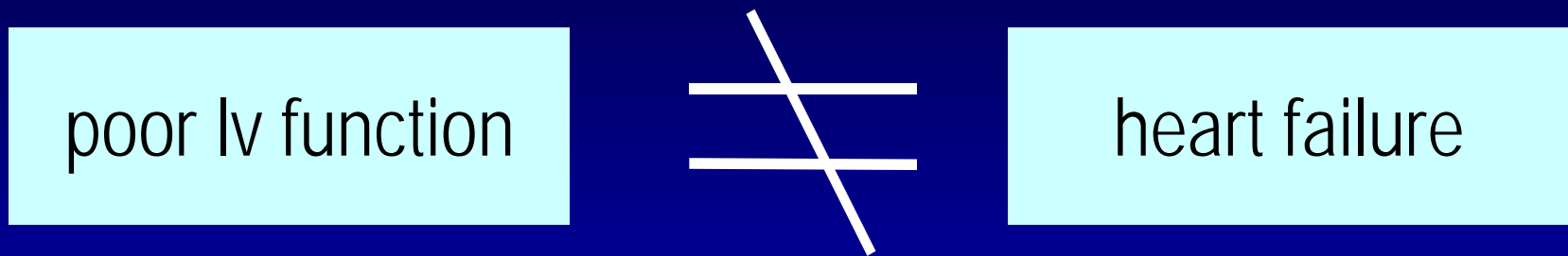
American College of Cardiology 2001

Cardinal Manifestations of HF



Cardinal Manifestations of HF

- point to keep in mind...



- no test for heart failure
 - it's a clinical diagnosis based on
 - history
 - physical examination
 - selected investigations

Epidemiology of HF

JACC 1993;6A-13A

- Framingham Study
- 1948:
 - 5,209 residents entered
 - 5,135 offspring entered as well
 - history, physical exam, and lab q2 yearly

Incidence of CHF

JACC Vol. 22, No. 4 (Supplement A)
October 1993:6A-13A

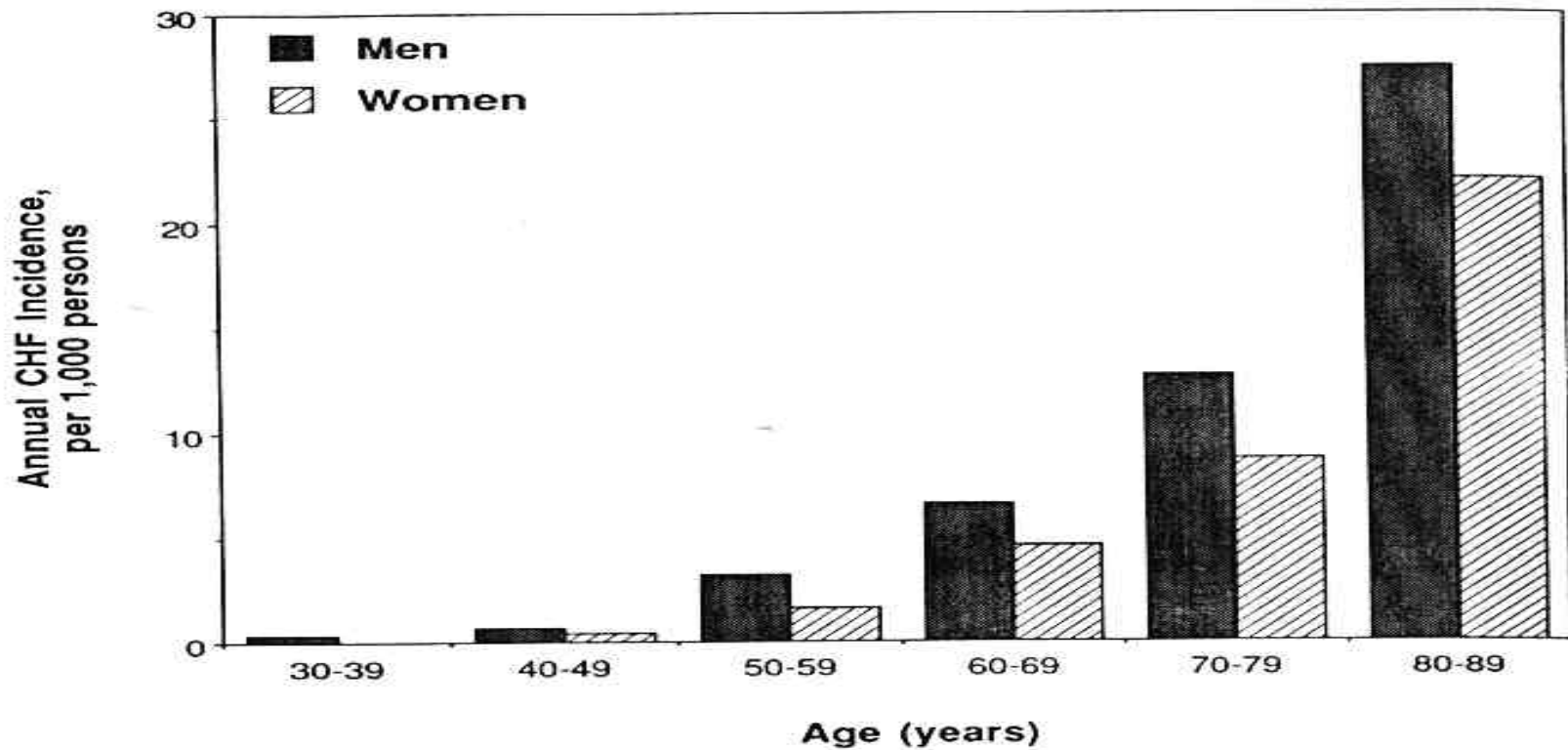
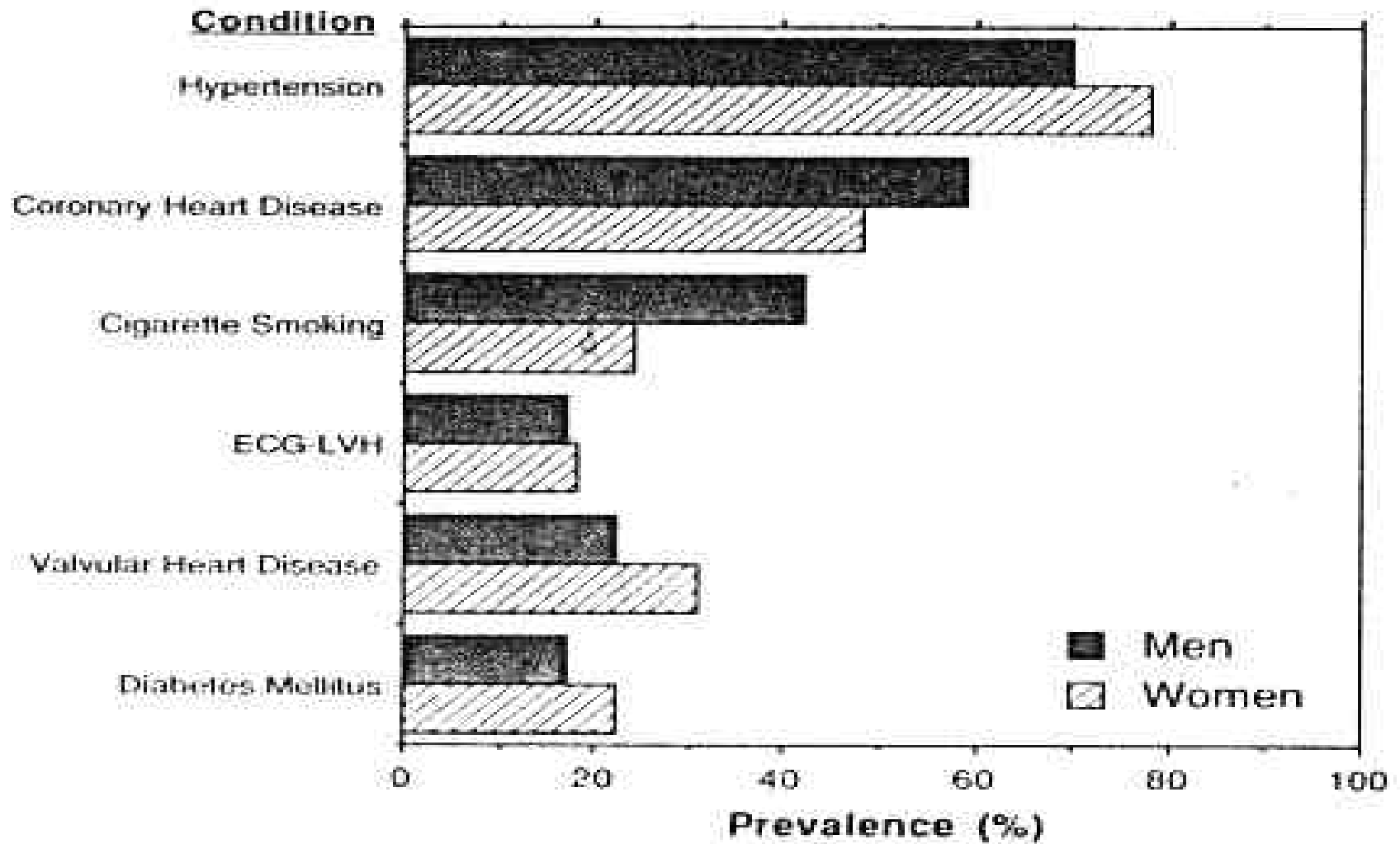


Figure 1. Incidence rates of congestive heart failure (CHF) among Framingham Heart Study subjects, by gender and age.

Prevalence of selected conditions in HF



Prognosis of HF

Table 2. Overall Survival After Congestive Heart Failure as Estimated by Kaplan-Meier Methods

	Subjects (no.)	Median Survival Time (yr)	Survival Rates				
			90 days	1 yr	2 yr	5 yr	10 yr
All subjects with congestive heart failure							
Men	331	1.66	0.73	0.57	0.46	0.25	0.11
Women	321	3.17	0.72	0.64	0.56	0.38	0.21
Subjects with congestive heart failure who survived ≥ 90 days							
Men	237	3.21	—	0.79	0.63	0.35	0.15
Women	230	5.39	—	0.88	0.78	0.53	0.29

Staging of Heart Failure

NYHA Cardiac Status

- Class I: uncompromised
 - Class II: slightly compromised
 - Class III: moderately compromised
 - Class IV: severely compromised
- updated from old NYHA Classification
- ‘usual activities’ ‘minimal exertion’

Specific Activity Scale

Goldman Circulation 64:1227, 1981

Stage I

- patients can perform to completion any activity requiring 7 metabolic equivalents
 - can carry 24 lb up eight steps
 - carry objects that weigh 80 lb
 - do outdoor work [shovel snow, spade soil]
 - do recreational activities [skiing, basketball, squash, handball, jog/walk 5 mph]

Specific Activity Scale

Goldman Circulation 64:1227, 1981

Stage II

- patients can perform to completion any activity requiring 5 metabolic equivalents
 - have sexual intercourse without stopping
 - garden, rake, weed, roller skate
 - dance fox trot, walk at 4 mph on level ground
 - but cannot and do not perform to completion activities requiring 7 metabolic equivalents

Specific Activity Scale

Goldman Circulation 64:1227, 1981

Stage III

- patients can perform to completion any activity requiring 2 metabolic equivalents
 - dress, shower without stopping, strip and make bed, clean windows
 - walk 2.5 mph, bowl, play golf, dress without stopping
 - but cannot and do not perform to completion any activities requiring 5 metabolic equivalents

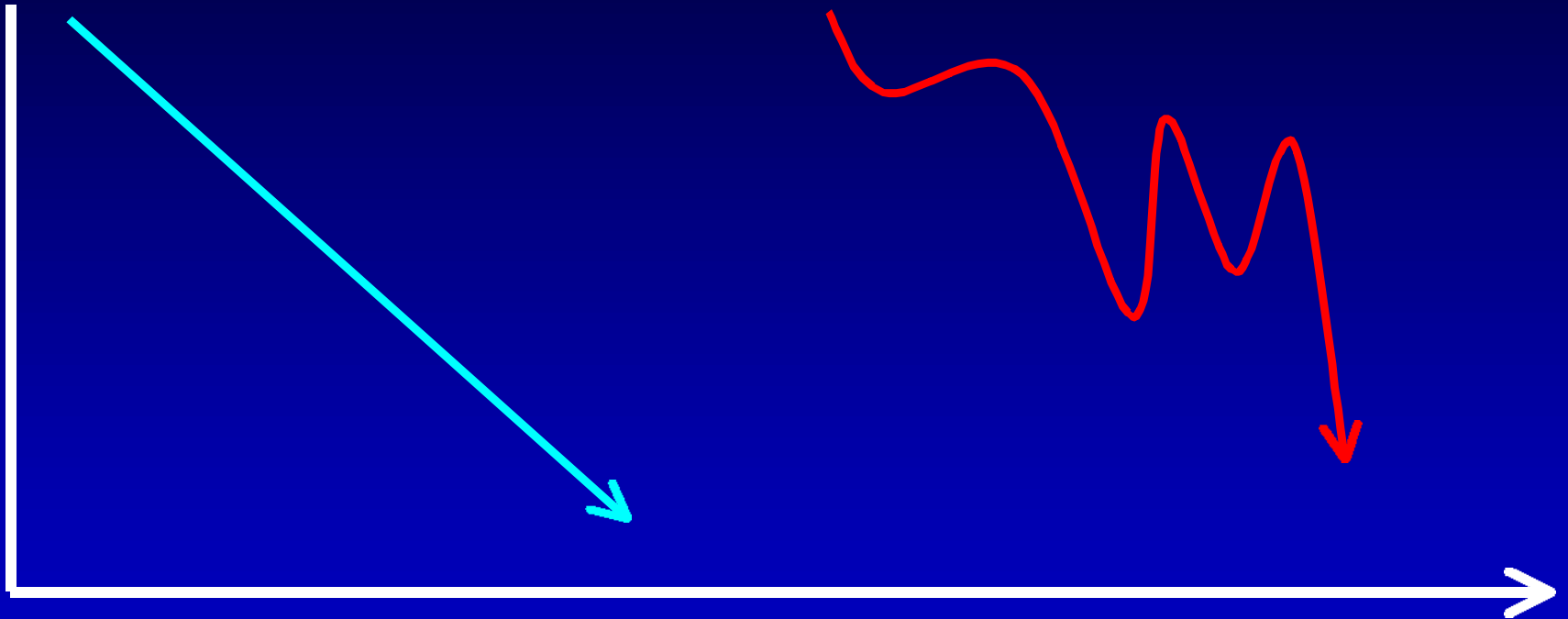
Specific Activity Scale

Goldman Circulation 64:1227, 1981

Stage IV

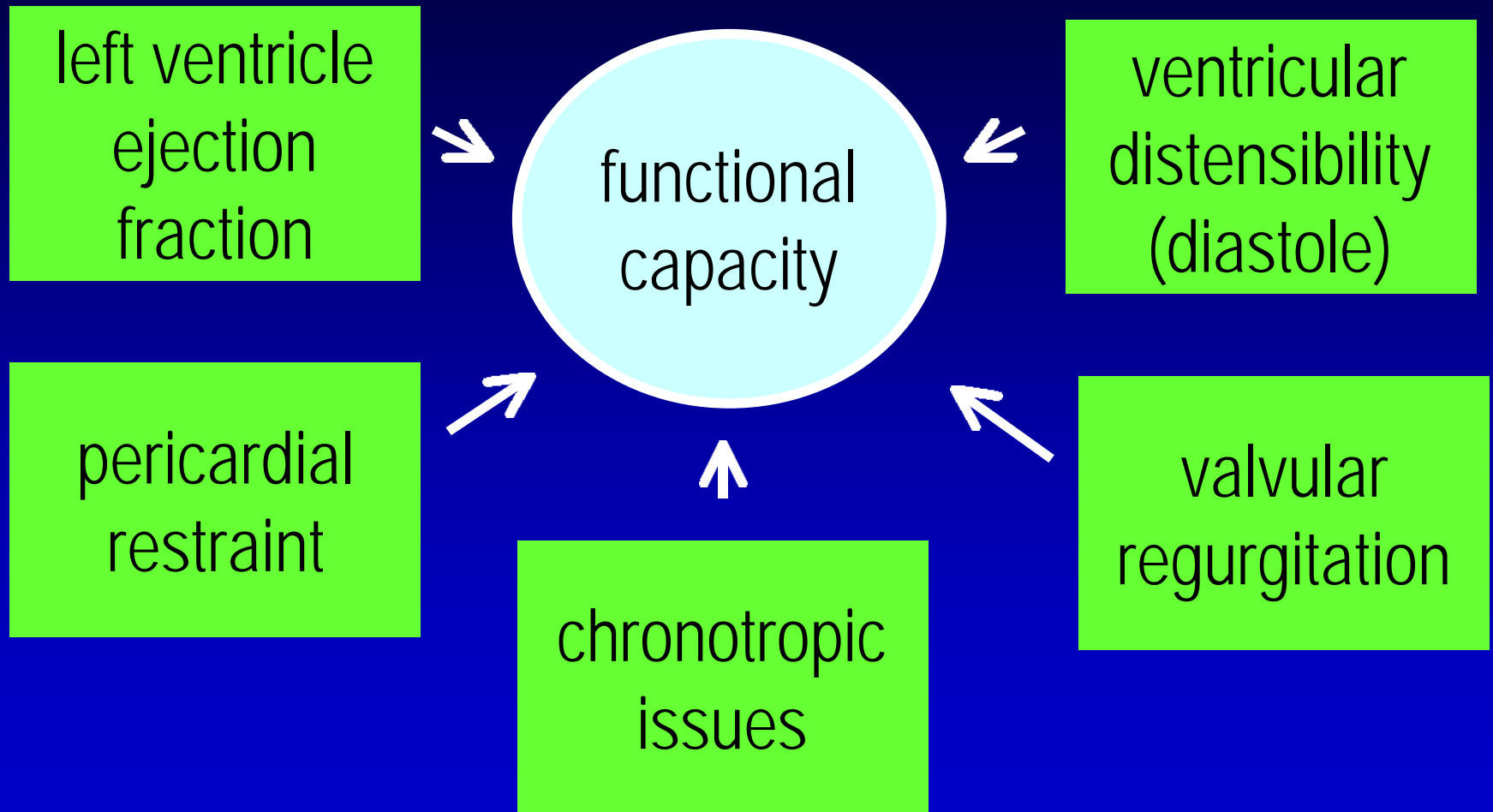
- patients cannot or do not perform to completion activities requiring 2 metabolic equivalents
 - CAN'T:
 - dress without stopping
 - shower without stopping
 - strip and make bed
 - walk 2.5 mph
 - bowl, play golf

Progression of Cardiac Status

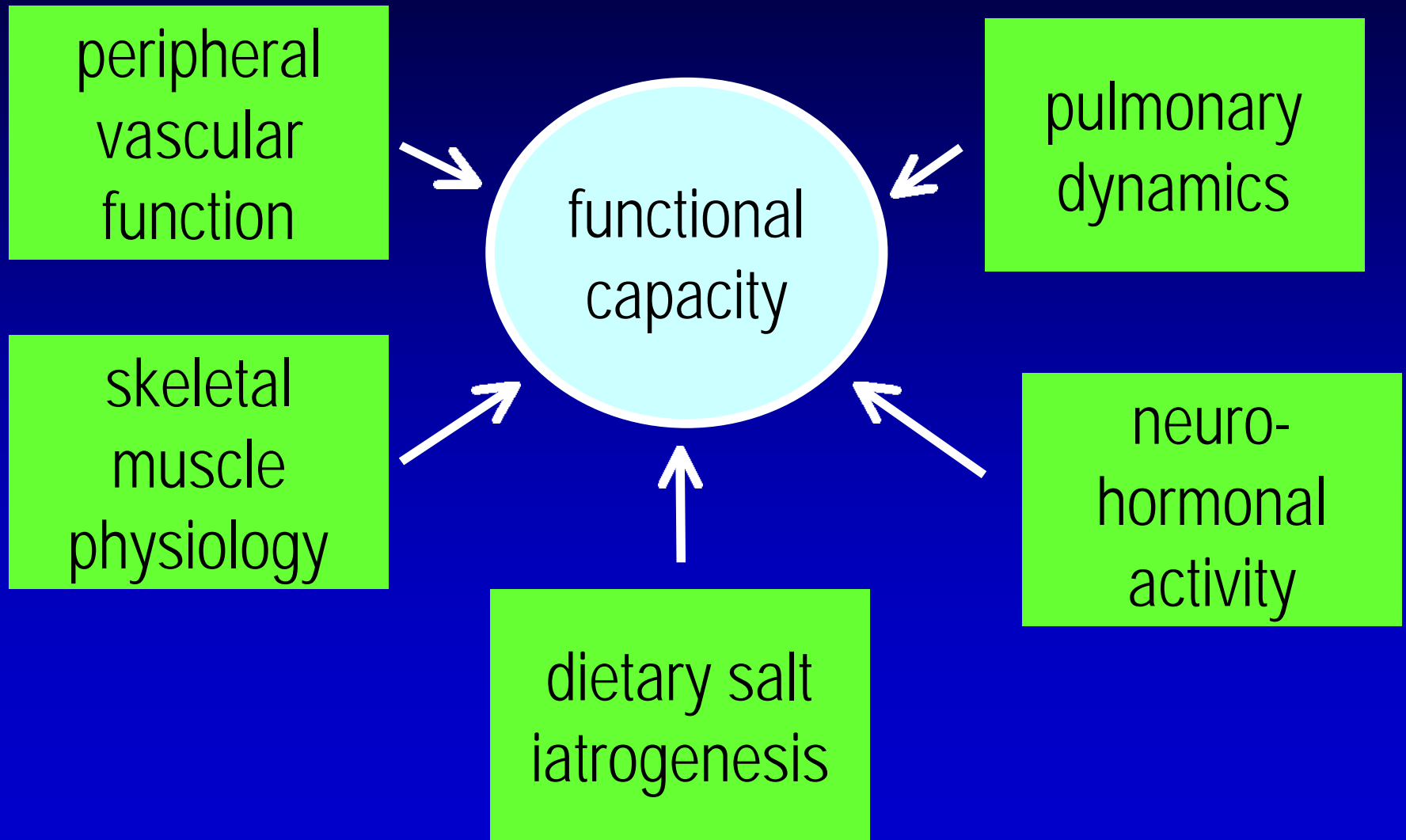


- most patients do not show an uninterrupted and inexorable deterioration
- deterioration may be independent of LV function

Cardiac factors impact on Status



Non-cardiac factors impact on Status



Diagnosis of Heart Failure

- Heart Failure is mainly a clinical diagnosis
- HF is correctly diagnosed initially in 50% of affected patients. Eur Heart J 1991

Symptoms of Heart Failure

- pulmonary
 - resting or exertional dyspnea
 - orthopnea
 - paroxysmal nocturnal dyspnea
 - cough
 - wheezes

Symptoms of Heart Failure

- other volume issues
 - nocturia
 - lower limb edema
 - gastrointestinal symptoms
 - abdominal bloating
 - anorexia
 - fullness in the right upper quadrant
- fatigue
- cachexia
- delirium

Signs of Heart Failure

- vital signs - normal or abnormal
- peripheral edema
 - detected when extracellular volume > 5 l
 - stasis dermatitis
 - chronic venous stasis
 - hyperpigmentation
 - ulceration



Signs of Heart Failure

elevation of JVP > 4.5 cm

spec = 90% sens = 30%

Distinguishing JVP/CP

variation with respiration

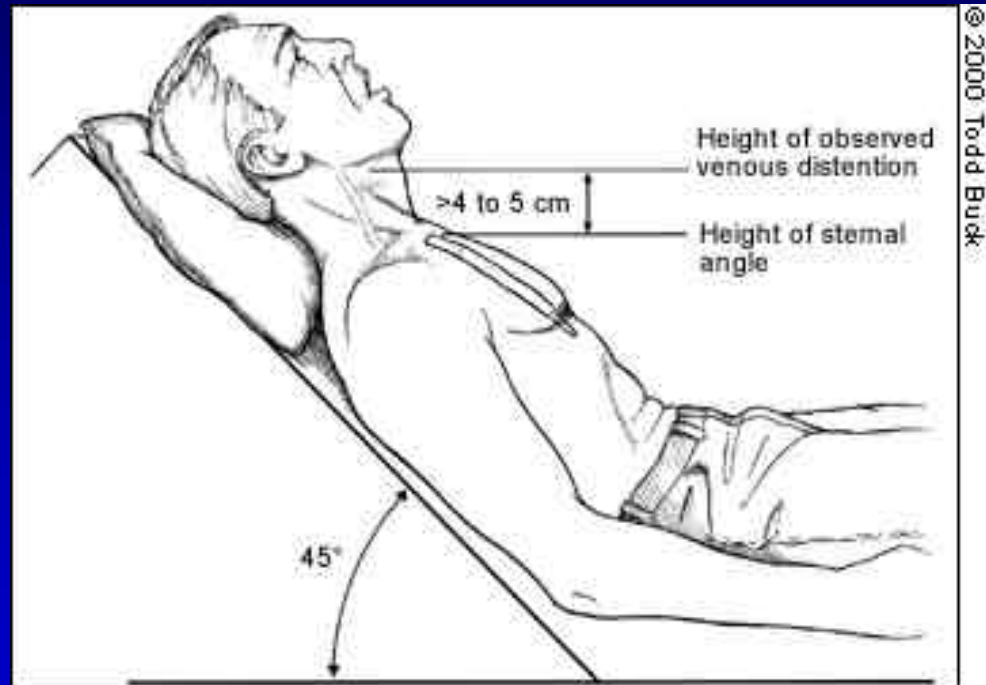
variation with position

varies with hepatic pres

occludes

non-palpable

wave form



Palpate Contralateral Carotid Artery

- if what you FEEL is not= to what you SEE --> JVP

Signs of Heart Failure

– S3

- sensitivity for HF = 24%
- specificity for HF = 99%

– S4

- reduced ventricular compliance

– pulmonary examination

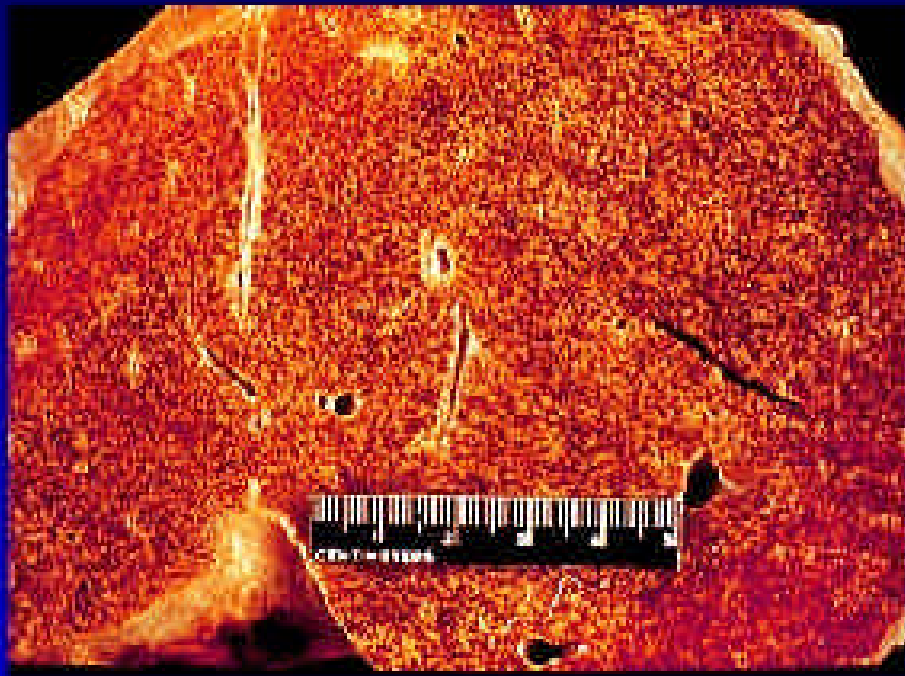
- crackles (may be absent even with edema)
- signs of pleural effusion
- wheezes

Signs of Heart Failure

- Hepatojugular reflux
 - performed with patient at 45 degrees
 - apply moderate pressure over liver
 - 3 - 5 cardiac cycles is usually sufficient
 - positive if increase in JVP during maneuver
- Liver enlargement

“Nutmeg” Liver

“Nutmeg” Liver



Cross Section of a Nutmeg



Would you confuse the two????

Let's see ... Liver? Nutmeg? hhhmmmm

Nutmeg??? Liver??? Oh!! I get it!!!

Laboratory

- Troponin T
 - increases reflect myocardial necrosis
 - prognosis relates to degree of elevation
 - become elevated 6 - 8 hours after onset of necrosis
 - peak at 12 - 24 hours
 - remain elevated for 7 - 10 days after necrosis

Laboratory

- Troponin T
 - TnT < 0.03 ug/l
 - not c/w MI provided specimen was collected > 6 h from onset of symptoms
 - TnT < 0.03 - 0.09 ug/l
 - inconclusive for MI provided the specimen was collected > 6 hours from onset of symptoms
 - TnT > = 10.0 ug/l
 - indicates myocardial damage (necrosis)

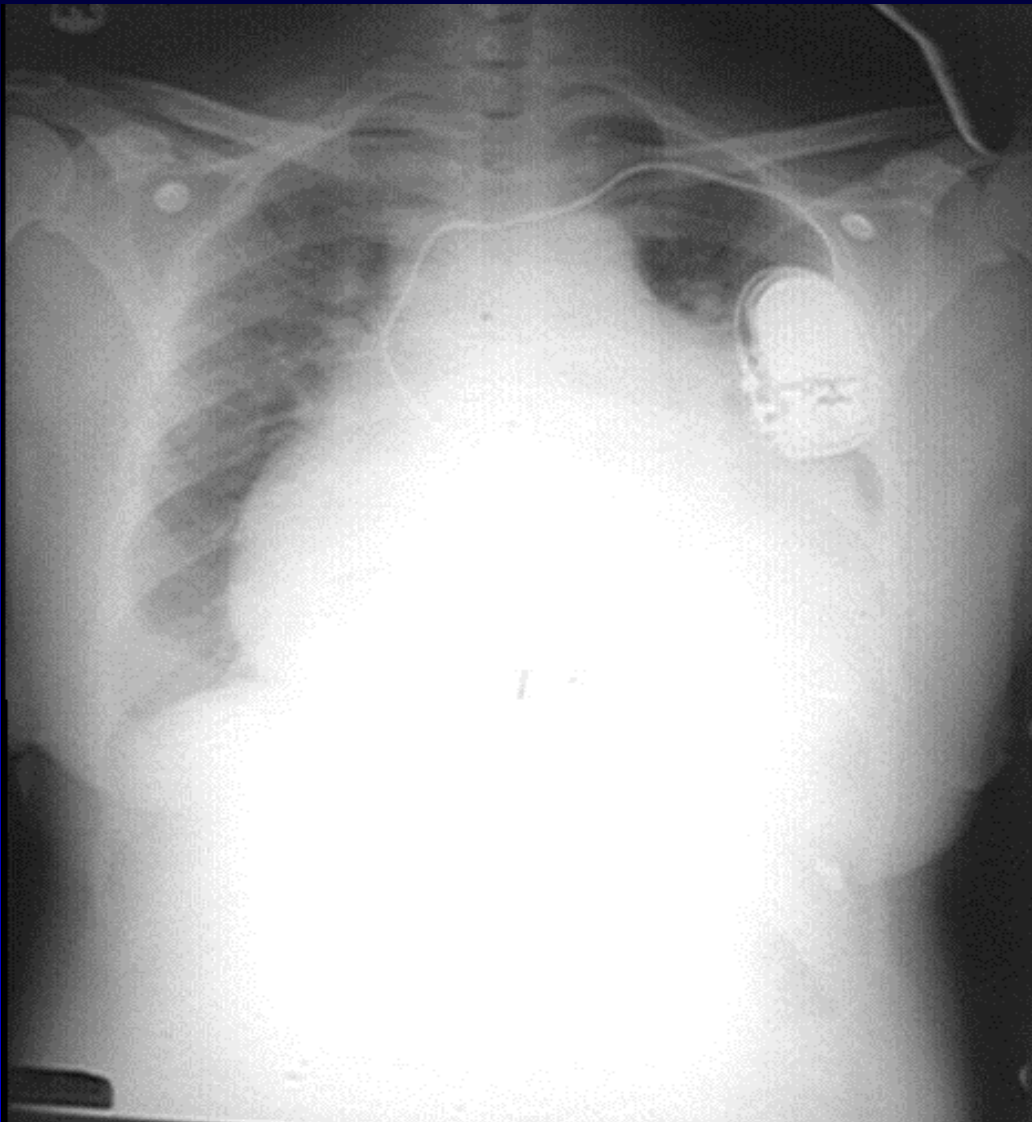
Hemodialysis patients may have increased TnT.

algorithm

Laboratory

- TnT < 0.03 - 0.09 ug/l
 - inconclusive for MI provided the specimen was collected > 6 hours from onset of symptoms
- Now what? In my humble opinion....
 - is the necrosis due to coronary plaque rupture for which an ACS protocol is undertaken?
 - if yes, is this patient eligible for management with such interventions?
 - if no, maximize non-CCU interventions
 - or....is the necrosis due to insufficient oxygen delivery in the setting of a fixed coronary lesion?
 - if yes, maximize pulmonary and cardiac functions

Diagnostic Imaging



pulmonary edema

pleural effusions

Kerley's lines

alveolar pattern

indistinct arteries

interstitial markings

increased

redistributed

peribronchial cuff

ventricular dx

increased CT ratio

enlarged silhouette

Diagnostic Imaging



Common causes of Heart Failure

- coronary artery disease
- hypertension
- aortic and/or mitral valve disease

Other causes of Heart Failure

Infections (viruses (including HIV) bacteria, parasites)

Pericardial diseases

Drugs (alcohol, doxorubicin, cyclophosphamide, cocaine)

Connective tissue disease

Infiltrative disease (e.g., amyloidosis, sarcoidosis, hemochromatosis, malignancy)

Persisting tachycardia

Obstructive cardiomyopathy

Neuromuscular disease (e.g., muscular or myotonic dystrophy, Friedreich's ataxia)

Metabolic disorders (e.g., glycogen storage disease type 2 [Pompe's disease] and type 5 [McArdle's disease])

Nutritional disorders (e.g., beriberi, kwashiorkor)

Pheochromocytoma

Radiation

Endomyocardial fibrosis

Eosinophilic endomyocardial disease

High-output heart failure (e.g., intracardiac shunt, atrioventricular fistula, beriberi, pregnancy, Paget's disease, hyperthyroidism, anemia)

Peripartum cardiomyopathy

Dilated idiopathic cardiomyopathy

Approach to causes of Heart Failure

- Cardiac causes
 - pericardium
 - myocardium
 - endocardium
 - conducting system
- Non-cardiac causes
 - pre-load issues
 - afterload issues
 - medication issues

Approach to causes of Heart Failure

- 1 Pericardium

- tamponade, constrictive pericardial disease

- 2 Myocardium

- ischemia

- coronary, non-coronary ischemia (hypoxia / anemia)

- cardiomyopathy

- dilated: idiopathic, alcoholic, end stage CAD-HTN, peripartum, post-viral

- hypertrophic obstructive cardiomyopathy

- restrictive: hemochromatosis, amyloidosis, sarcoidosis

- endocrinopathy

- thyroid, adrenal disease (cortico / pheo)

Approach to causes of Heart Failure

- **3 Endocardium**

- valvular heart disease (including infective)
- tumors (myxomas, sarcomas, melanomas)

- **4 Conducting System**

- tachycardia
 - mostly atrial fibrillation
 - hyperthyroidism
 - sepsis (use acetaminophen in vulnerable febriles)
- bradycardia
 - excess medication effect
 - third degree heart block

Approach to causes of Heart Failure

- **Pre-load issues**

- excess salt intake or saline
- post-inflammatory volume shifts
- renal disease
 - NSAIDs
 - chronic renal failure

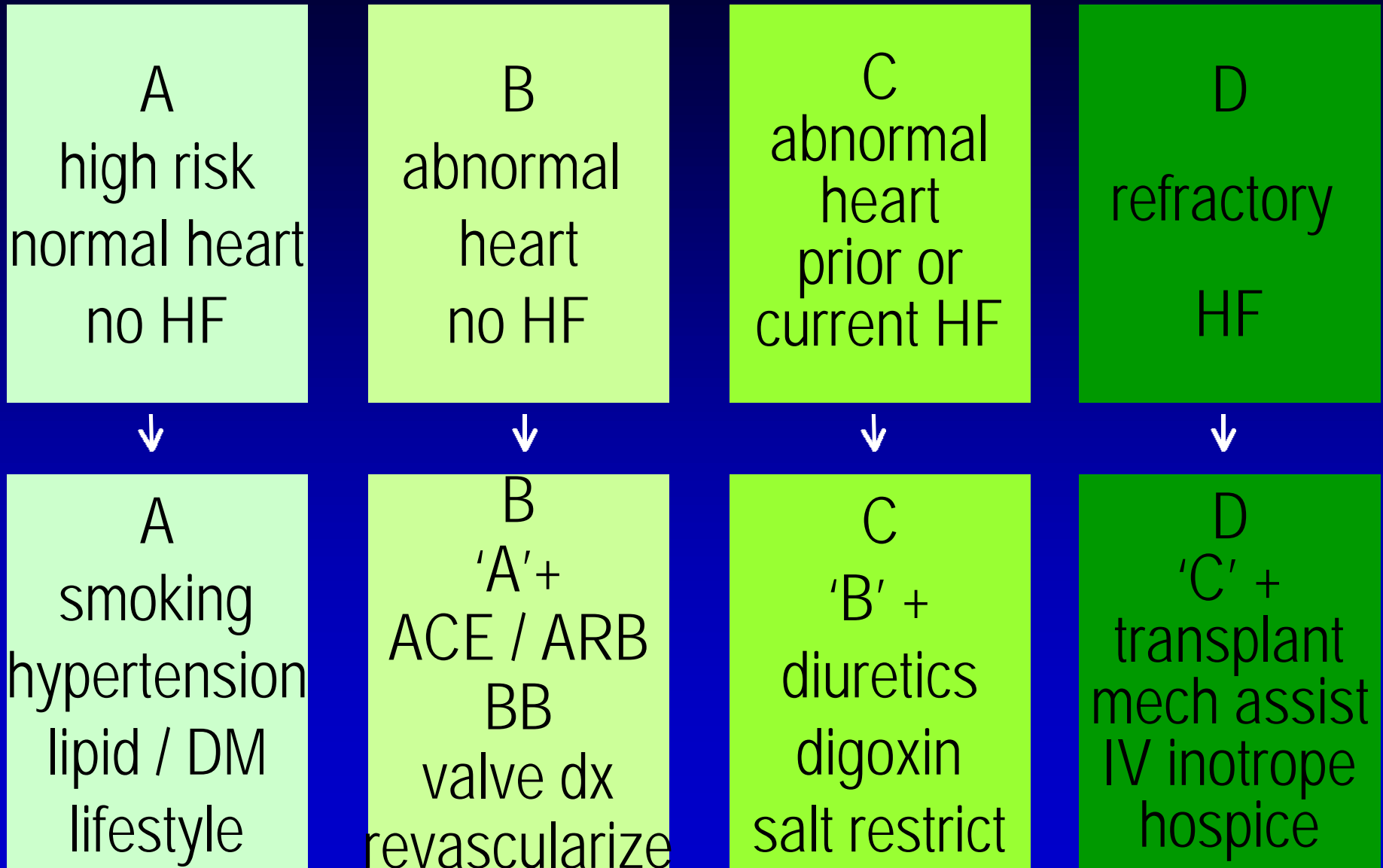
- **Afterload issues**

- hypertension (acute and/or chronic)

- **Medication issues**

- adherence, bioavailability

Management of HF



Medical Management of HF

- Diuretics
- Beta-blockers
- Digoxin
- Renin Angiotensin System
 - ACE - inhibitors
 - Angiotensin Receptor Blockers
 - Spironolactone

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Diuretics

- most rapid benefit
- should not be used alone
- dose needs titration
- patients should be educated about weight
- Under-appreciated Issues:
 - oral bioavailability decreases in gut edema
 - no NSAIDs
 - always treat pulmonary edema even if blood pressure is low

Medical Management of HF

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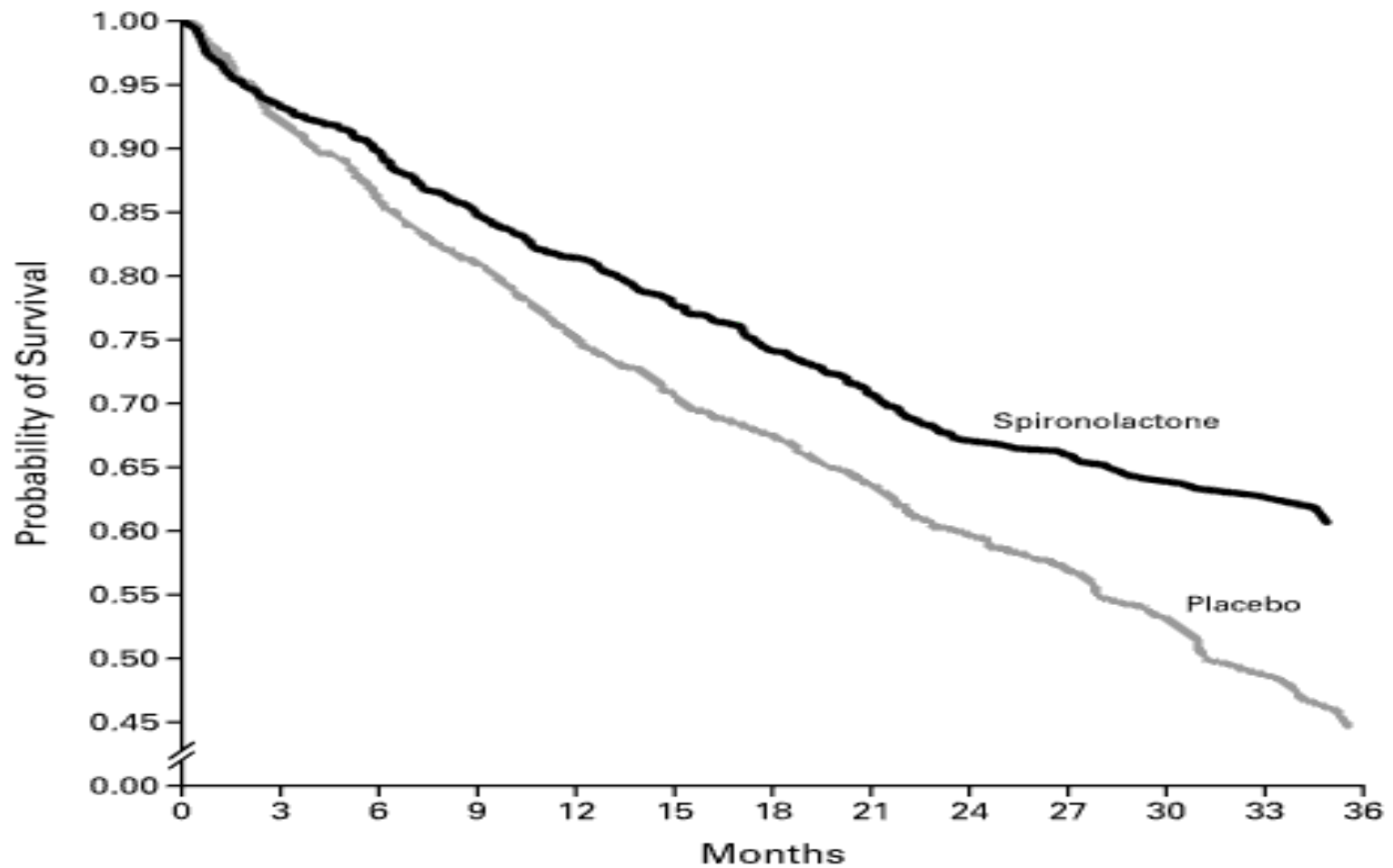
Randomized Aldactone Evaluation Study

N Engl J Med 1999;341:709-17

- Objective:
 - determine the effect of **spironolactone 25 - 50 mg po od** on mortality among those severe HF
- Methods
 - randomized double-blind study
 - n = 1663
 - NYHA Class IV HF
 - left ventricular ejection fraction $\leq 35\%$
 - co-treated with ACE-I, diuretic, usually digoxin

Randomized Aldactone Evaluation Study

N Engl J Med 1999;341:709-17



NO. AT RISK

Placebo	841	775	723	678	628	592	565	483	379	280	179	92	36
Spironolactone	822	766	739	698	669	639	608	526	419	316	193	122	43

Randomized Aldactone Evaluation Study

N Engl J Med 1999;341:709-17

TABLE 3. RELATIVE RISKS OF THE COMBINED END POINTS OF DEATH OR HOSPITALIZATION IN THE SPIRONOLACTONE GROUP.*

END POINT	RELATIVE RISK (95% CI)	P VALUE
Death from cardiac causes or hospitalization for cardiac causes	0.68 (0.59–0.78)	<0.001
Death from any cause or hospitalization for any reason	0.77 (0.68–0.86)	<0.001
Death from any cause or hospitalization for cardiac causes	0.68 (0.60–0.77)	<0.001

*Each analysis represents the time to the first occurrence of an event. For patients with both events, the analysis includes only the first event. CI denotes confidence interval.

Medical Management of HF

- Diuretics
- **Beta-blockers**
- Digoxin
- Renin Angiotensin System
 - ACE - inhibitors
 - Angiotensin Receptor Blockers
 - Spironolactone

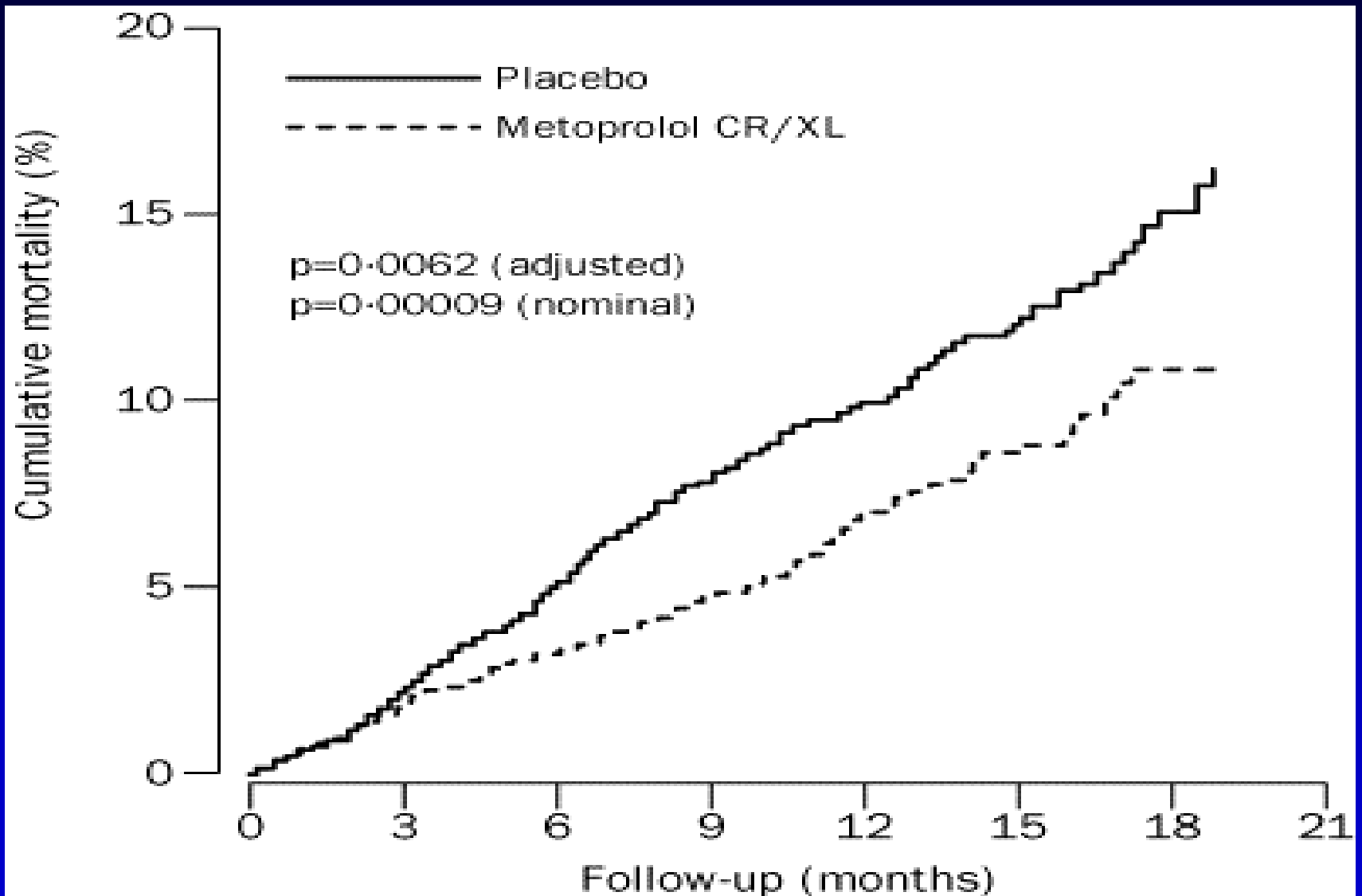
MERIT-HF Study Group

Lancet 1999; 353: 2001-07

- Objectives
 - what is the effect of metoprolol CR/XL once daily on mortality among HF
- Methods
 - double blind randomized trial n = 3991
 - NYHA class II-IV
 - ejection fraction $\leq 40\%$
 - randomized to metoprolol CR/XL 12.5 - 25 mg with upward titration vs placebo

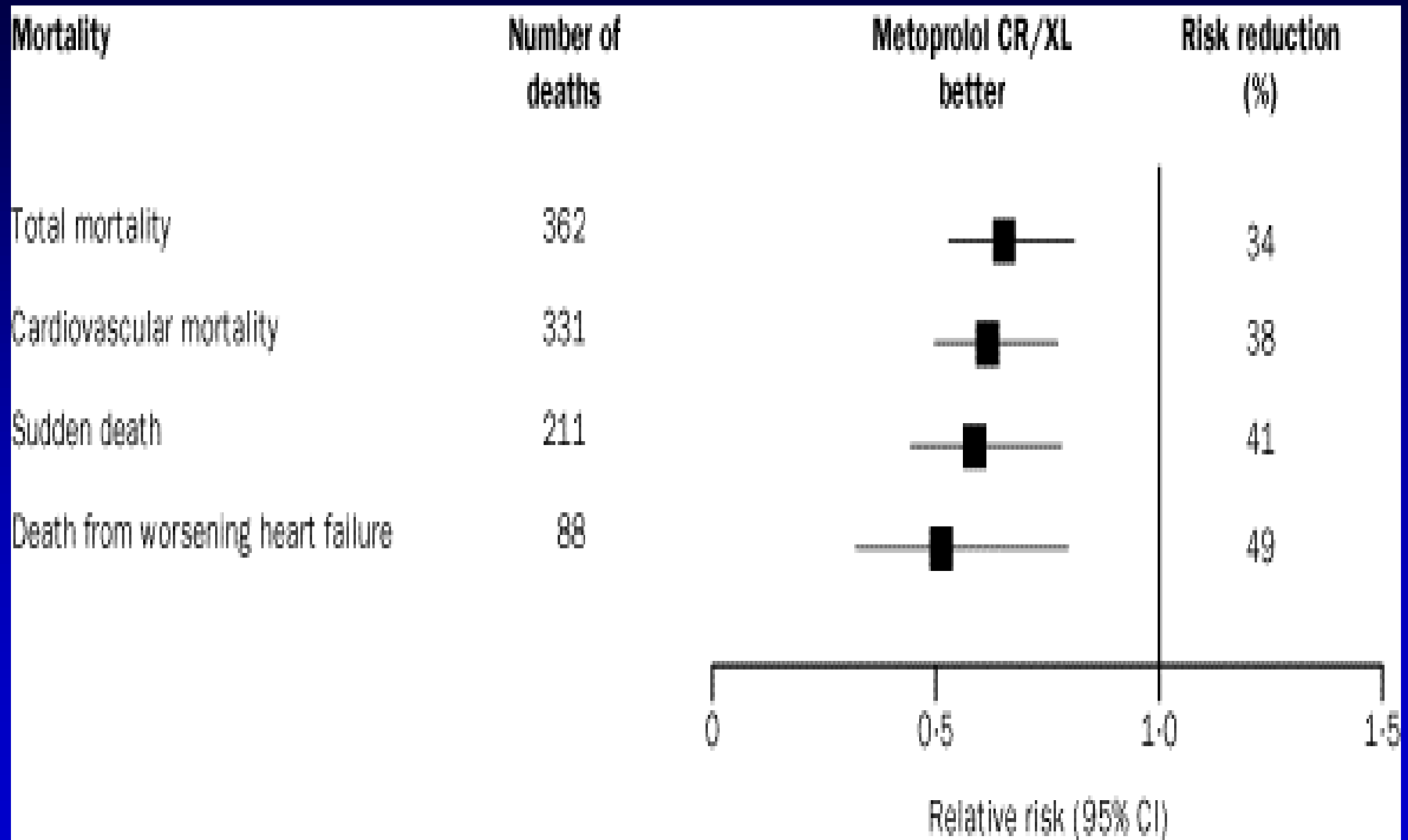
MERIT-HF Study Group

Lancet 1999; 353: 2001-07



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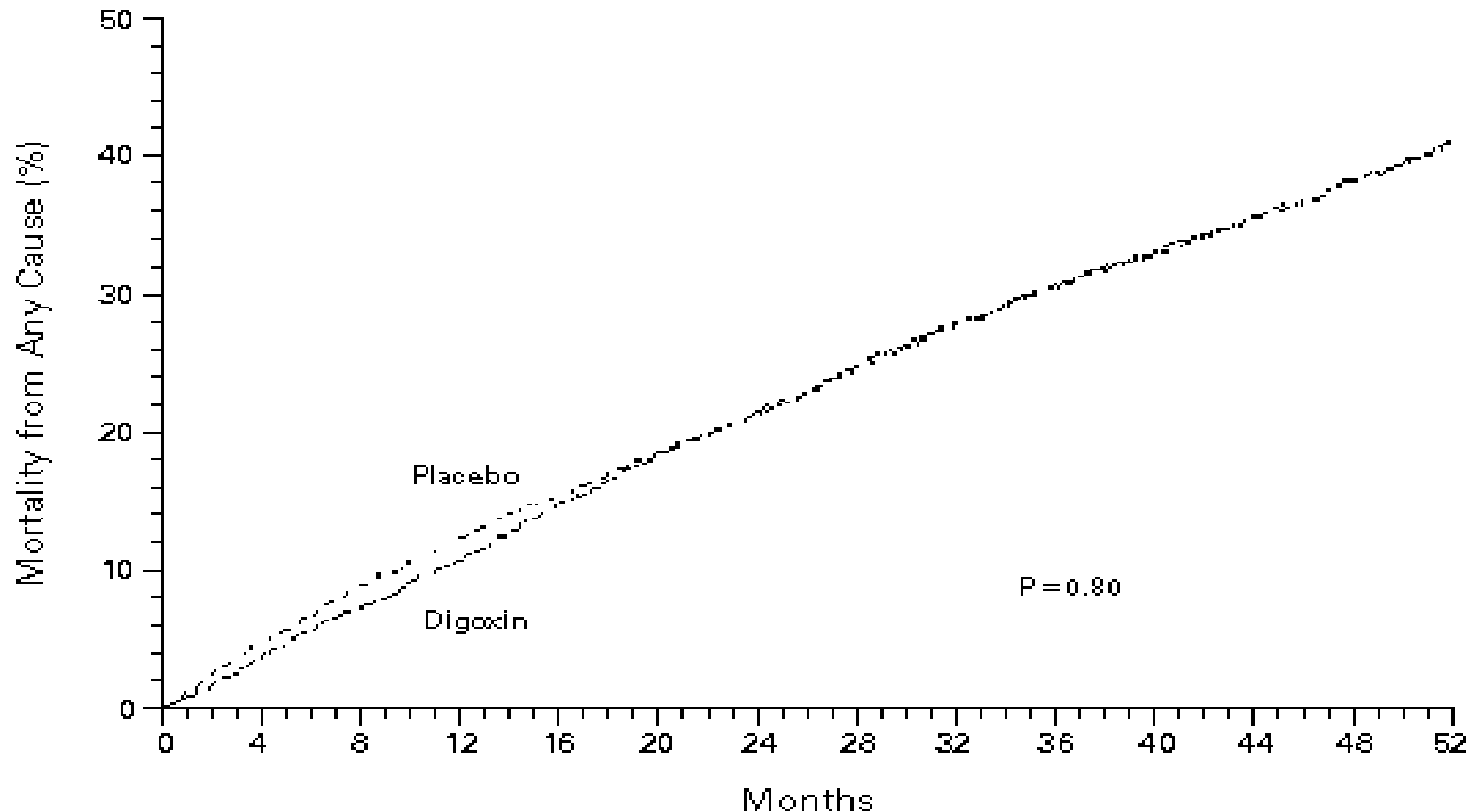
The Digitalis Investigation Group

N Engl J Med 1999;341:709-17

- Objective:
 - determine the effect of digoxin on mortality and hospitalization
- Methods:
 - main trial - ejection fraction of $\leq 45\%$
 - randomized to digoxin 3397 or placebo 3403
 - diuretics, ACE-I continued
 - ancillary trial - ejection fractions $> 45\%$
 - randomized to digoxin 492 or placebo 496

The Digitalis Investigation Group

N Engl J Med 1999;341:709-17

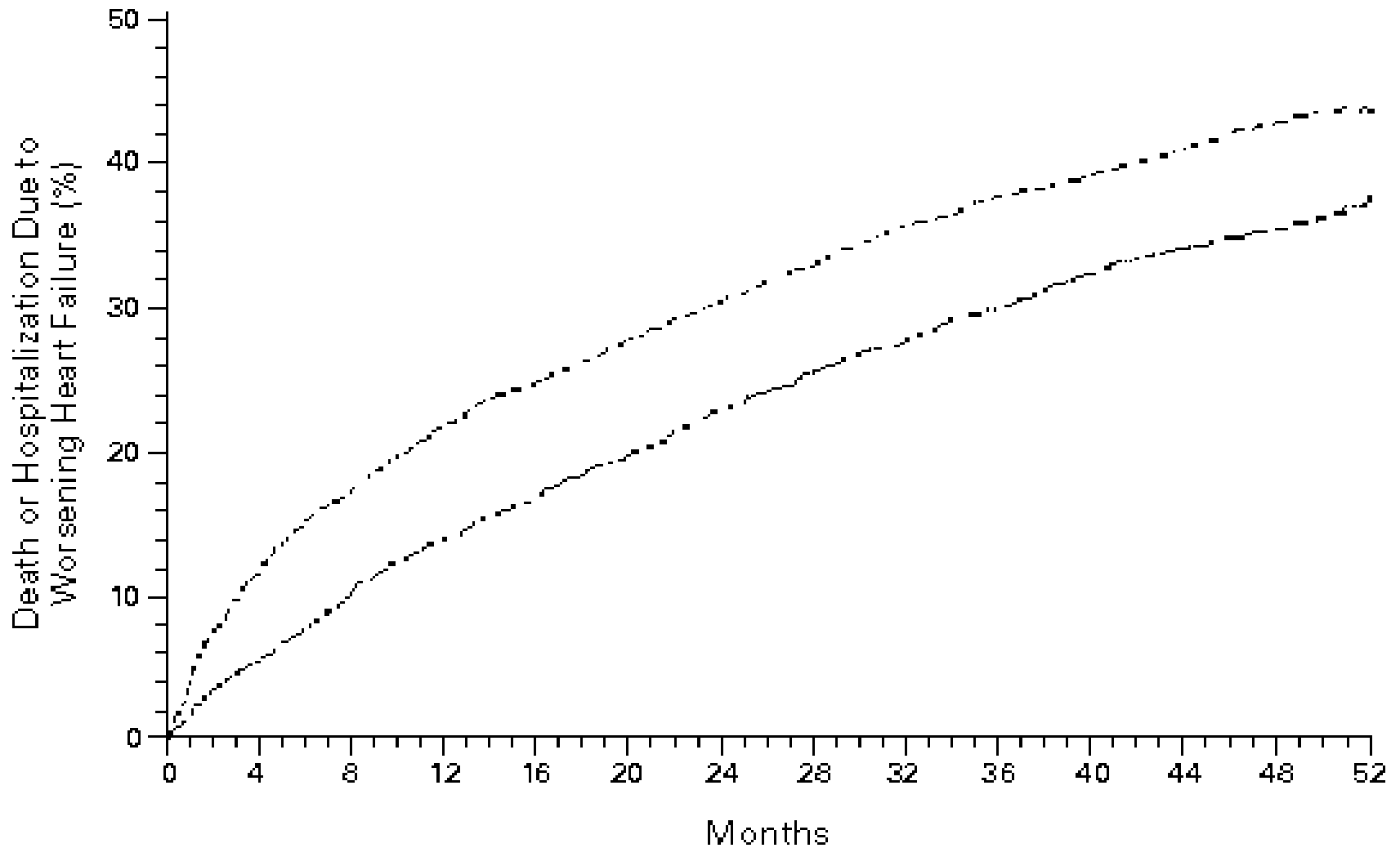


NO. OF PATIENTS AT RISK

Placebo	3403	3239	3105	2976	2868	2758	2652	2551	2205	1881	1506	1168	734	339
Digoxin	3397	3269	3144	3019	2882	2759	2644	2531	2184	1840	1475	1156	737	335

The Digitalis Investigation Group

N Engl J Med 1999;341:709-17



Medical Management of HF

- Diuretics
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Heart Outcomes Prevention Evaluation Trial

Lancet 2000; 355: 253-59

- Objectives

- determine the effect of ramipril on risk of CVD among patients at high risk for, but no history of LV dysfunction or HF

- Methods

- randomized, 2x2 factorial design n=9297
 - > 55 yrs
 - evidence of vascular disease or diabetes plus one other cardiovascular risk factor
 - were not known to have a low ejection fraction or heart failure

Heart Outcomes Prevention Evaluation Trial

Lancet 2000; 355: 253-59

- Methods
 - randomized ramipril 10 mg od or placebo
 - vitamin E 400 IU per day or placebo
- Outcome
 - primary outcome was a composite of myocardial infarction, stroke, or death from cardiovascular causes

Heart Outcomes Prevention Evaluation Trial

Lancet 2000; 355: 253-59

CHARACTERISTIC	RAMIPRIL GROUP (N=4645)	PLACEBO GROUP (N=4652)
Age — yr	66±7	66±7
Blood pressure — mm Hg	139±20/79±11	139±20/79±11
Heart rate — beats/min	69±11	69±11
Body-mass index	28±4	28±4
Female sex — no. (%)	1279 (27.5)	1201 (25.8)
History of coronary artery disease — no. (%)	3691 (79.5)	3786 (81.4)
Myocardial infarction	2410 (51.9)	2482 (53.4)
Within ≤1 year	452 (9.7)	446 (9.6)
Within >1 year	1958 (42.2)	2036 (43.8)
Stable angina pectoris	2544 (54.8)	2618 (56.3)
Unstable angina pectoris	1179 (25.4)	1188 (25.5)
CABG	1192 (25.7)	1207 (25.9)
PTCA	853 (18.4)	806 (17.3)
Stroke or transient ischemic attacks — no. (%)	500 (10.8)	513 (11.0)
Peripheral vascular disease — no. (%)†	1966 (42.3)	2085 (44.8)

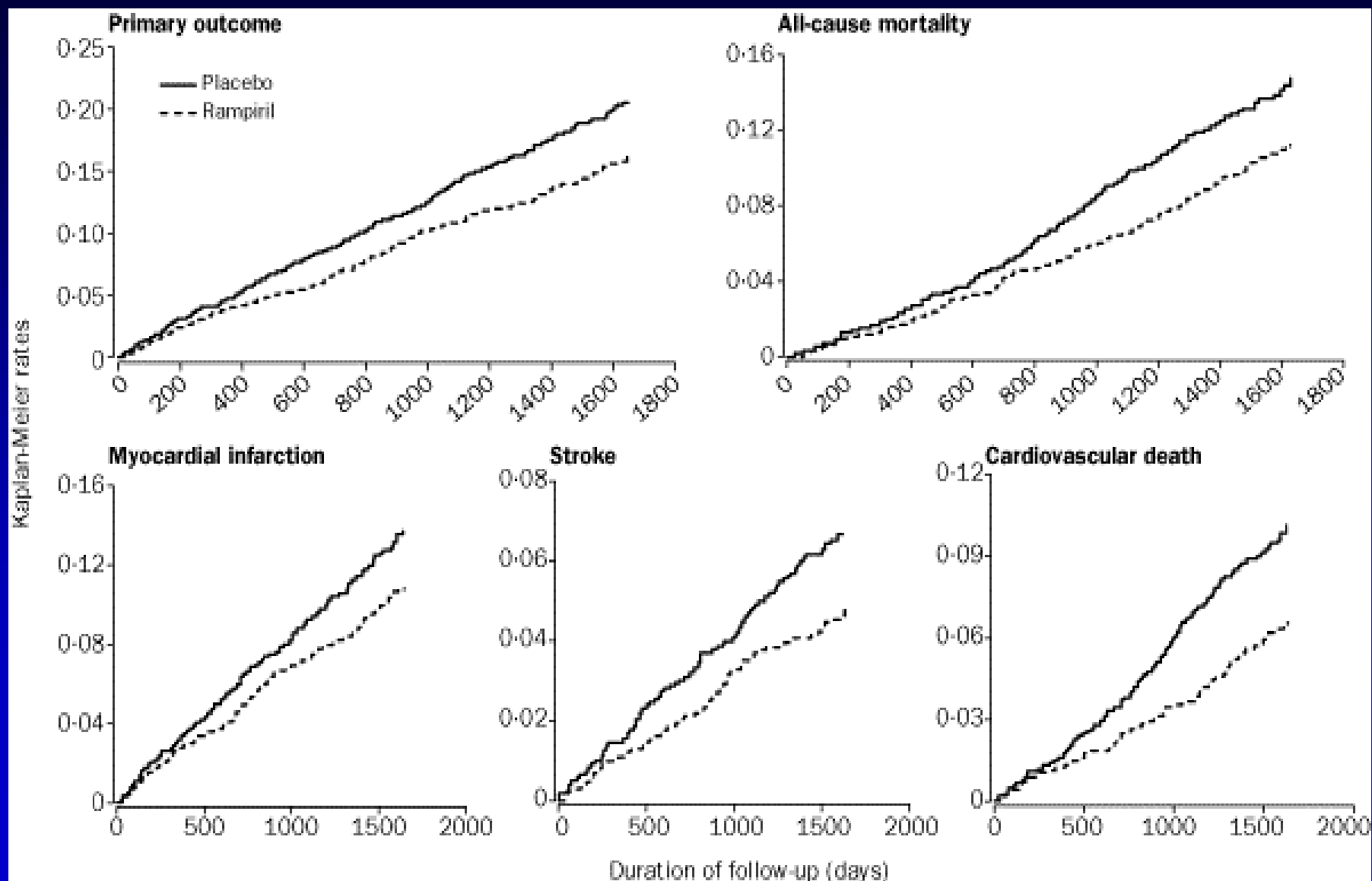
Heart Outcomes Prevention Evaluation Trial

Lancet 2000; 355: 253-59

Hypertension — no. (%)	2212 (47.6)	2143 (46.1)
Diabetes — no. (%)	1808 (38.9)	1769 (38.0)
Documented elevated total cholesterol level — no. (%)	3036 (65.4)	3089 (66.4)
Documented low HDL cholesterol level — no. (%)	842 (18.1)	881 (18.9)
Current cigarette smoking — no. (%)	645 (13.9)	674 (14.5)
Medications — no. (%)		
Beta-blockers	1820 (39.2)	1853 (39.8)
Aspirin or other antiplatelet agents	3497 (75.3)	3577 (76.9)
Lipid-lowering agents	1318 (28.4)	1340 (28.8)
Diuretics	713 (15.3)	706 (15.2)
Calcium-channel blockers	2152 (46.3)	2228 (47.9)
Left ventricular hypertrophy on electrocardiography — no. (%)	379 (8.2)	406 (8.7)
Microalbuminuria — no. (%)	952 (20.5)	1004 (21.6)

Heart Outcomes Prevention Evaluation Trial

Lancet 2000; 355: 253-59



Heart Outcomes Prevention Evaluation Trial

Lancet 2000; 355: 253-59

TABLE 3. INCIDENCE OF THE PRIMARY OUTCOME AND OF DEATHS FROM ANY CAUSE.

OUTCOME	RAMIPRIL GROUP (N=4645)	PLACEBO GROUP (N=4652)	RELATIVE RISK (95% CI)*	Z STATISTIC	P VALUE†
	no. (%)				
Myocardial infarction, stroke, or death from cardiovascular causes‡	651 (14.0)	826 (17.8)	0.78 (0.70–0.86)	–4.87	<0.001
Death from cardiovascular causes§	282 (6.1)	377 (8.1)	0.74 (0.64–0.87)	–3.78	<0.001
Myocardial infarction§	459 (9.9)	570 (12.3)	0.80 (0.70–0.90)	–3.63	<0.001
Stroke§	156 (3.4)	226 (4.9)	0.68 (0.56–0.84)	–3.69	<0.001
Death from noncardiovascular causes	200 (4.3)	192 (4.1)	1.03 (0.85–1.26)	0.33	0.74
Death from any cause	482 (10.4)	569 (12.2)	0.84 (0.75–0.95)	–2.79	0.005

*CI denotes confidence interval.

†P values were calculated with use of the log-rank test.

‡In the substudy, 34 of 244 patients (13.9 percent) assigned to take a low dose of ramipril (2.5 mg per day) reached the composite end point, as compared with 31 of 244 assigned to take 10 mg of ramipril per day (12.7 percent) and 41 of 244 assigned to placebo (16.8 percent). The inclusion of the data from the low-dose group did not change the overall results (relative risk of the primary outcome, 0.78; 95 percent confidence interval, 0.70 to 0.86).

§All patients with this outcome are included.

Heart Outcomes Prevention Evaluation Trial

Lancet 2000; 355: 253-59

TABLE 4. INCIDENCE OF SECONDARY AND OTHER OUTCOMES.

OUTCOME	RAMPRIIL GROUP (N=4645)	PLACEBO GROUP (N=4652)	RELATIVE RISK (95% CI)*	Z STATISTIC	P VALUE†
	no. (%)				
Secondary outcomes‡					
Revascularization	742 (16.0)	852 (18.3)	0.85 (0.77–0.94)	–3.17	0.002
Hospitalization for unstable angina	554 (11.9)	565 (12.1)	0.98 (0.87–1.10)	–0.41	0.68
Complications related to diabetes§¶	299 (6.4)	354 (7.6)	0.84 (0.72–0.98)	–2.16	0.03
Hospitalization for heart failure	141 (3.0)	160 (3.4)	0.88 (0.70–1.10)	–1.16	0.25
Other outcomes					
Heart failure§	417 (9.0)	535 (11.5)	0.77 (0.67–0.87)	–4.09	<0.001
Cardiac arrest	37 (0.8)	59 (1.3)	0.62 (0.41–0.94)	–2.28	0.02
Worsening angina§	1107 (23.8)	1220 (26.2)	0.89 (0.82–0.96)	–2.91	0.004
New diagnosis of diabetes	102 (3.6)	155 (5.4)	0.66 (0.51–0.85)	–3.31	<0.001
Unstable angina with electrocardiographic changes‡	175 (3.8)	180 (3.9)	0.97 (0.79–1.19)	–0.30	0.76

*CI denotes confidence interval.

†P values were calculated with use of the log-rank test.

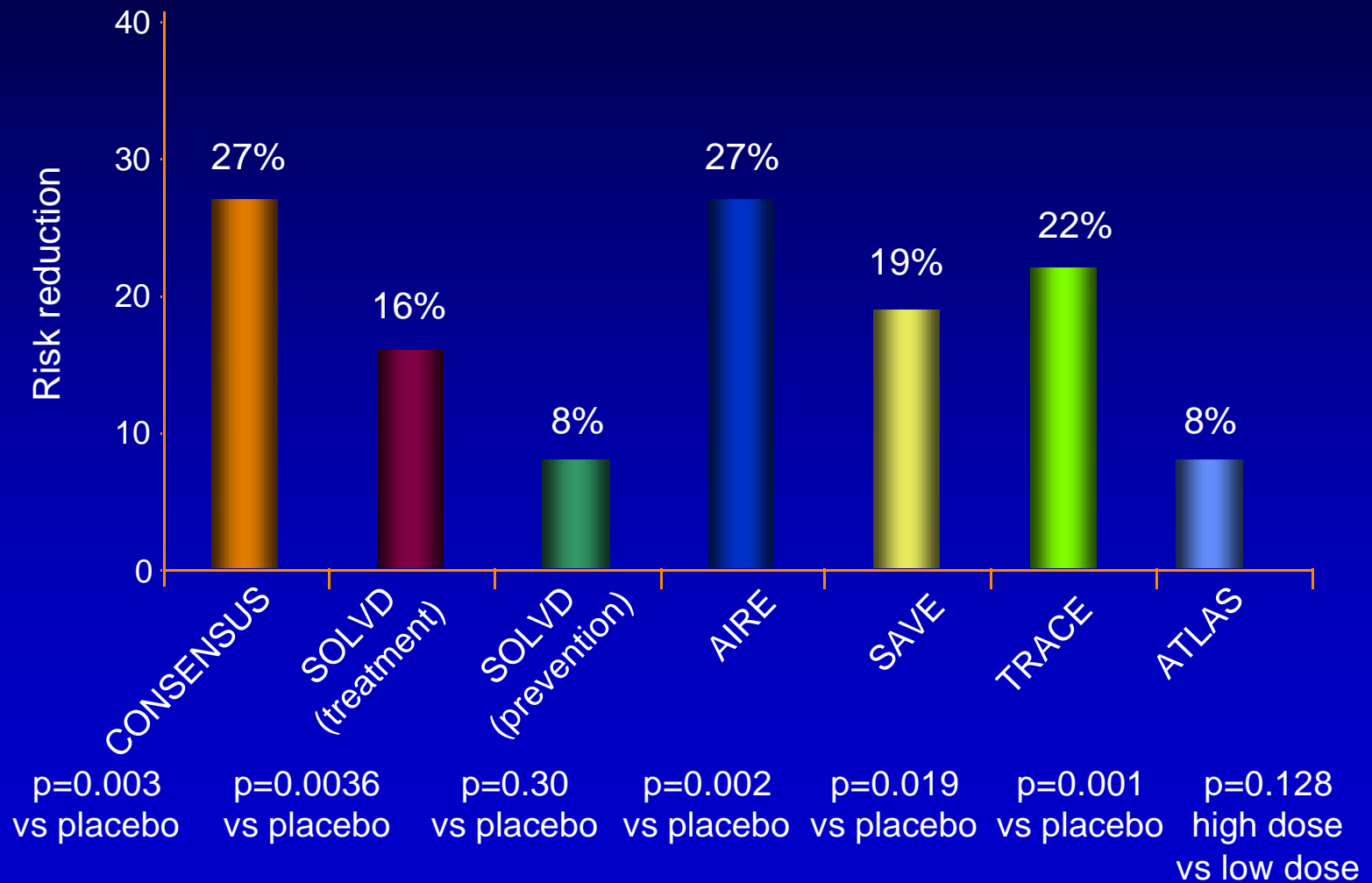
‡These events were centrally adjudicated.

§All cases are included, whether or not hospitalization was required.

¶Complications related to diabetes include diabetic nephropathy (defined as urinary albumin excretion of at least 300 mg per day or urinary protein excretion of 500 mg per day), the need for renal dialysis, and the need for laser therapy for diabetic retinopathy.

||The denominator in the ramipril group is the 2837 patients who did not have diabetes at base line. The denominator in the placebo group is the 2883 patients who did not have diabetes at base line.

Primary Outcomes of ACE Inhibitors in Heart Failure and/or LV Dysfunction: Mortality

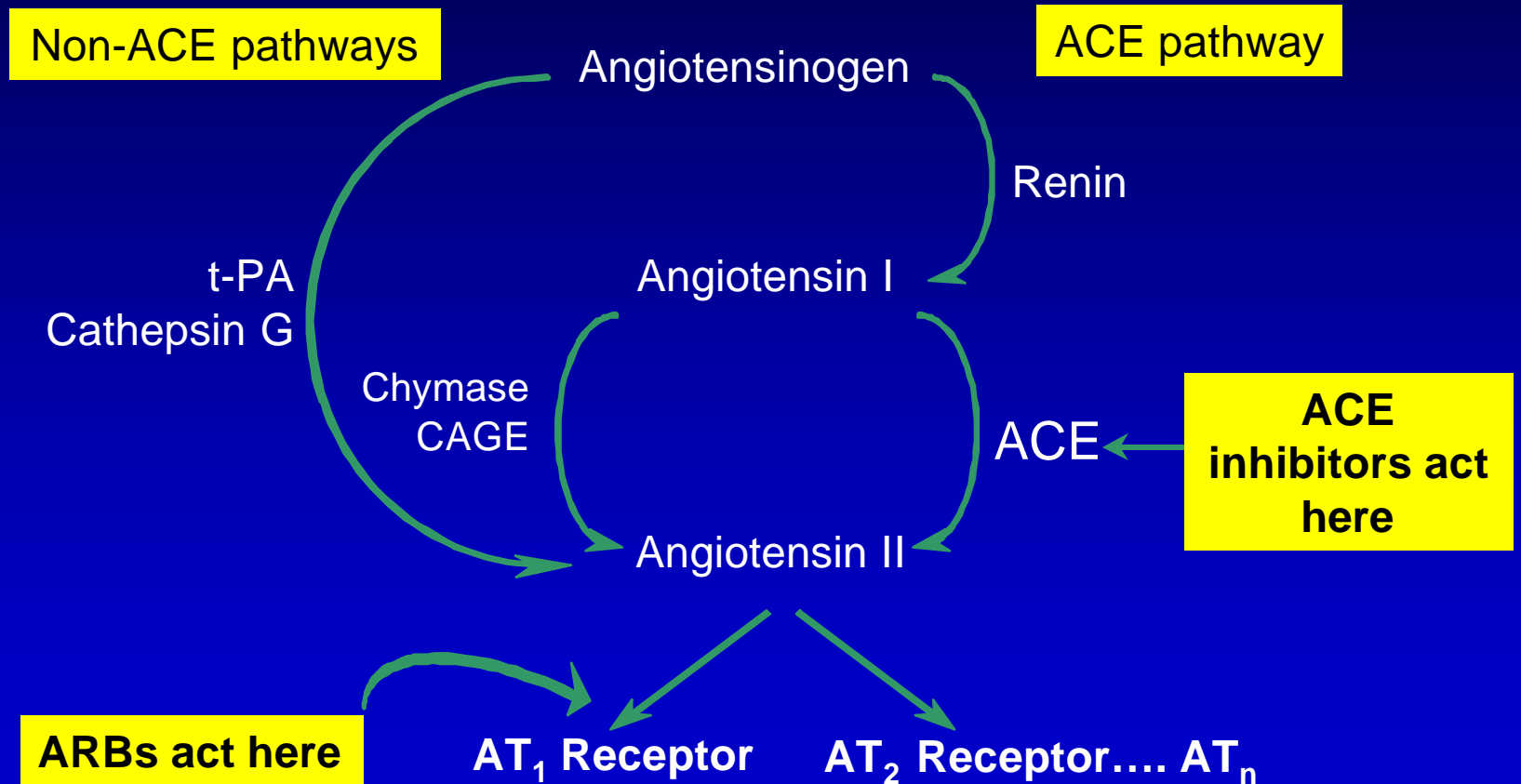


Medical Management of HF

- Diuretics
- Beta-blockers
- Digoxin
- Renin Angiotensin System
 - ACE - inhibitors
 - Angiotensin Receptor Blockers
 - Spironolactone

Angiotensin Receptor Blockers

Production and Blockade of Angiotensin II



Physiological Effects of Angiotensin II

Angiotensin II



AT₁ Receptor

- Vasoconstriction
- ↑ sympathetic tone
- ↑ sodium resorption
- ↑ aldosterone
- ↑ smooth muscle proliferation

AT₂ Receptor

- Vasodilation
- ↓ sympathetic tone
- ↓ sodium resorption
- ↓ aldosterone
- Antiproliferative effect

Valsartan Heart Failure Trial Investigators

N Eng J Med 2000;345:1667-1675

- Objective

- determine the effect of valsartan on risk of cardiovascular disease among HF patients receiving standard therapy

- Methods

- randomized double blinded trial n= 5010
- NYHA class II, III, or IV
- randomized to valsartan 160 mg bid or placebo

Valsartan Heart Failure Trial Investigators

N Eng J Med 2000;345:1667-1675

CHARACTERISTIC	VALSARTAN GROUP (N=2511)	PLACEBO GROUP (N=2499)
Age (yr)	62.4±11.1	63.0±11.0
Male sex (% of patients)	79.9	80.0
Race (% of patients)		
White	89.8	90.9
Black	7.2	6.5
Other	2.9	2.6
Primary cause of heart failure (% of patients)		
Coronary heart disease	57.6	56.8
Idiopathic	31.1	31.2
Hypertension	6.1	7.3
Other	5.2	4.7
NYHA class (% of patients)†		
II	62.1	61.4
III	36.1	36.3
IV	1.7	2.2
Diabetes (% of patients)	25.9	25.1
Atrial fibrillation (% of patients)	12.0	12.2
Ejection fraction (%)	26.6±7.3	26.9±7.0
Left ventricular internal diastolic diameter (cm/m ²)	3.7±0.5	3.7±0.5
Blood pressure (mm Hg)		
Systolic	123.0±18.4	124.0±18.6
Diastolic	76.0±10.5	76.0±10.7
Background therapy (% of patients)		
Diuretic	85.8	85.2
Digoxin	67.1	67.6
Beta-blocker	34.5	35.3
ACE inhibitor	92.6	92.8

Valsartan 2511

Placebo 2499

Similar Baseline

diuretics 85%

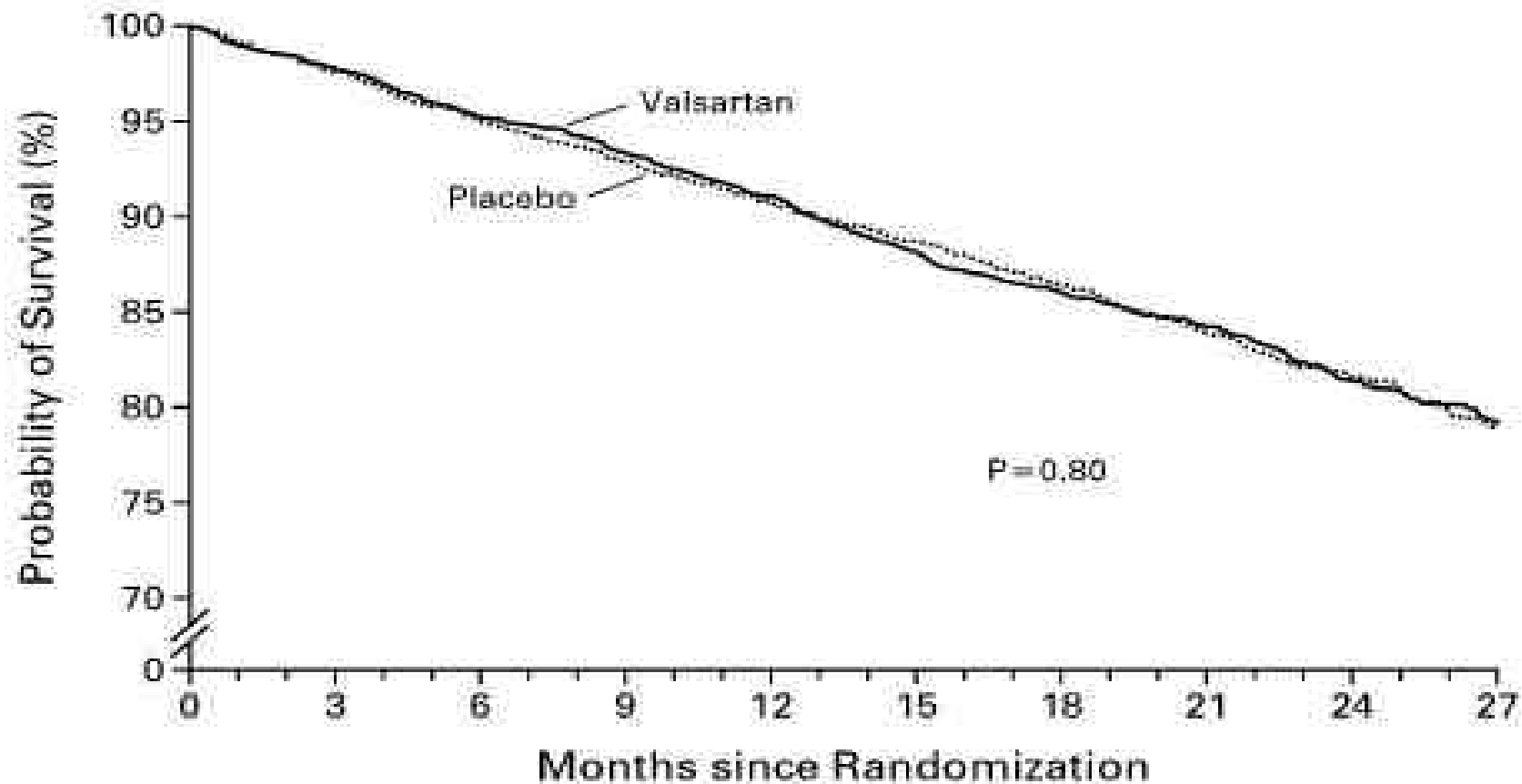
digoxin 67%

β-blocker 35%

ACE-I 93%

Valsartan Heart Failure Trial Investigators

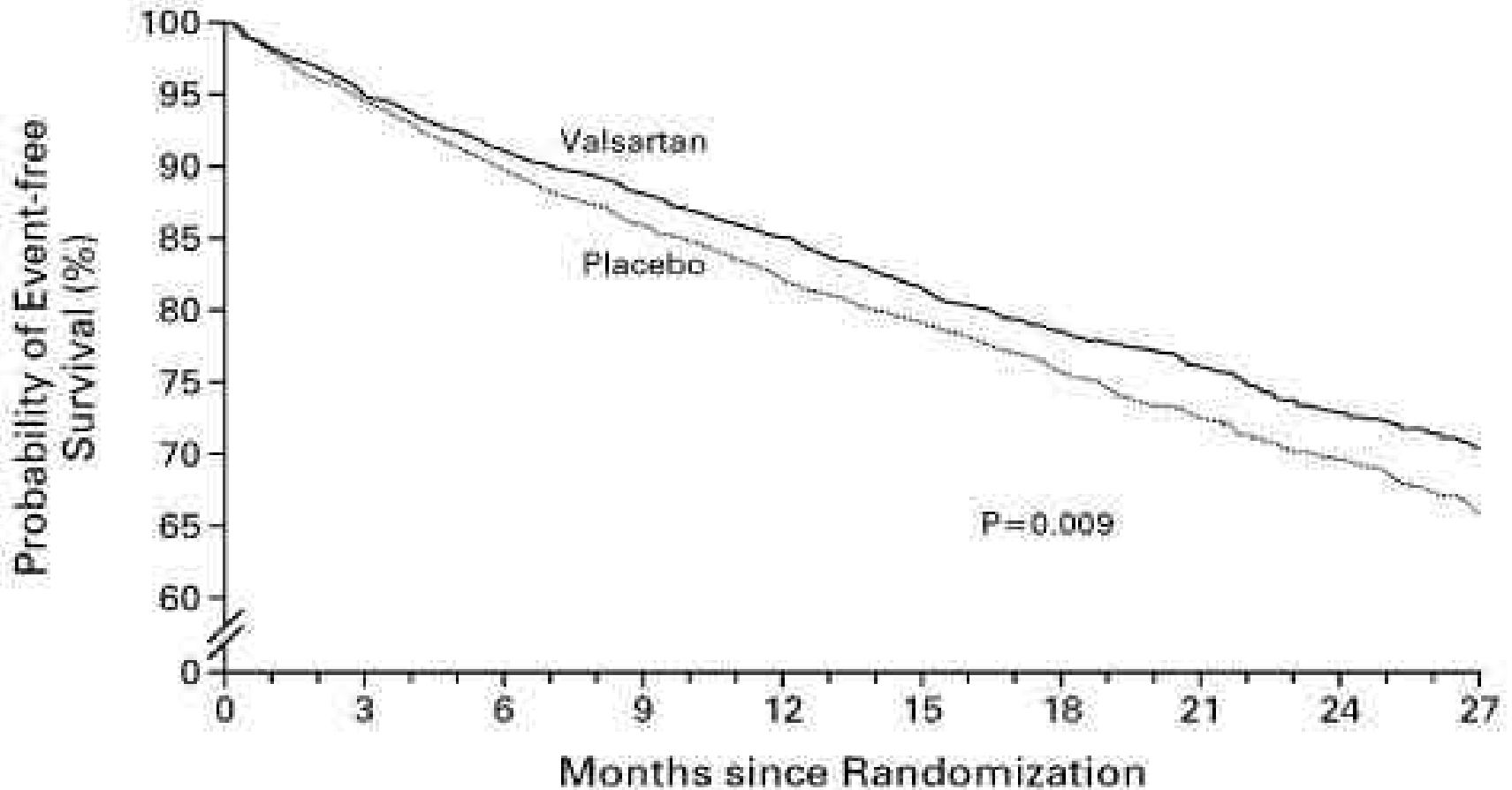
N Eng J Med 2000;345:1667-1675



No mortality difference

Valsartan Heart Failure Trial Investigators

N Eng J Med 2000;345:1667-1675



Death from Any Cause, Cardiac Arrest with Resuscitation, Hospitalization for Worsening Heart Failure, or Therapy with Intravenous Inotropes or Vasodilators

Valsartan Heart Failure Trial Investigators

N Eng J Med 2000;345:1667-1675

TABLE 2. INCIDENCE AND RELATIVE RISK OF THE PRIMARY END POINTS.

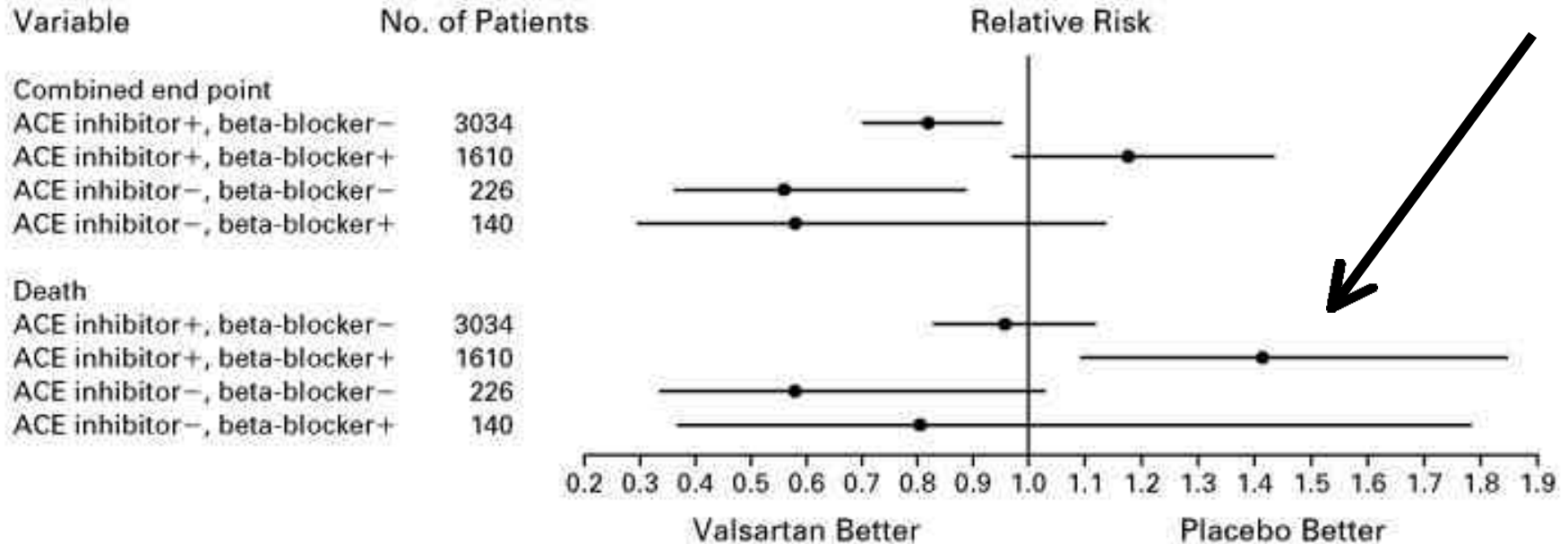
EVENT	VALSARTAN GROUP (N=2511)	PLACEBO GROUP (N=2499)	RELATIVE RISK (CI)*	P VALUE†
	no. with event (%)			
Death from any cause (during entire trial)	495 (19.7)	484 (19.4)	1.02 (0.88-1.18)	0.80
Combined end point	723 (28.8)	801 (32.1)	0.87 (0.77-0.97)	0.009
Death from any cause (as first event)	356 (14.2)	315 (12.6)	0.73 (0.63-0.83)	0.00001
Hospitalization for heart failure	346 (13.8)	455 (18.2)		
Cardiac arrest with resuscitation	16 (0.6)	26 (1.0)		
Intravenous therapy	5 (0.2)	5 (0.2)		

*The 98 percent confidence interval (CI) was calculated for the mortality end point (death from any cause), and the 97.5 percent confidence interval was calculated for the combined mortality-morbidity end point.

†P values were calculated by the log-rank test from time to first event.

Valsartan Heart Failure Trial Investigators

N Eng J Med 2000;345:1667-1675



Post-hoc analysis revealed that the combination of valsartan + ACE-I + β -blocker was associated with an increased mortality risk

Losartan Intervention For Endpoint reduction in hypertension study (LIFE) Lancet 2002;359

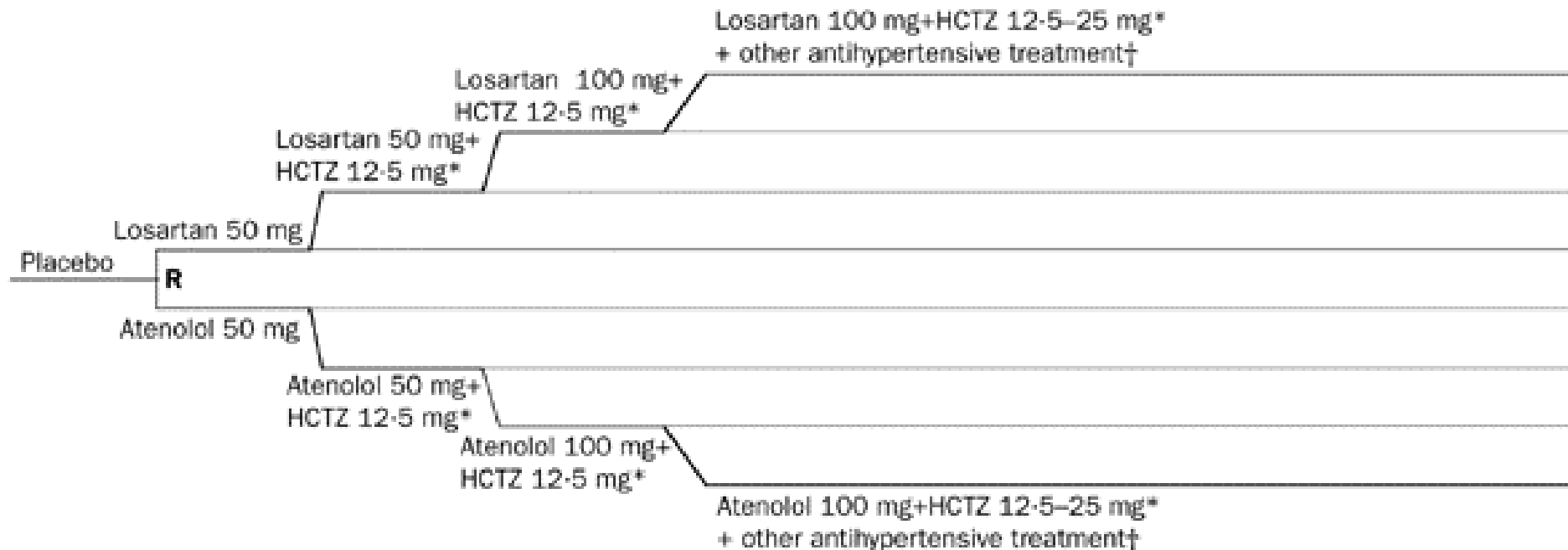
- Objective:
 - compare effects of losartan based versus atenolol based hypertensive therapy among those with LVH
- Methods:
 - double blind randomized controlled trial
 - 9193 patients aged 55-80 yrs
 - HTN 160-200/ 95-115 mm Hg
 - LVH

Losartan Intervention For Endpoint reduction in hypertension study (LIFE) Lancet 2002;359

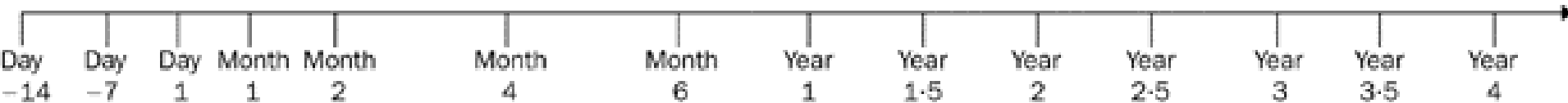
- Intervention:
 - losartan 50 mg - 100 mg po od +/- diuretics
 - atenolol 50 mg - 100 mg po od +/- diuretics

- Composite Outcome:
 - death
 - MI
 - stroke

Losartan Intervention For Endpoint reduction in hypertension study (LIFE) Lancet 2002;359



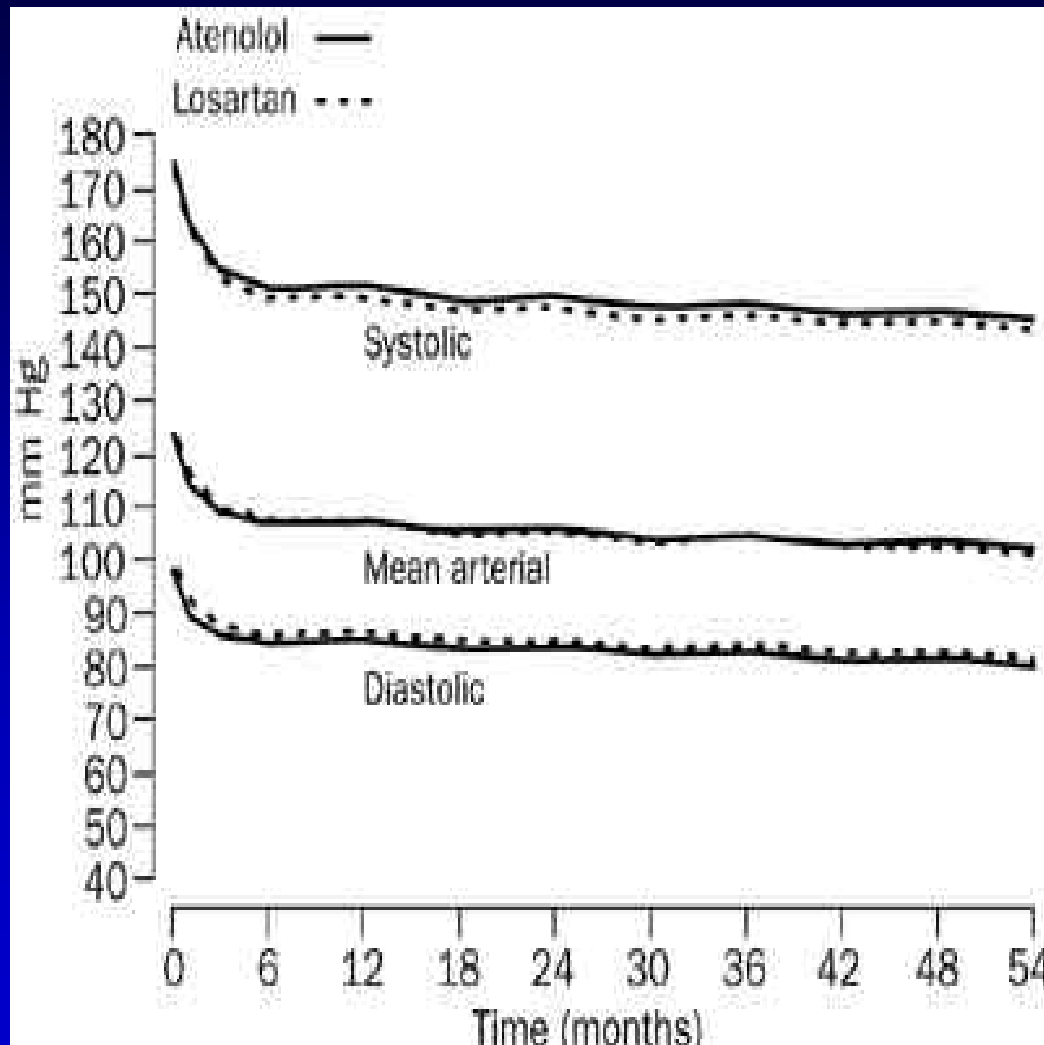
Patients randomised (R) with sitting diastolic blood pressure 95–115 mm Hg and/or sitting systolic blood pressure 160–200 mm Hg at days -7 and 1, and left ventricular hypertrophy present by Cornell product ($[(QRS \times (RaVL + SV3))]mm \times ms$) or Sokolow-Lyon ($[SV1 + RV5 \text{ or } V6]mm$)



*Titration upward if sitting diastolic blood pressure ≥ 90 mm Hg or sitting systolic blood pressure ≥ 140 mm Hg.

†Titration encouraged if sitting diastolic blood pressure ≥ 90 mm Hg or sitting systolic blood pressure ≥ 140 mm Hg but mandatory if sitting blood pressure $\geq 180/95$ mm Hg. Addition of angiotensin-converting-enzyme inhibitors, angiotensin II type 1-receptor antagonists, or β -blockers prohibited.

Losartan Intervention For Endpoint reduction in hypertension study (LIFE) Lancet 2002;359



BP Reduction
losartan atenolol

- 30

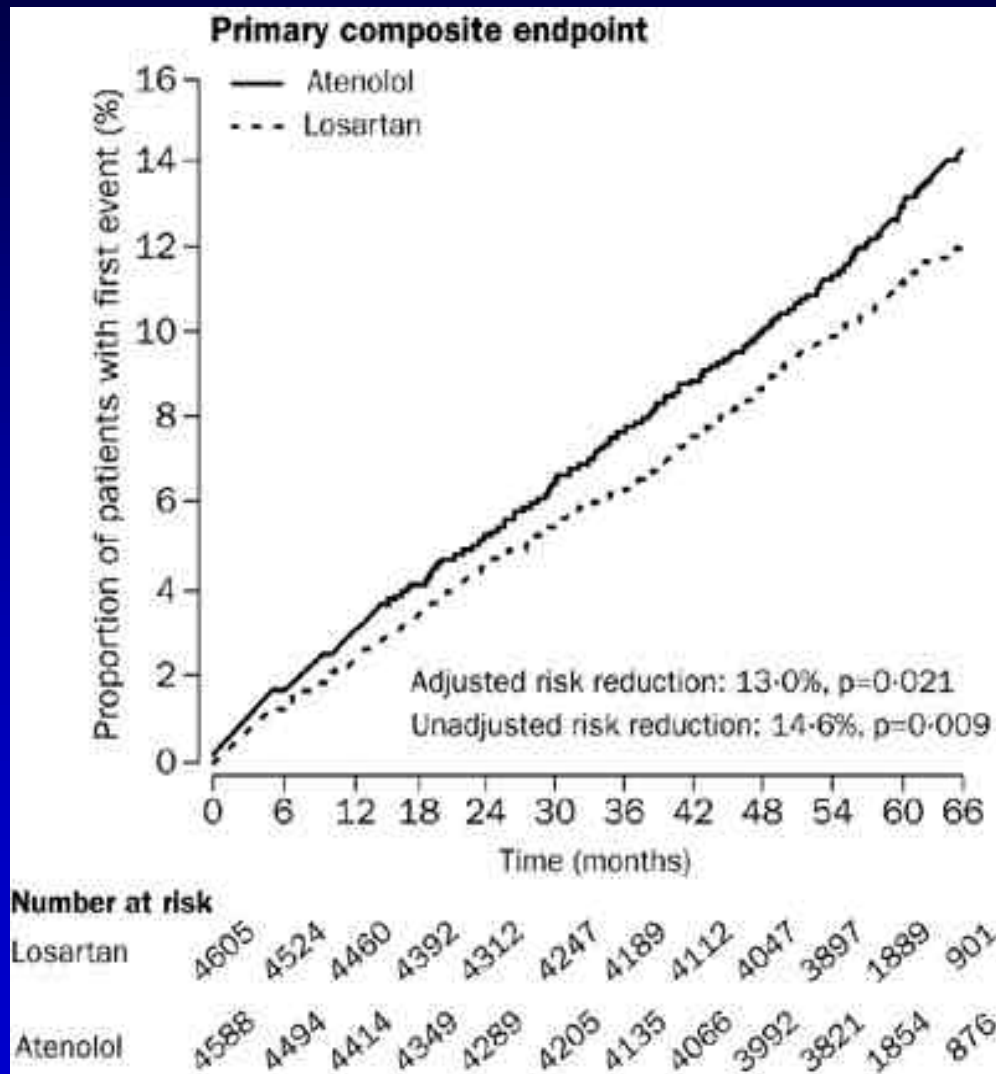
- 29

- 16

- 16

(no difference)

Losartan Intervention For Endpoint reduction in hypertension study (LIFE) Lancet 2002;359



Composite
(mi, cva, death)

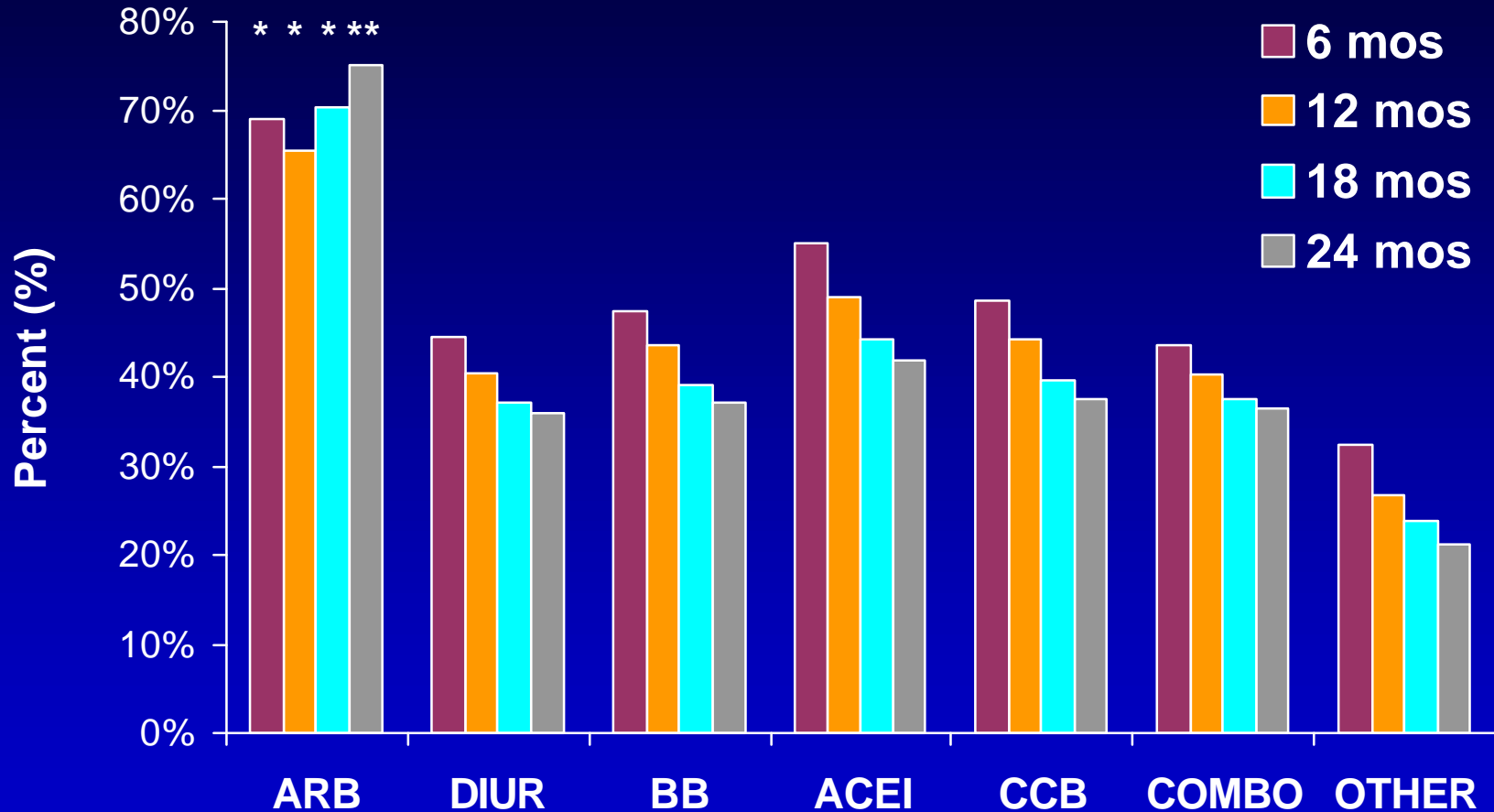
13.0% (CI 0.77-0.98)
risk reduction

adjusted for:

LVH / Framingham

Advantage of ARBS: Tolerability

Persistency with AHT classes at 6, 12, 18, 24 mo.



*p=0.001 vs. each of the other classes (Chi-Square)

**p=0.030 vs. DIUR, p=0.002 vs. OTHER (Fisher's Exact Test 2-tailed)

Chaput AJ. Saskatchewan Health Database.

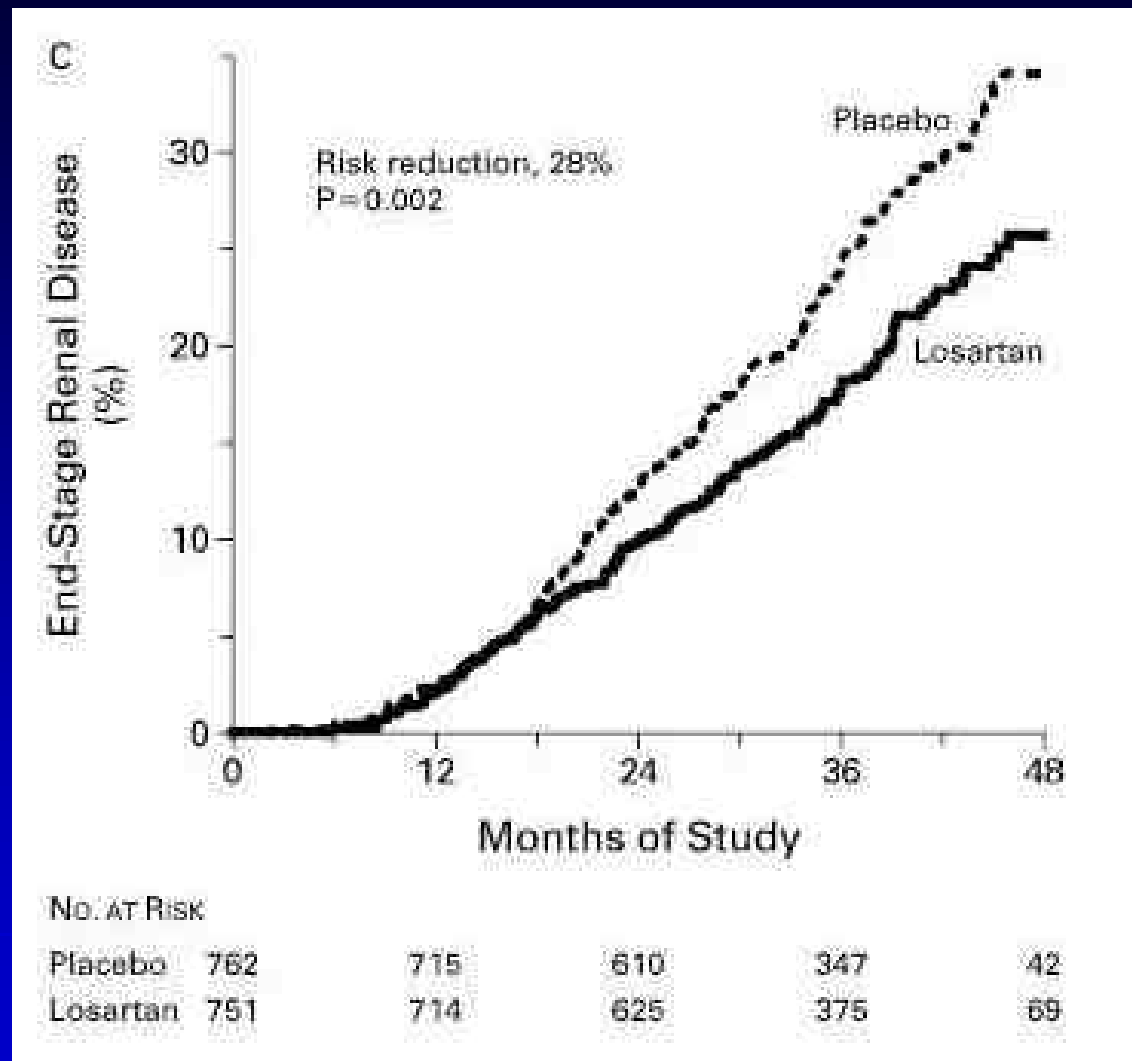
Advantage of ARBS: Renal Function Protection

ACE Inhibitor Trials in Type 2 Diabetics with >1 Yr Follow-up of ESRD*	Total Sample	Reduction of Proteinuria	Endpoints Studied	
			Reduction of Fall in GFR	Reduction in Risk
Ravid et al <i>Ann Int Med</i> 1993	94	YES	YES	NO
Lebovitz et al <i>Kid Int</i> 1994	121	YES	YES	NO
Bakris et al <i>Kid Int</i> 1996	52	YES	YES	NO
Ahmad et al <i>Diab Care</i> 1996	103	YES	YES	NO
Nielsen et al <i>Diabetes</i> 1997	43	YES	YES	NO
UKPDS et al <i>Br Med J</i> 1998	758	YES	YES	NO
Fogari et al <i>J Hum Hypertens</i> 1999	107	YES	YES	NO
ABCD <i>Diab Care</i> 2000	470	YES	YES	NO
Ruggenenti et al (REIN) <i>Am J Kid Dis</i> 2000	352 (27)	NO	YES	YES
MICRO-HOPE** <i>Lancet</i> 2000	3577	YES	NO	YES

Advantage of ARBS: Renal Function Protection

Renaal Trial

- losartan vs placebo
- n = 1513
- risk of ESRF reduced by 28%

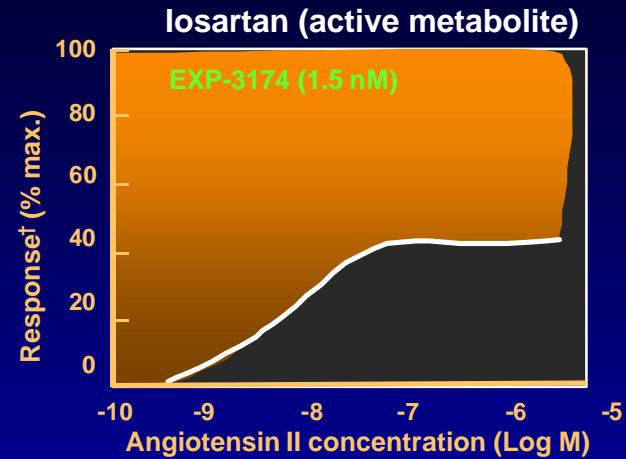
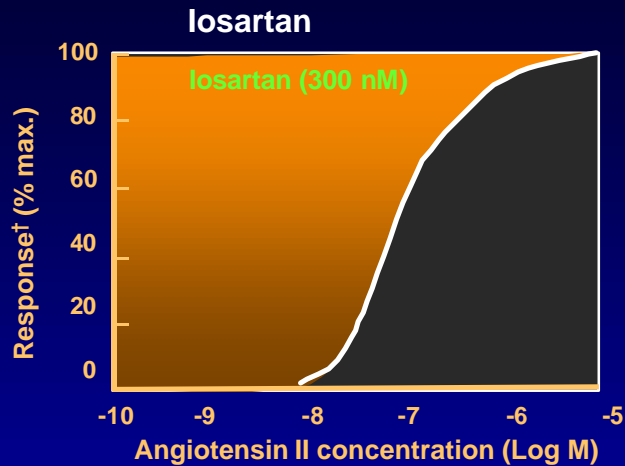


AT₁ receptor blockers pharmacokinetics

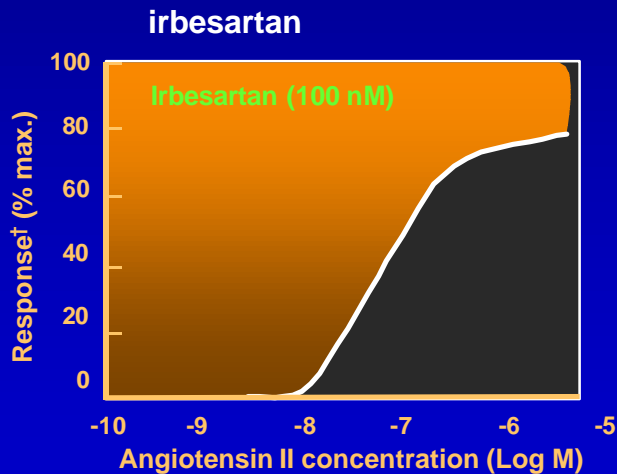
	Atacand®	losartan [EXP-3174]	valsartan	irbesartan	telmisartan
Prodrug	Completely converted on absorption	14% converted by liver	No	No	No
Bioavailability (%)	42	33	23	60-80	50%
t _{max} (h)	3-4	1 [3-4]	2	1-2	0.5-1
t _{1/2} (h)	9	2 [4-6]	6-7	11-15	24
Elimination route (oral dose)	33% urine 68% faeces	35% urine 65% faeces	13% urine 86% faeces	20% urine 80% faeces	1% urine 97% faeces
Interactions	No	No	Food ↓ AUC	No	digoxin levels monitored
Binding profile	Insurmountable	Surmountable [intermediate]	Intermediate	Intermediate	Intermediate

Binding profiles of ARBs

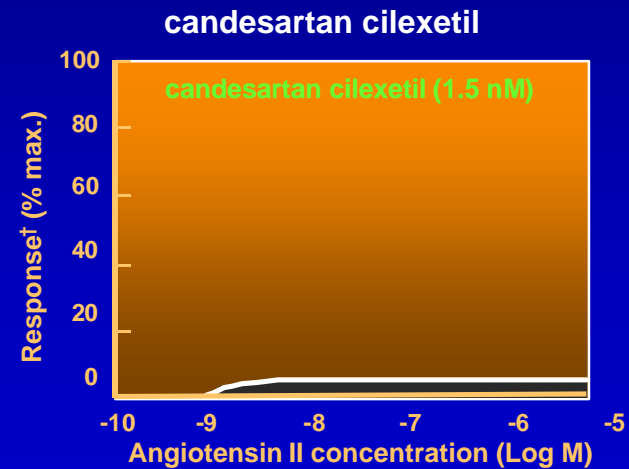
Contractile Response



Surmountable



Intermediate



Intermediate

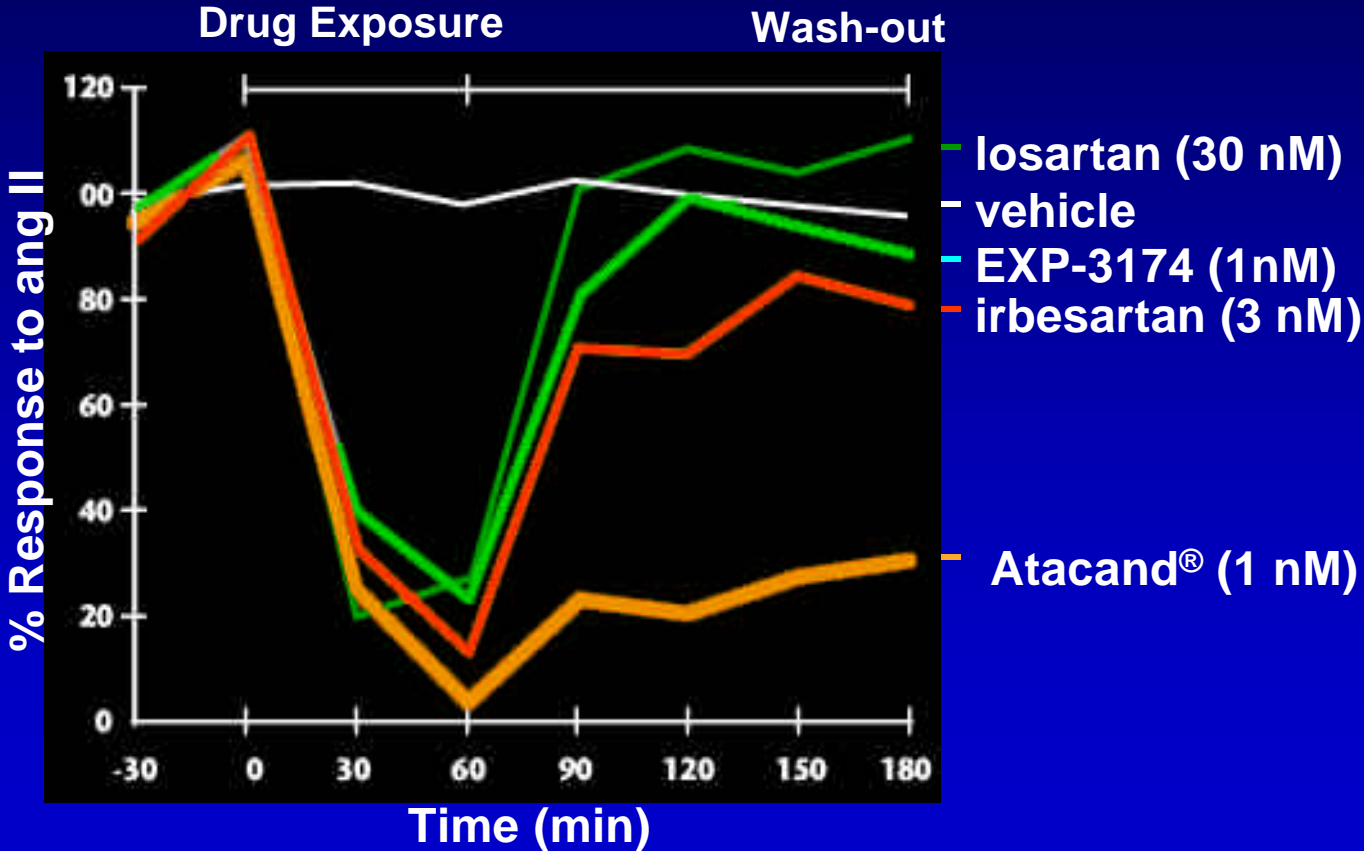
Insurmountable

adapted from Vanderheyden et al

Slow dissociation of Atacand® from the AT₁ receptor ensures long duration of action

Contractile response to angiotensin II

% response measured in isolated blood vessels 3 hours after exposure to angiotensin II

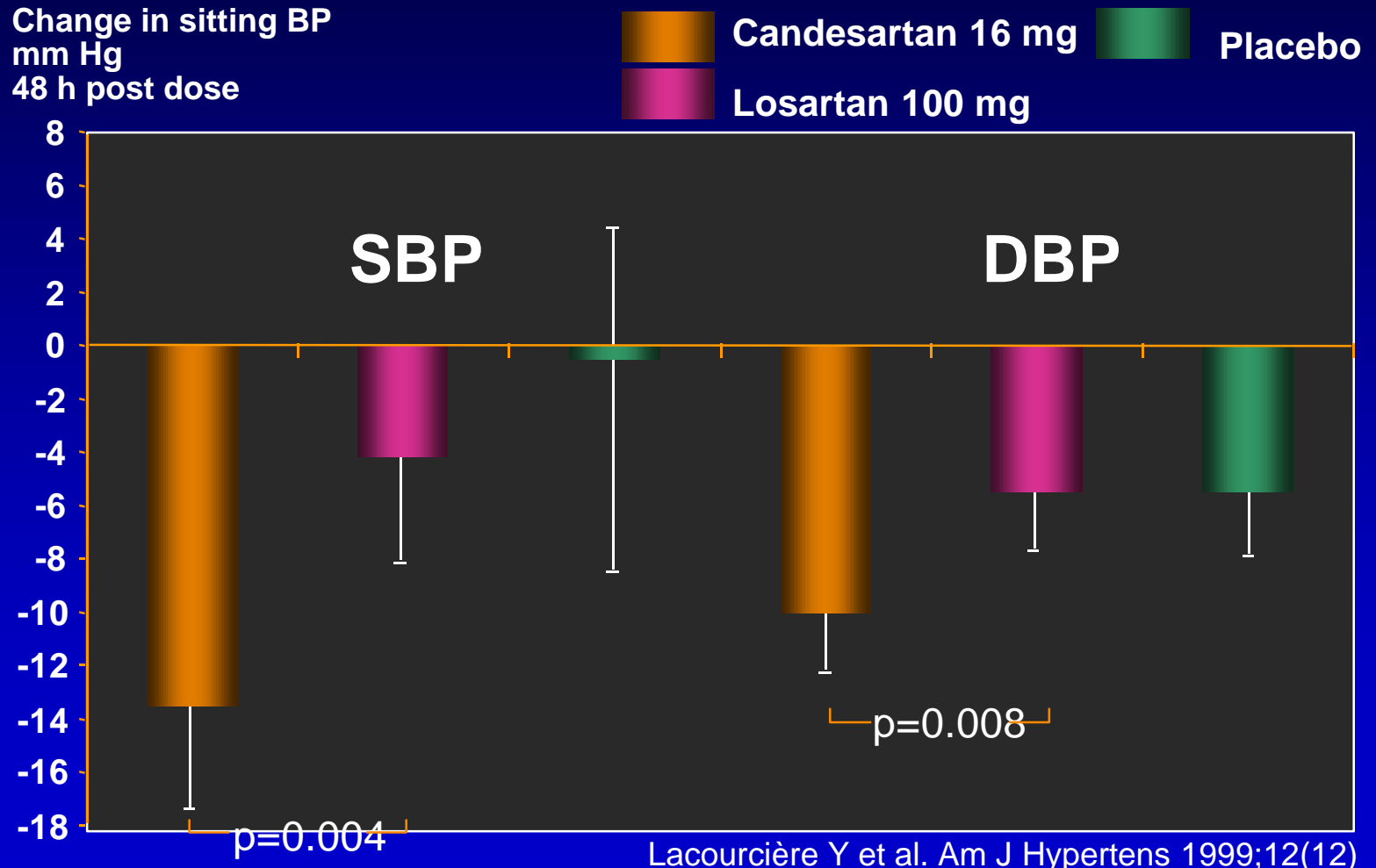


drug groups n=8-15

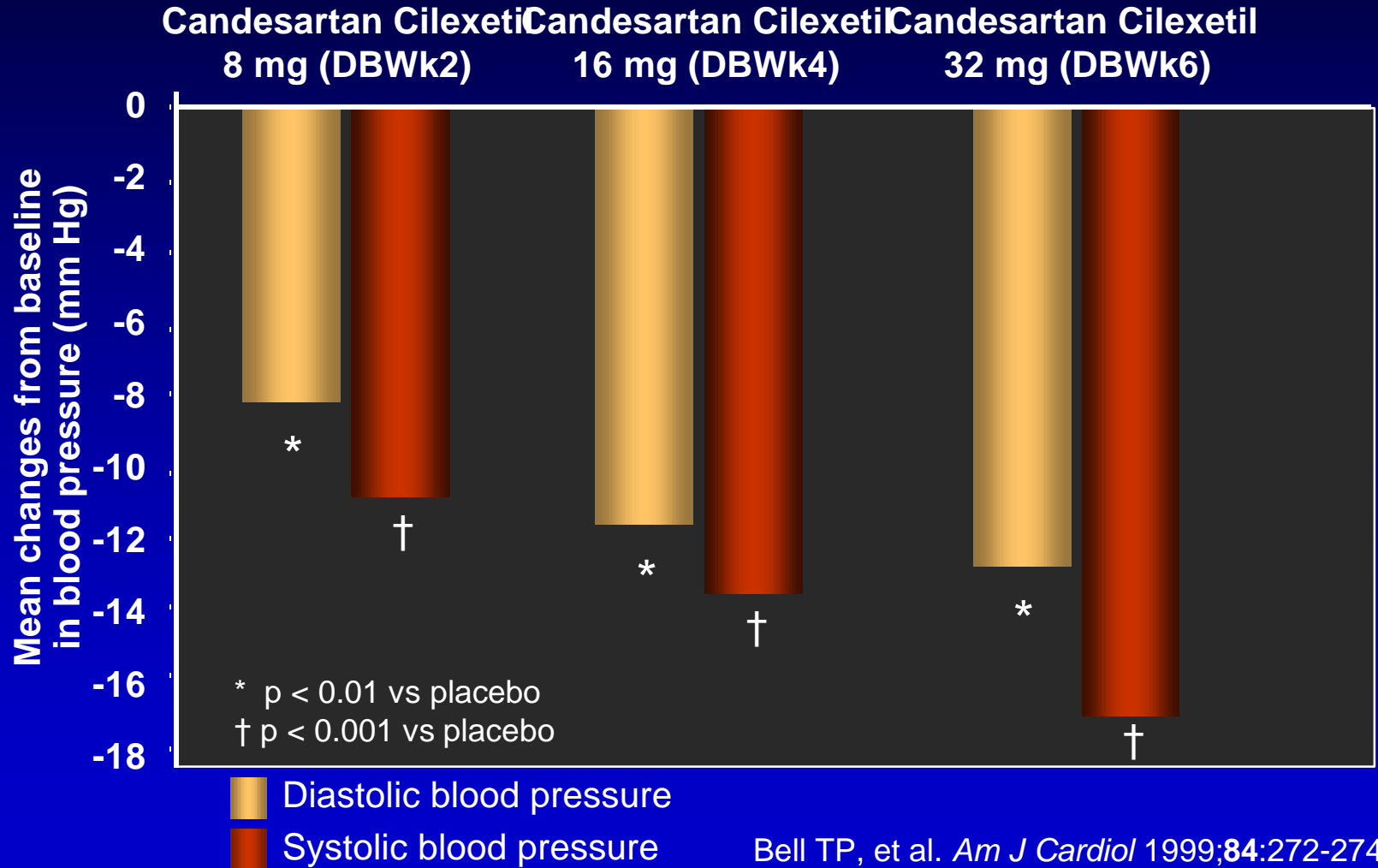
vehicle group n=75

Morsing et al 1999.

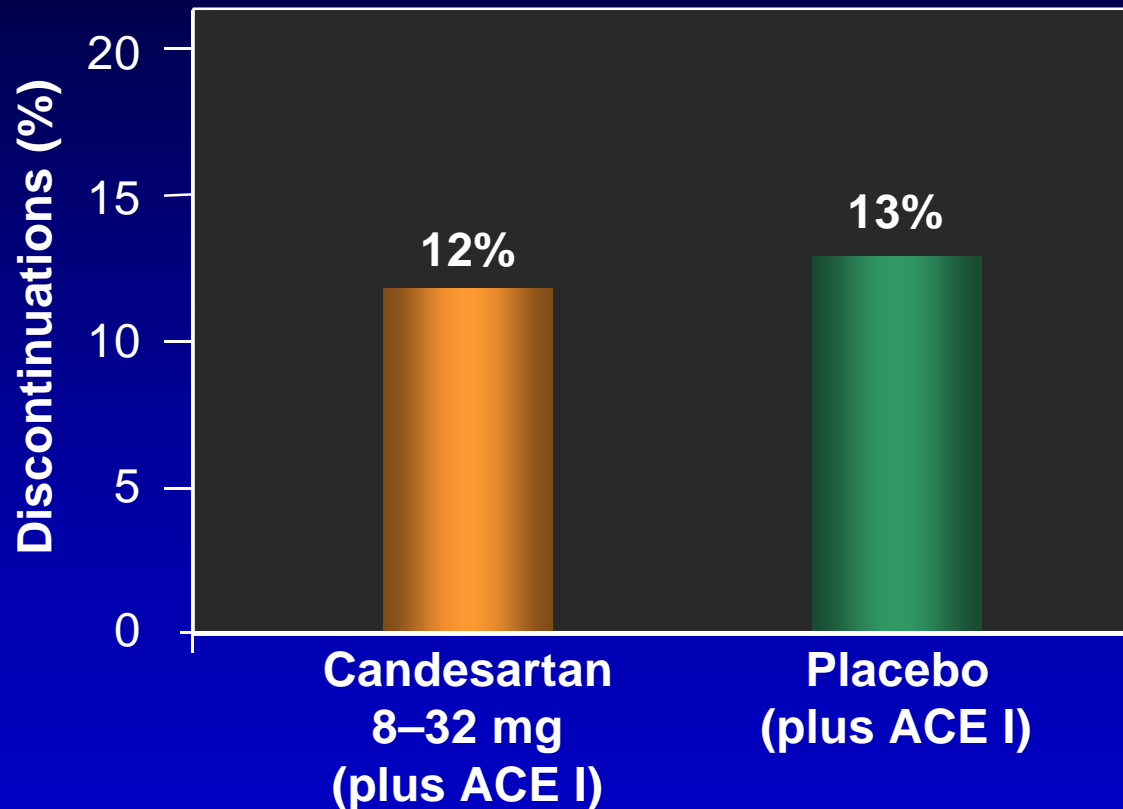
Mean Change in BP from baseline 48 h after a missed dose Candesartan 16mg & Losartan 100mg



Dose-dependent Blood Pressure Reduction with Candesartan Cilexetil Between 8–32 mg



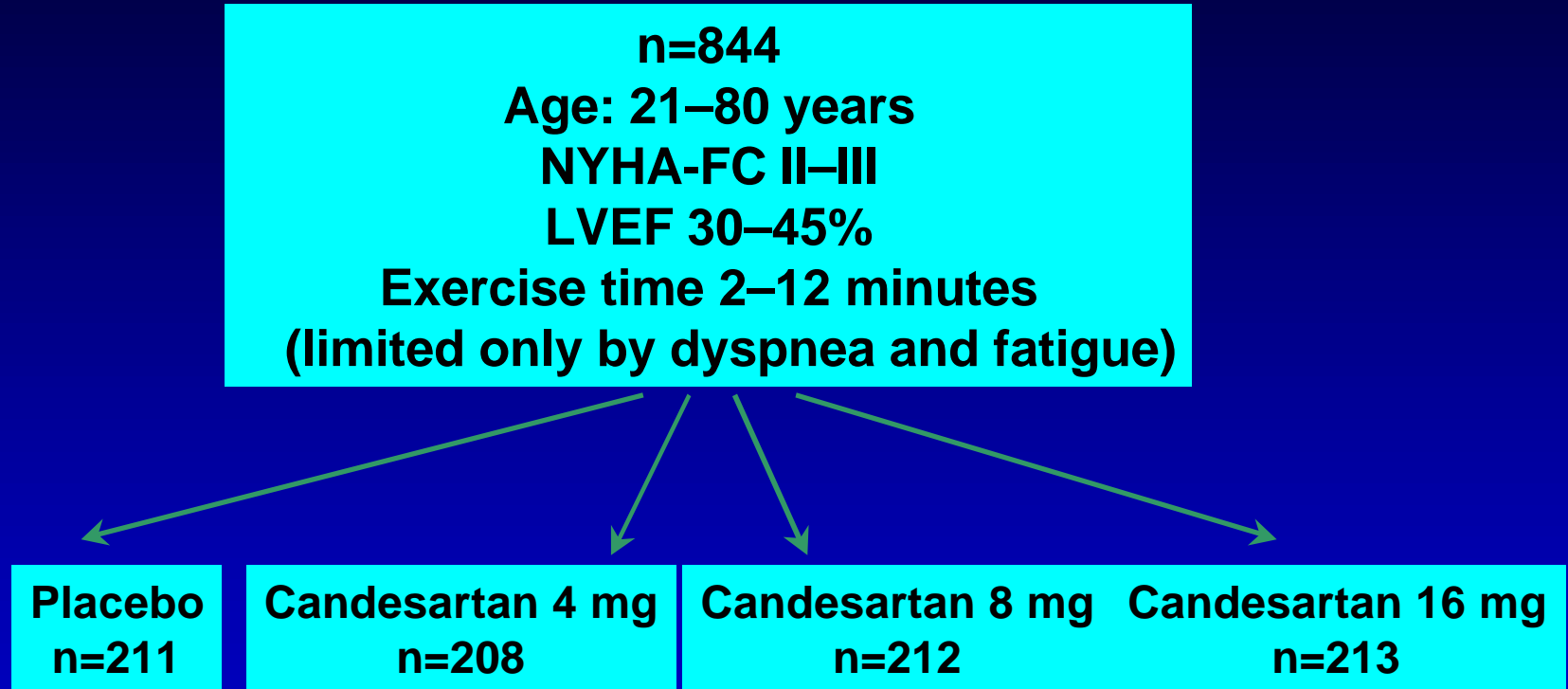
Tolerability and Safety of High Dose Candesartan in Combination with ACE I in Heart Failure



n=98 patients, randomized 2:1 on candesartan vs placebo

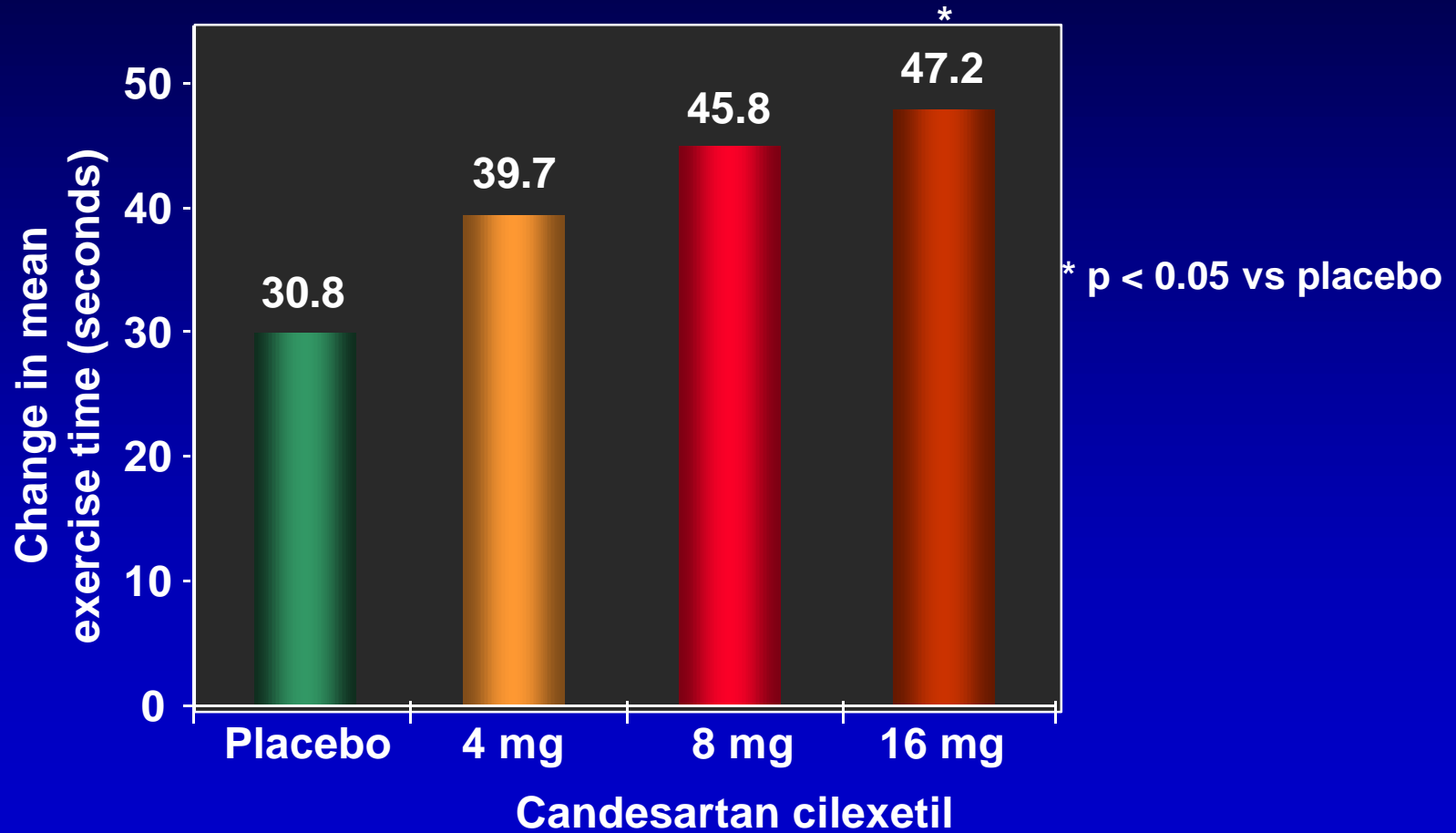
Gradman AH, et al. *Circulation* 1999;100(abstract):I-783

Riegger et al: Trial Design



- Treatment duration: 3 months
- Primary endpoint: exercise time, signs and symptoms of heart failure

Riegger Trial: Change in Total Exercise Time Baseline to Study Endpoint



Riegger GAJ, et al. *Circulation* 1999;100:2224-2230

Candesartan: Summary of Clinical Effects

- Long duration of action
- Excellent efficacy and a clear dose-related response in patients with hypertension
- Tolerable and safe at high doses in heart failure patients
- Dose-related response in heart failure patients \

Lacourcière Y et al. *Am J Hypertens* 1999;12(12)

Bell TP, et al. *Am J Cardiol* 1999;84:272-274

Gradman AH, et al. *Circulation* 1999;100(abstract):I-783

Riegger GAJ, et al. *Circulation* 1999;100:2224-2230

McKelvie RS. *Circulation* 1999;100:1056-1064

Acknowledgements

- You
 - thank you for your kind attention
- AstraZeneca - Cardiovascular Specialty