Clinical Efficacy

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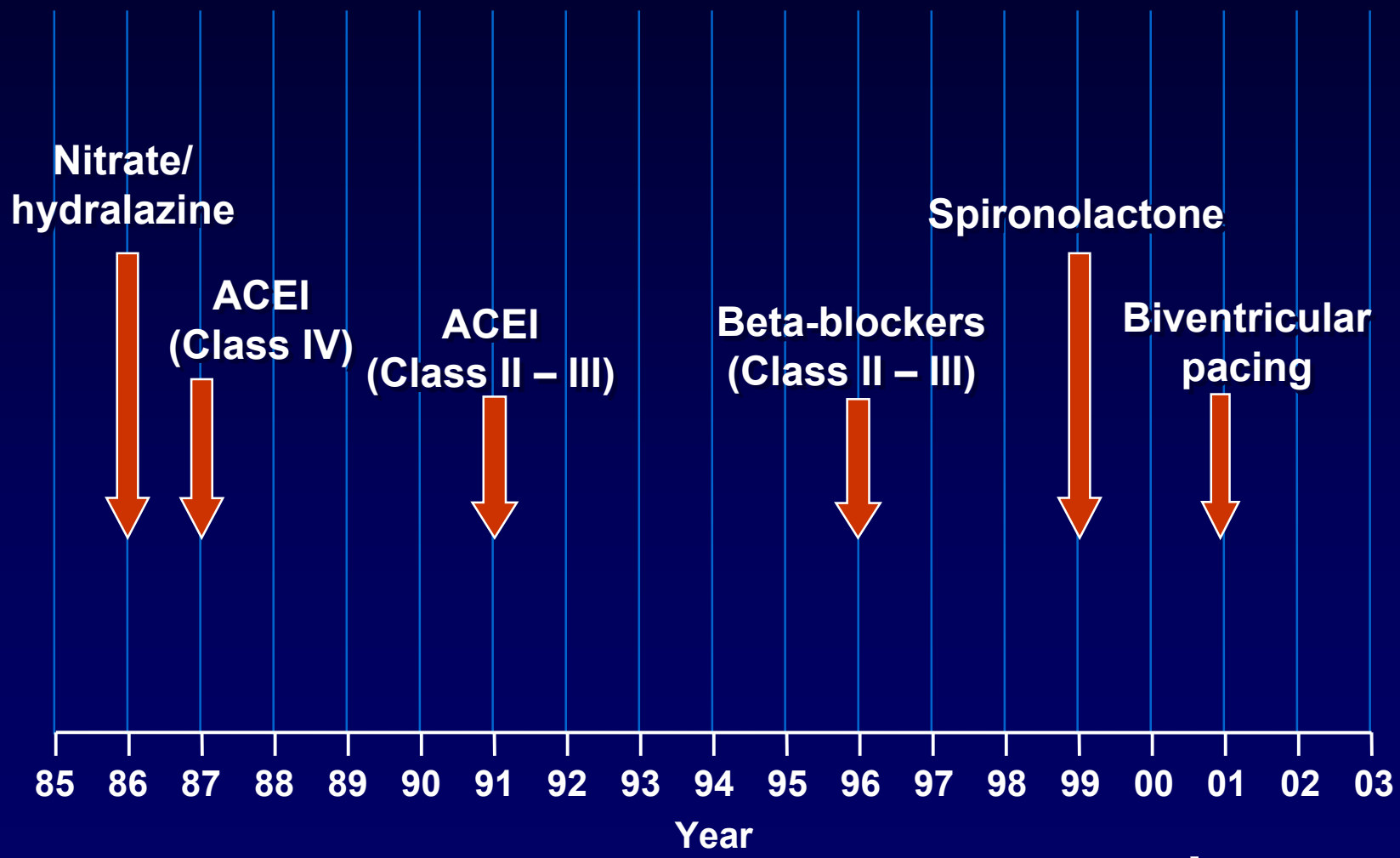
Development of Heart Failure Treatments



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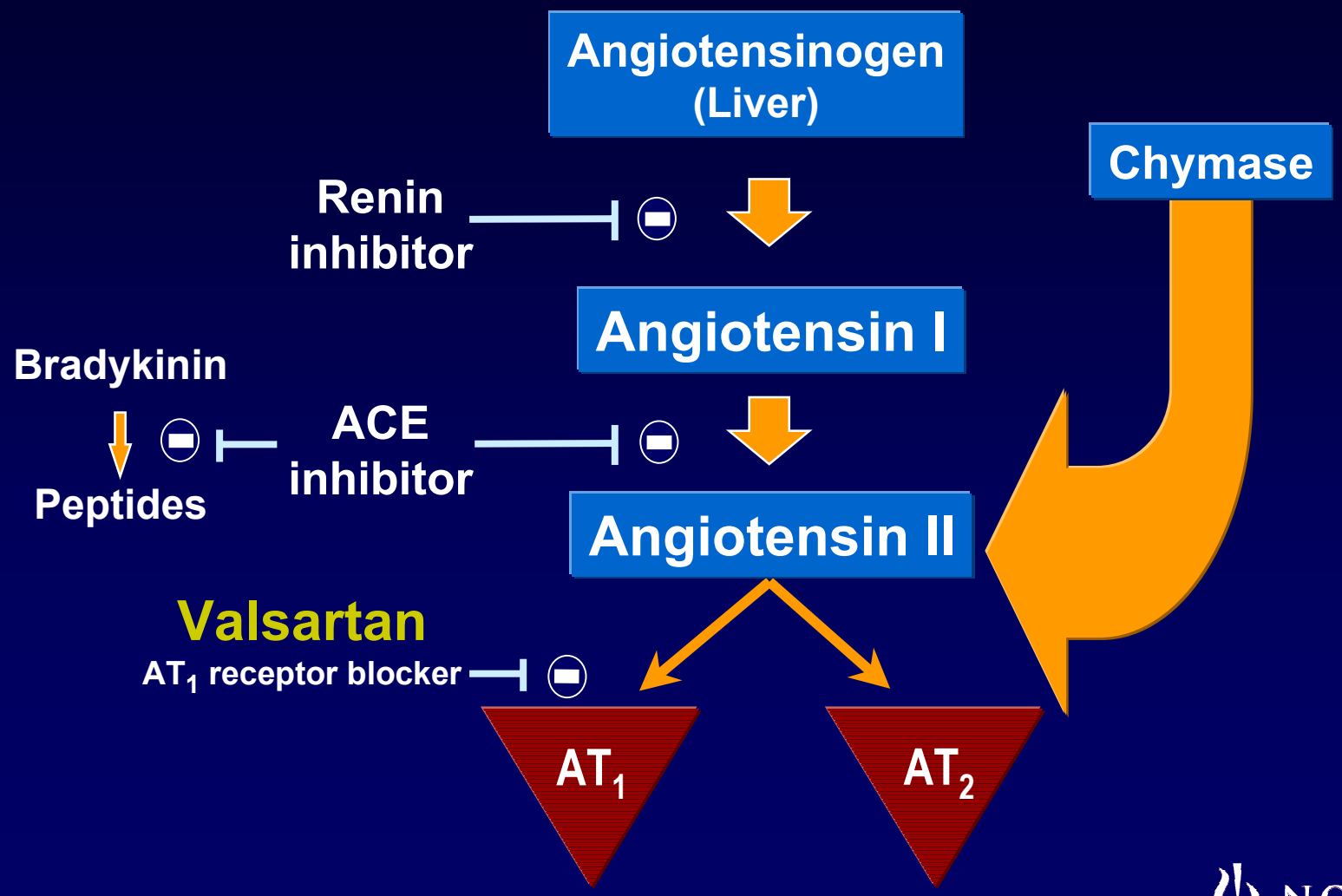
Rationale For Use of Valsartan in Heart Failure



Valsartan Clinical Studies in Heart Failure

> 6,100 patients in 5 controlled, randomized, multicenter, parallel, double-blind studies

Study	Background therapy§		Control	Patients	Primary efficacy	
	ACEI	BB			Duration	assessments
103	N‖	N‖	Placebo/ Lisinopril	116	4 wk	Hemodynamics
104	Y‖	N‖	Placebo	83	4 wk	Hemodynamics
106	Y	Y	Placebo	770	16 wk	ETT, QOL
110	N‖	Y	Enalapril	141	12 wk	Walk test
Val-HeFT	Y	Y	Placebo	5,010	24 - 36 mo	Morbidity/Mortality Walk test

§Post randomization
‖Required by protocol.

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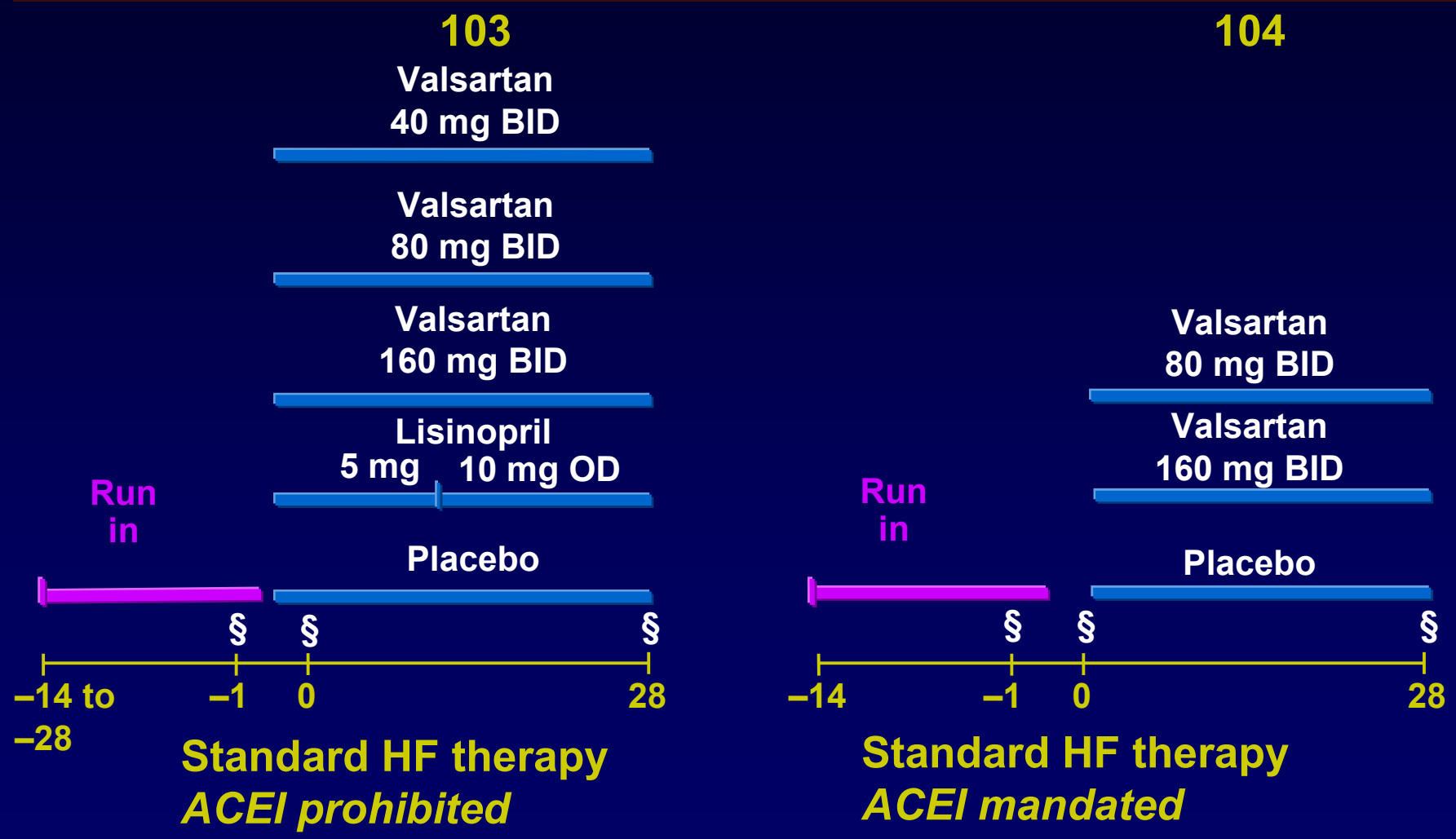
Study Design (103, 104)



§Pulmonary capillary wedge pressure assessment.

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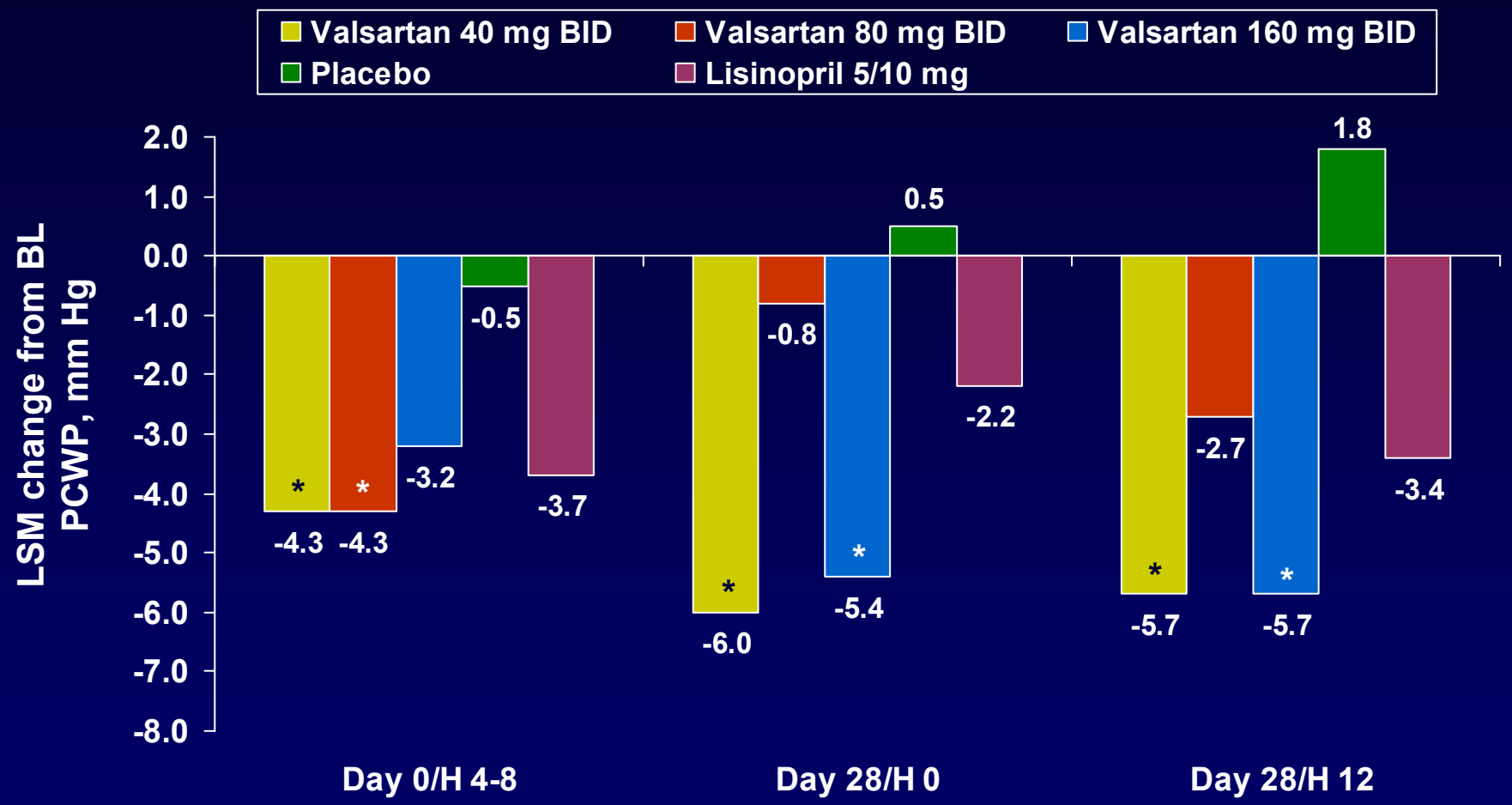
Pulmonary Capillary Wedge Pressure Least Square Mean Change From Baseline (103)



*P < .017 versus placebo.

Mazayev VP, et al. *Int J Cardiol*. 1998;65:239-246.

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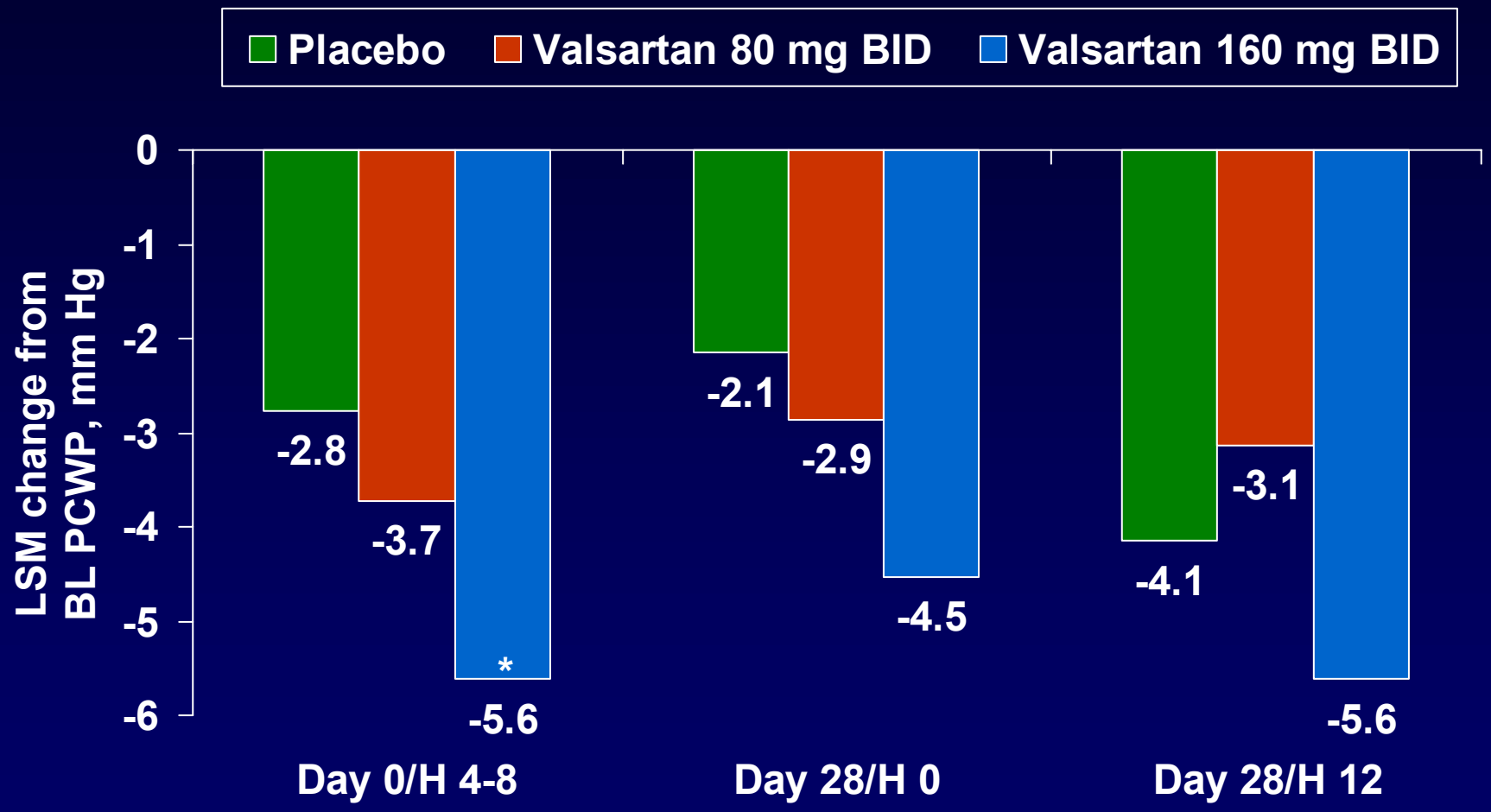
Pulmonary Capillary Wedge Pressure Least Square Mean Change From Baseline - Patients on ACEI (104)



*P < .025 versus placebo.

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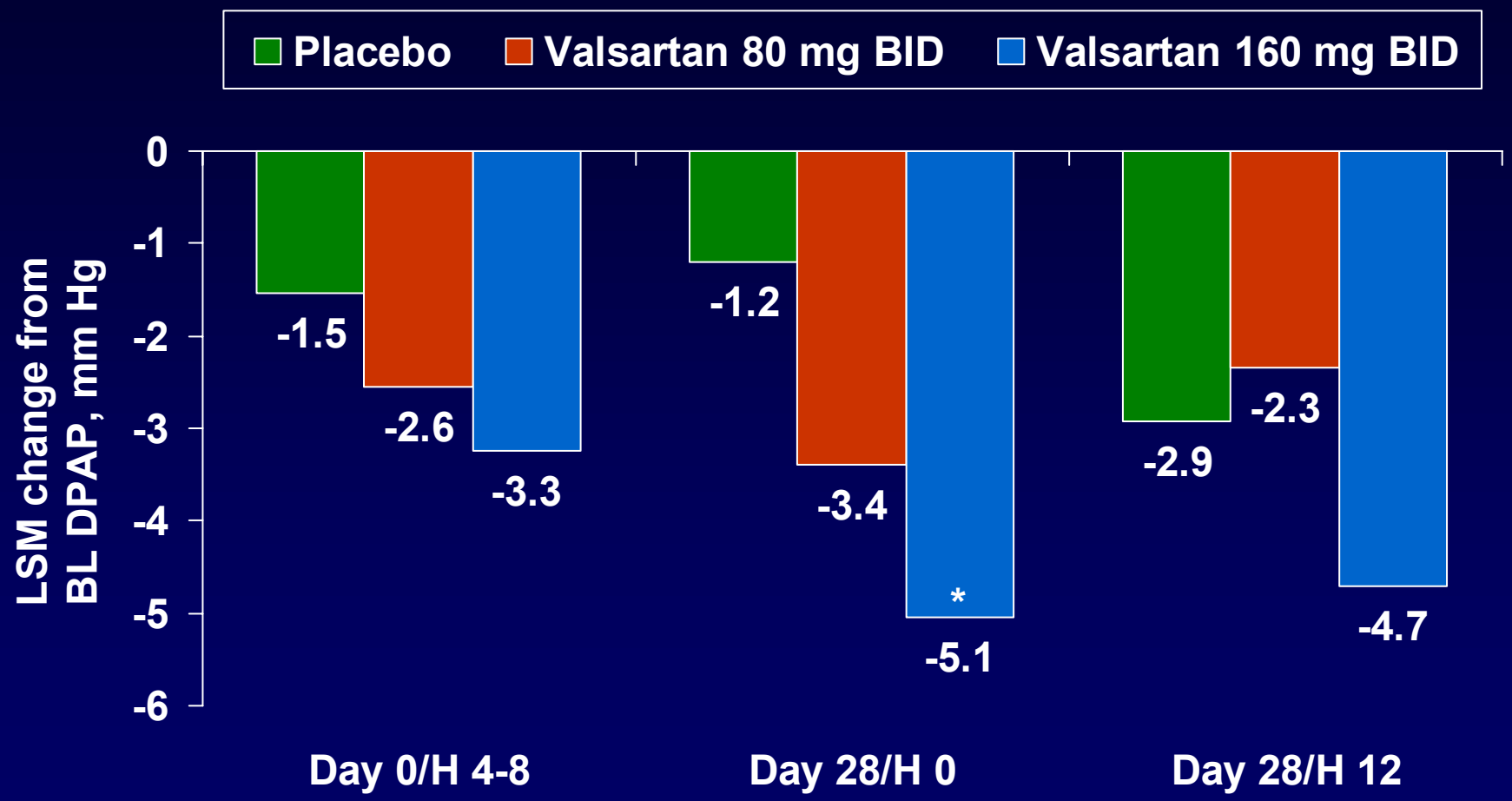
Diastolic Pulmonary Artery Pressure Least Square Mean Change From Baseline - Patients on ACEI (104)



*P < .025 versus placebo.

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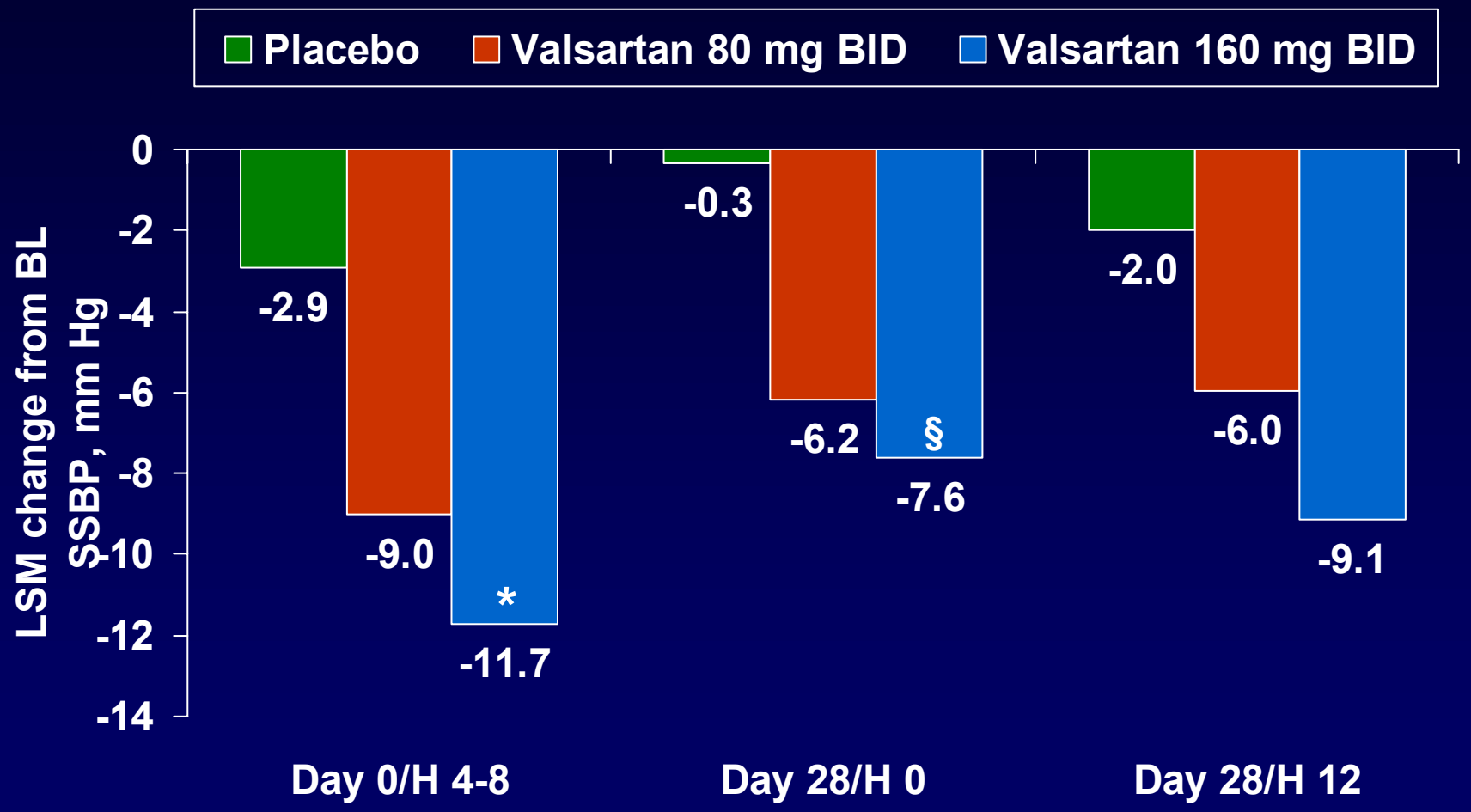
Systolic Systemic Blood Pressure Least Square Mean Change From Baseline - Patients on ACEI (104)



*$P < .025$ versus placebo.
§$P = .051$ versus placebo.

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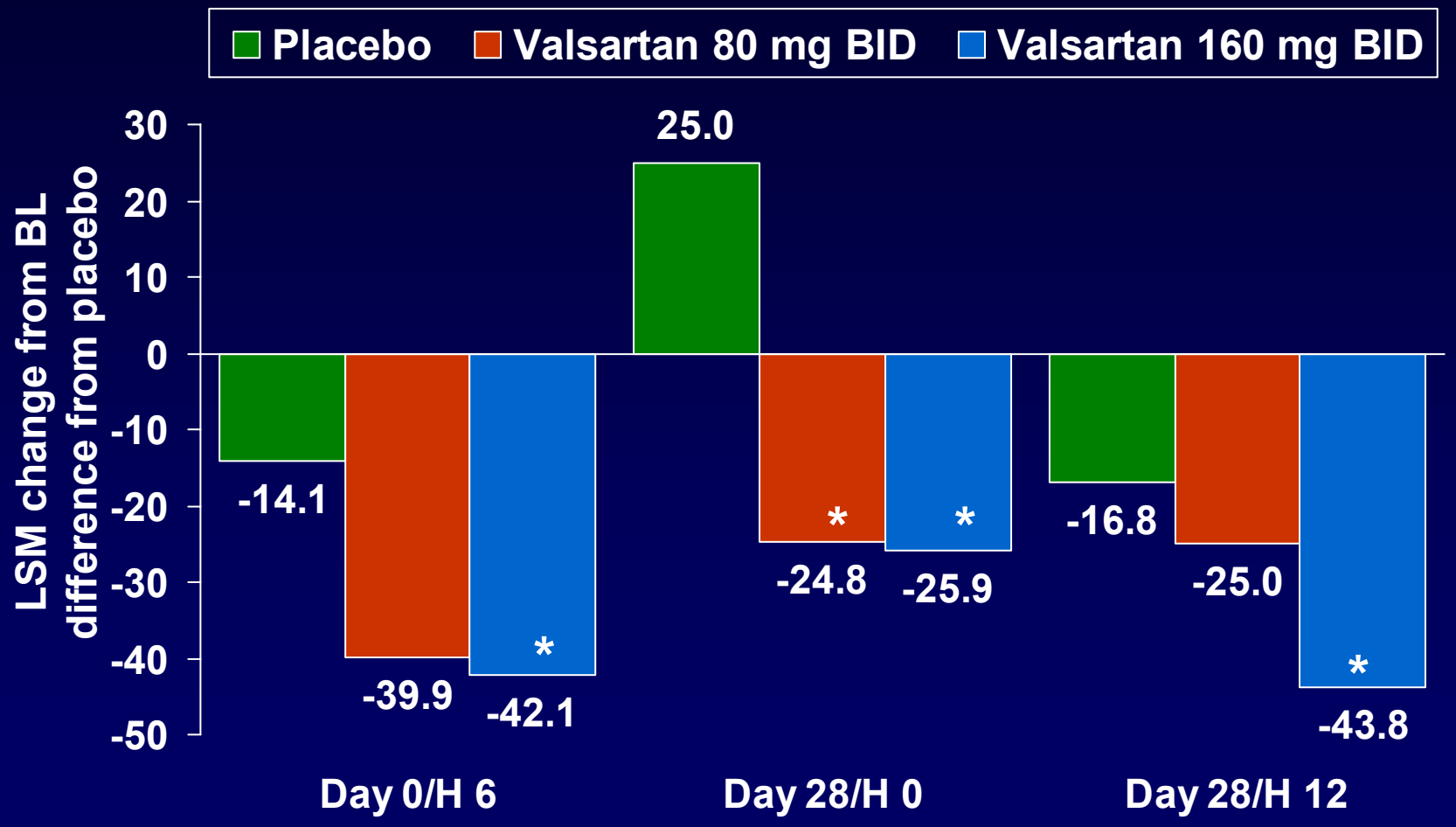
Plasma Aldosterone Least Square Mean Change From Baseline - Patients on ACEI (104)



*P < .025 versus placebo.

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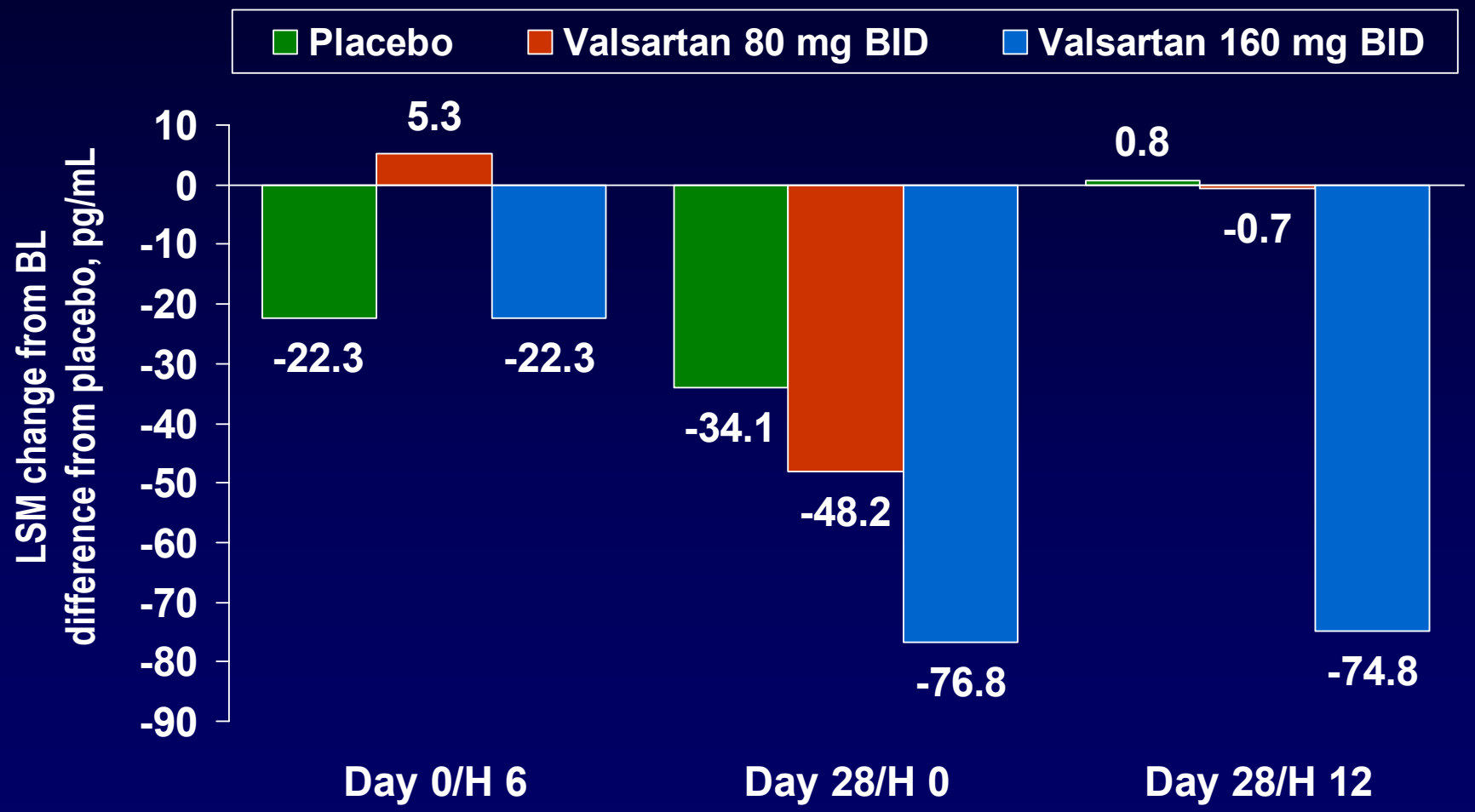
Plasma Norepinephrine Least Square Mean Change From Baseline - Patients on ACEI (104)



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Exercise Tolerance and 6-Minute Walk Tests

Exercise Duration Mean Change From Baseline at Endpoint (106)§

	Valsartan, mg BID			
	40 N = 168	80 N = 180	160 N = 182	Placebo N = 179
BL mean (SD)	438.8 (138.2)	430.0 (142.8)	430.8 (141.4)	434.5 (132.2)
LSM change from BL, sec	85.1	85.4	68.6	65.7
LSM difference (SE) from placebo	19.4 (16.1)	19.7 (15.8)	2.9 (15.7)	
P value	.2296	.2119	.8530	

§Assessed by maximal exercise testing, at endpoint, with 0 assigned for death or inability to walk due to HF.

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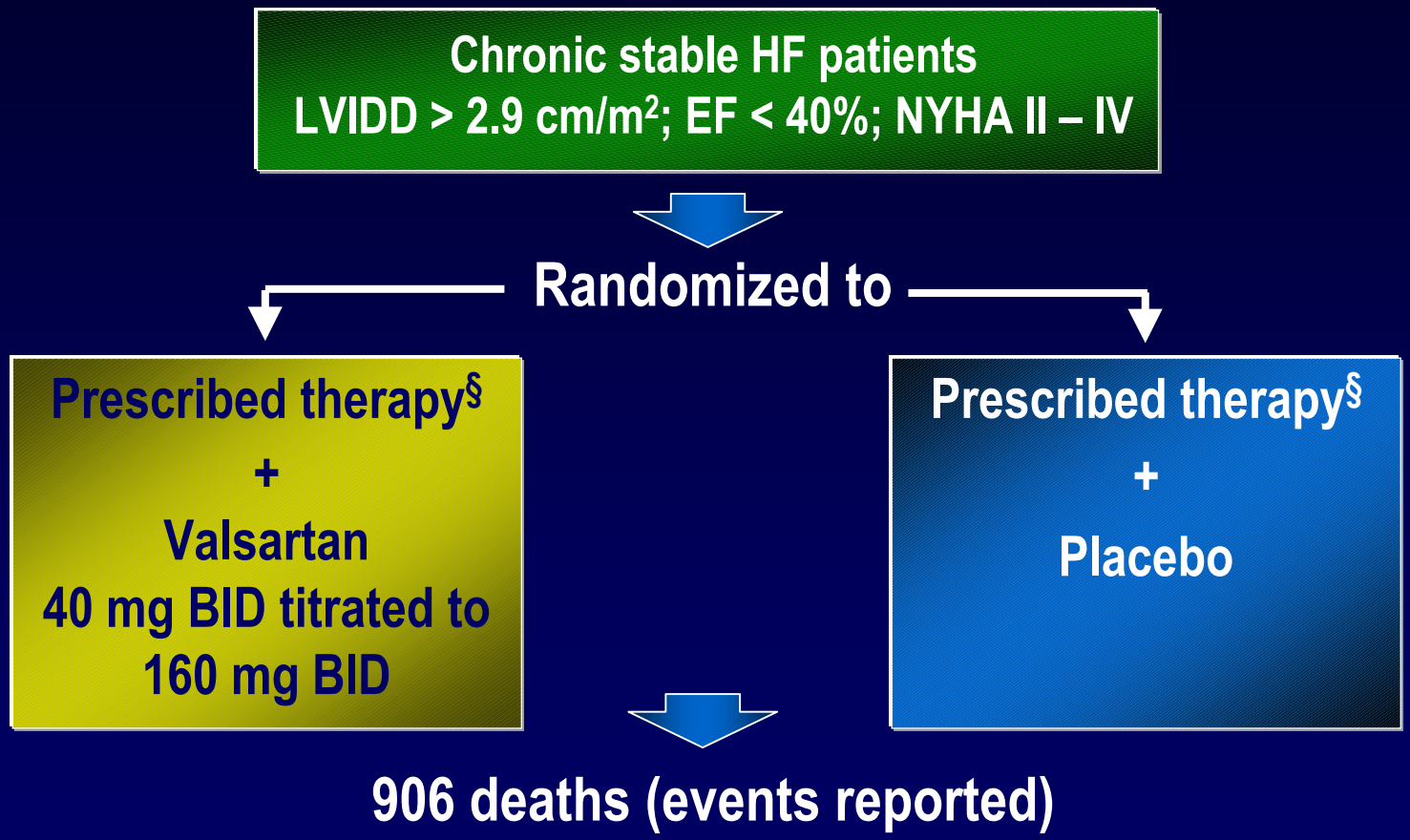
6-Minute Walk Test Trials Least Square Mean Change From Baseline at Endpoint

Treatment group	N	Mean BL (SD), meters	LSM change (SE)	LSM treatment difference (95% CI)	*P* value
Val-HeFT exercise substudy endpoint					
Valsartan	320	372.7 (110.2)	14.91 (4.61)	1.18 (–11.2, 13.6)	.852
Placebo	313	373.6 (113.4)	13.73 (4.66)		
Exercise capacity at endpoint (Study 110)					
Valsartan	67	421. 7 (113.3)	3.01 (8.54)	1.12 (–21.89, 24.12)	.462
Enalapril	67	426.0 (114.4)	1.90 (8.51)		

Morbidity and Mortality Val-HeFT

Study Design (Val-HeFT)



§Prescribed therapy = ACE inhibitors, diuretics, digoxin, beta-blockers (stratified randomization).

Cohn JN, et al. *J Card Fail.* 1999;5:155-160.

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2 Primary Efficacy Variables (Val-HeFT)

Mortality	Morbidity
Time to death	Time to first morbid event ◆ Death ◆ Sudden death with resuscitation ◆ Need for therapeutic doses of an intravenous inotropic or vasodilating agent for HF for at least 4 hr ◆ Hospitalization for HF

Statistical Considerations (Val-HeFT)

- 2-sided significance
  - Morbidity .025
  - Mortality .020
- Adjustment for interim analysis (O'Brien-Fleming)
- Assumptions for sample size (906 deaths)
  - Placebo death rate 12% per year
  - Reduction in death rate 20%
  - Power 90%
  - 2-sided significance .025

Primary Efficacy Variables (Val-HeFT)

- All patients followed to study end
- Censoring at
  - Time to study end
  - Time to loss to follow-up
  - Time to heart transplant
- Independent endpoints committee
- Semiannual interim analysis of time to death
  - Independent Data Safety Monitoring Board

Major Inclusion Criteria (Val-HeFT)

- Age ≥ 18 yr
- Chronic stable HF
  - NYHA class II to IV
  - LVEF < 40% (echo)
  - LVIDD > 2.9 cm/m^2 (echo)
- Stable regimen of prescribed HF therapy (4 to 6 wk)

LVEF = Left ventricular ejection fraction; LVIDD = Left ventricular internal diastolic diameter.

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Major Exclusion Criteria (Val-HeFT)

- Significant primary mitral valve disease or obstructive lesion of LV outflow
- MI, unstable angina, syncope, CVA, cardiac surgery, PTCA in previous 3 mo
- CAD likely to need CABG or PTCA
- Rapidly deteriorating heart failure
- Heart transplant or awaiting transplant
- Right heart failure due to pulmonary disease
- Class 1C antiarrhythmics, IV inotropes, or IV vasodilators in previous 3 mo

Participating Countries (Randomized Patients)

Australia (132)	France (93)	South Africa (99)
Belgium (109)	Germany (358)	Spain (155)
Czech Republic (86)	Hungary (92)	Sweden (142)
Denmark (45)	Italy (712)	UK (138)
Finland (89)	The Netherlands (535)	USA (2,178)
	Norway (47)	

302 Centers in 16 Countries
(5,010 patients total)

Drug Exposure by Duration and Mean Daily Dose (Val-HeFT)

	Valsartan N = 2,511	Placebo N = 2,499
Duration of follow-up, days (SD)	699.0 (245)	699.0 (246)
By daily dose§		
Mean, mg (SD)	254.4 (83.7)	283.2 (62.2)
Median	307.4	310.0
Mean Duration of treatment, days (SD)	604.3 (299.6)	629.2 (281.2)
Patients achieving target dose, n (%)	2,120 (84.4)	2,316 (92.7)

§Mean daily dose (per patient) equals the sum of days on 80 mg × 80 days on 160 mg × 80 plus days on 320 mg × 360 divided by days on study trial.

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Patient Disposition (Val-HeFT)

	n (%)	
	Valsartan N = 2,511	Placebo N = 2,499
Completed (to death or trial end)	2,487 (99)	2,466 (99)
Premature trial termination (excluding death)	24 (1)	33 (1)
Heart transplant	18 (< 1)	23 (< 1)
Other	6 (< 1)	10 (< 1)
Lost to follow-up	3 (< 1)	4 (< 1)
Withdrew consent	3 (< 1)	6 (< 1)
Permanently discontinued trial treatment but remain in trial	448 (18)	339 (14)
Intolerable adverse experience(s)	215 (9)	136 (5)
Life-threatening laboratory abnormality	34 (1)	10 (< 1)
Persistent standing SBP < 80 mm Hg or symptoms of hypotension	30 (1)	11 (< 1)
Other	169 (7)	182 (7)

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Baseline Characteristics (Val-HeFT) (1)

	Valsartan N = 2,511	Placebo N = 2,499
Mean age, yr (SD)	62.4 (11.1)	63.0 (11.0)
Sex, % male	79.9	80.0
Race, %		
White	89.8	90.9
Black	7.2	6.5
Other	2.9	2.6
Etiology, %		
CHD	57.6	56.8
Idiopathic	31.1	31.2
Hypertension	6.1	7.3
Other	5.2	4.7
NYHA class, %		
II	62.1	61.4
III	36.1	36.3
IV	1.7	2.2

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Baseline Characteristics (Val-HeFT) (2)

	Valsartan N = 2,511	Placebo N = 2,499
Ejection fraction (SD)	26.6 (7.3)	26.9 (7.0)
LVIDD/BSA, cm/m^2 (SD)	3.6 (0.5)	3.7 (0.5)
Systolic blood pressure, mm Hg (SD)	124 (18.4)	124 (18.6)
Diastolic blood pressure, mm Hg (SD)	76 (10.5)	76 (10.7)
Background therapy, %		
Diuretic	85.8	85.2
Digoxin	67.1	67.6
Beta-blocker	34.5	35.3
ACE inhibitor	92.6	92.8
Quality of life, n§		
Overall score, mean (SD)	32.8 (23.1)	32.0 (22.8)
Emotional, mean (SD)	6.8 (6.7)	6.8 (6.6)
Physical, mean (SD)	14.9 (10.6)	14.3 (10.5)

§Overall n at baseline: valsartan 1,557, placebo 1,544.

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Doses of ACEI at Baseline (Val-HeFT)

	Valsartan		Placebo	
Therapy§	N	Mean dose (SD)	N	Mean dose (SD)
Enalapril	715	17.2 (11.0)	713	17.4 (11.1)
Lisinopril	553	18.6 (14.1)	555	19.7 (14.6)
Captopril	473	82.1 (62.0)	468	77.7 (58.4)
Ramipril	156	5.9 (3.8)	159	5.9 (3.6)
Quinapril	143	21.5 (16.4)	138	24.9 (21.0)
Fosinopril	98	19.6 (11.6)	105	18.7 (11.9)
Benazepril	90	22.1 (16.4)	91	23.9 (15.3)
Perindopril	57	3.7 (1.6)	52	4.3 (1.9)
Trandolapril	24	2.2 (1.7)	16	2.3 (1.4)
Moexipril	6	16.3 (8.8)	9	15.0 (6.5)

§Mean dose in mg/day for all therapies listed.

Doses of Beta-blockers at Baseline (Val-HeFT)

	Valsartan		Placebo	
Therapy§	N	Mean dose (SD)	N	Mean dose (SD)
Carvedilol	359	28.3 (21.0)	373	33.0 (24.1)
Metoprolol	310	64.2 (40.5)	311	67.6 (42.2)
Atenolol	76	42.1 (23.9)	76	37.5 (20.4)
Sotalol	49	149.4 (90.4)	48	135.8 (58.8)
Bisoprolol	35	4.6 (2.2)	43	4.5 (2.5)

§Mean dose in mg/day for all therapies listed.

Primary Endpoints (Val-HeFT)

	Events, n (%)			
	Valsartan N = 2,511	Placebo N = 2,499	Hazard ratio§ (95% CI)	*P* value‖
Primary endpoints				
Mortality¶	495 (19.7)	484 (19.4)	1.02 (0.90, 1.15)	.801
Morbidity#	723 (28.8)	801 (32.1)	0.87 (0.79, 0.96)	.009*

*Statistically significant vs. placebo (*P* < .025).
§Cox regression.
‖Log-rank test.
¶All cause mortality to trial end.
#First event including all cause mortality.

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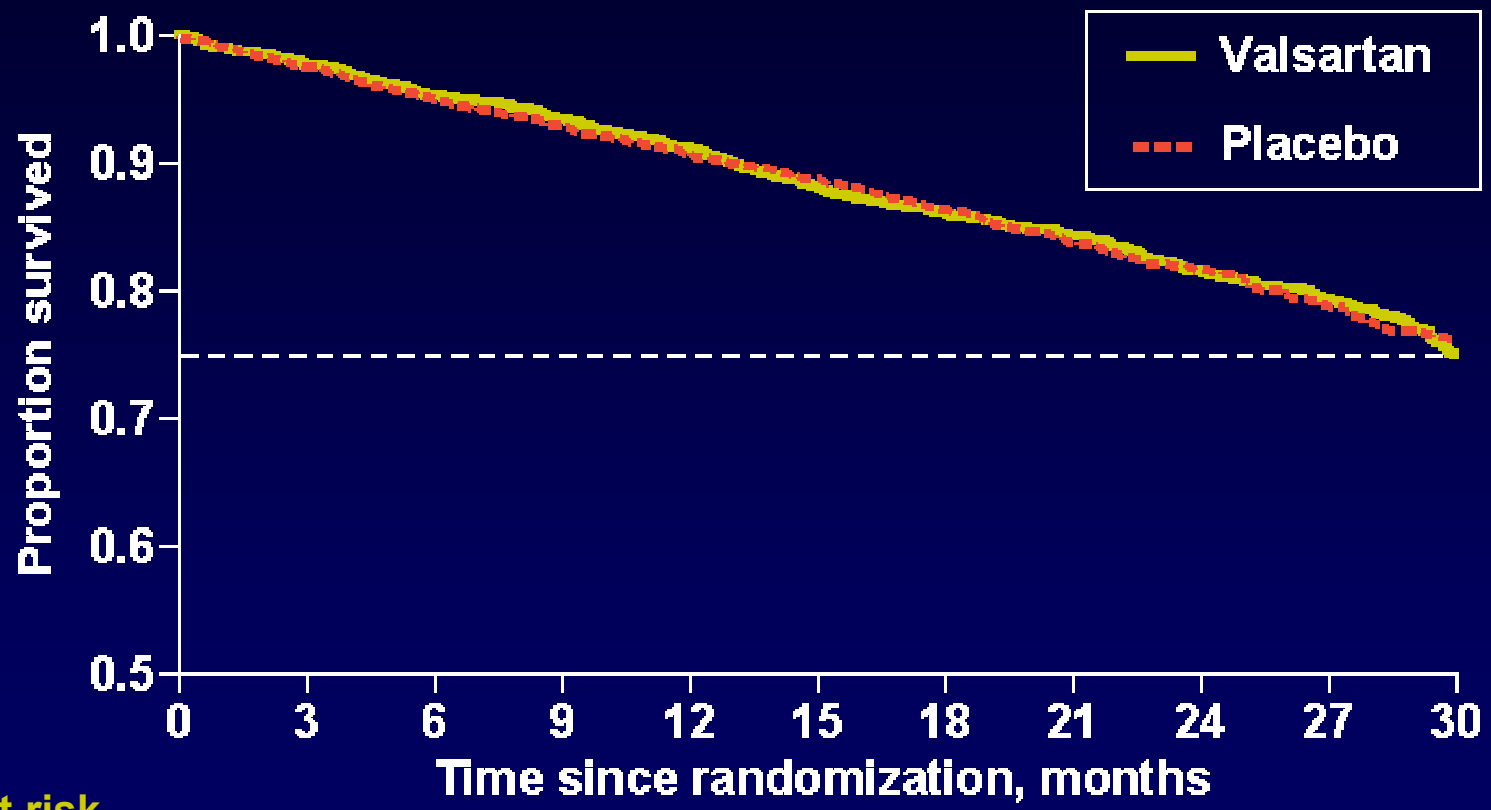
All Cause Mortality Kaplan-Meier Analysis (Val-HeFT)*



Patients at risk

Months	0	6	12	18	24	30
Valsartan	2,511	2,389	2,279	1,779	1,201	439
Placebo	2,499	2,370	2,260	1,784	1,196	440

**P* value (log-rank): .801, hazard ratio (Cox model): 1.017.

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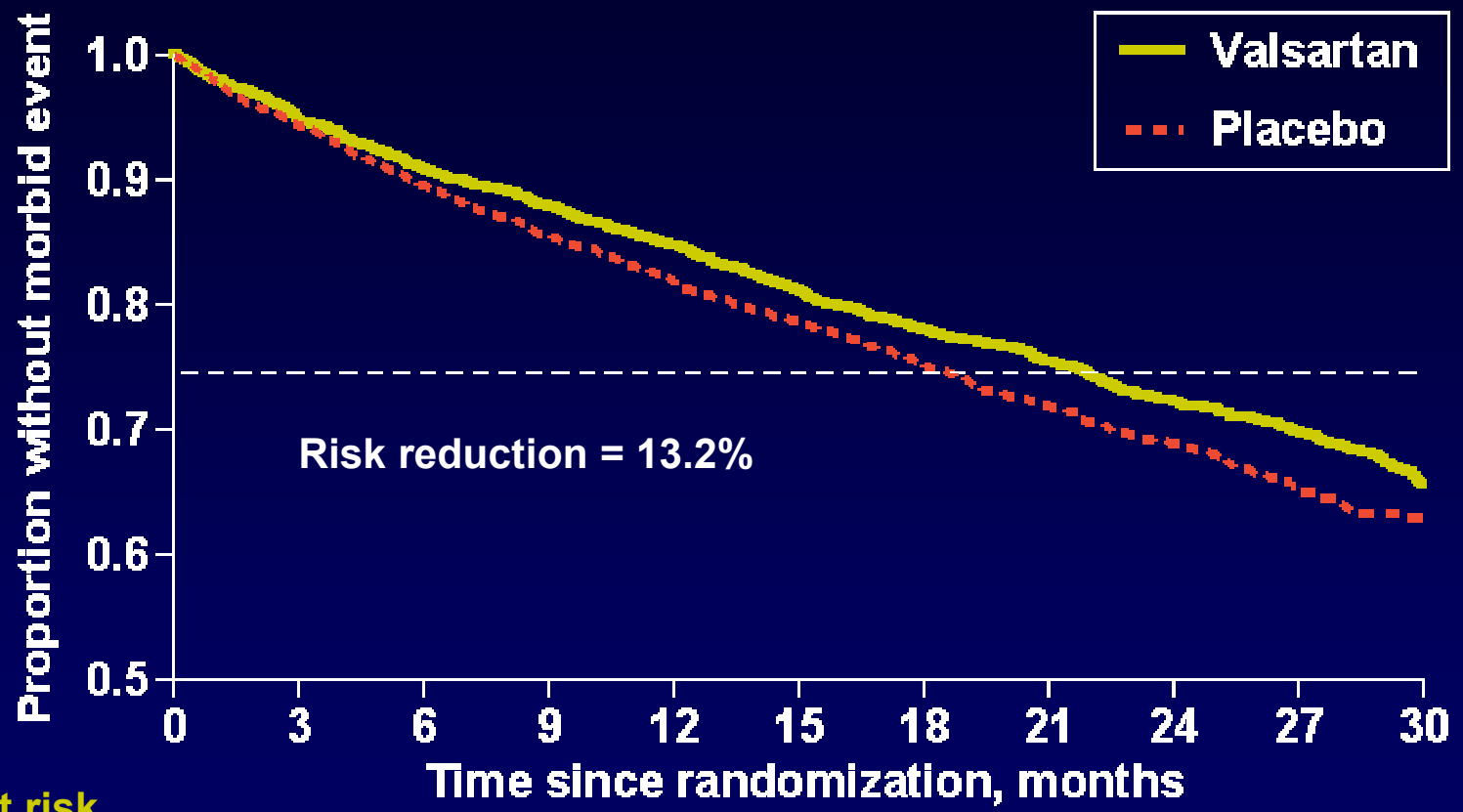
Causes of Death§ (Val-HeFT)

Category	n, (%) Valsartan N = 2,511	n, (%) Placebo N = 2,499
Deaths to trial end‖	495 (19.7)	484 (19.4)
CV-related deaths	427 (17.0)	419 (16.8)
Sudden death cardiac	230 (9.2)	212 (8.5)
Cardiac death—circulatory failure	118 (4.7)	125 (5.0)
Sudden death with worsening CHF	32 (1.3)	46 (1.8)
Other vascular causes	25 (1.0)	20 (0.8)
Cardiac death—acute MI	18 (0.7)	10 (0.4)
Cardiovascular procedures	4 (0.2)	6 (0.2)
Non-CV related deaths	64 (2.6)	60 (2.4)
Cancer	30 (1.2)	30 (1.2)
Other	34 (1.4)	30 (1.2)
Cause of death unclassified	4 (0.2)	5 (0.2)

§Assessed by Endpoint Committee.
‖Cutoff date of May 3, 2000.

Morbidity
Kaplan-Meier Analysis (Val-HeFT)*



Patients at risk

Months	0	6	12	18	24	30
Valsartan	2,511	2,280	2,125	1,612	1,067	378
Placebo	2,499	2,234	2,039	1,557	1,005	357

*P value (log-rank): .00852; hazard ratio (Cox model): 0.868.

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Primary Endpoints Analysis (Val-HeFT)

	Events, n (%)			
	Valsartan N = 2,511	Placebo N = 2,499	Hazard ratio (95% CI)	*P* value*
Primary endpoints				
Mortality§	495 (19.7)	484 (19.4)	1.02 (0.90, 1.15)	.801
Morbidity‖	723 (28.8)	801 (32.1)	0.87 (0.79, 0.96)	.009*
All-cause mortality¶	356 (14.2)	315 (12.6)		
Heart failure hospitalization	346 (13.8)	455 (18.2)		
Sudden death with resuscitation	16 (0.6)	26 (1.0)		
Intravenous therapy	5 (0.2)	5 (0.2)		

*Log-rank test.
§All cause mortality to trial end.
‖All cause morbidity to trial end.
¶First event including all cause mortality.

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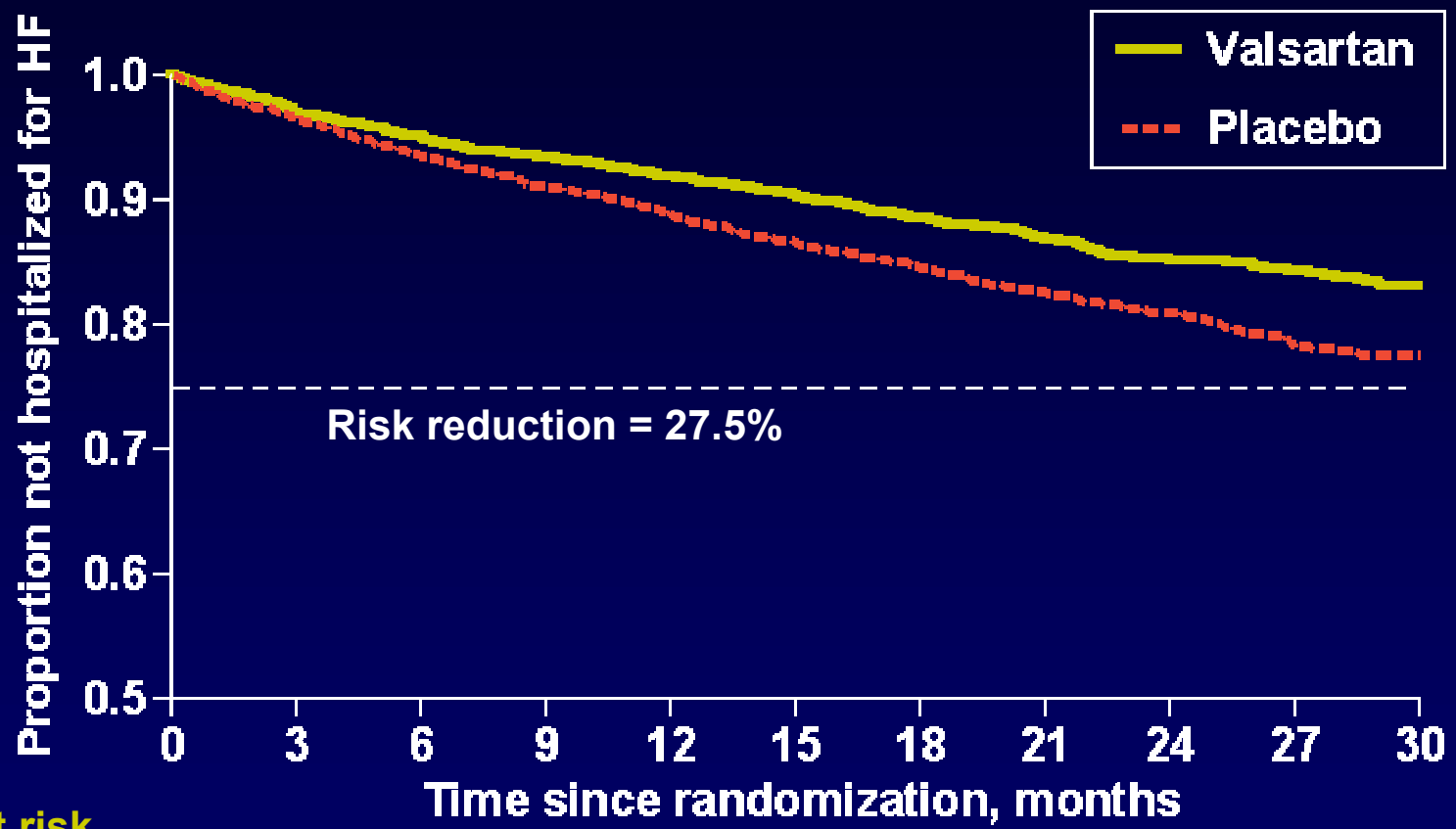
Secondary Endpoints (Val-HeFT)

	Events, n (%)			
	Valsartan N = 2,511	Placebo N = 2,499	Hazard ratio§ (95% CI)	*P* value‖
Cardiovascular deaths	427 (17.0)	419 (16.8)	1.012 (0.884, 1.158)	.857
First nonfatal morbid events	367 (14.6)	486 (19.4)	0.725 (0.633, 0.830)	.00001*
First HF hospitalization	349 (13.9)	463 (18.5)	0.725 (0.631, 0.833)	.00001*
First sudden death with resuscitation	20 (0.8)	30 (1.2)	0.653 (0.371, 1.150)	.151

*Statistically significant versus placebo.
§Cox regression.
‖Log-rank test.

Worsening Heart Failure Hospitalizations Kaplan Meier Analysis (Val-HeFT)*



Patients at risk

Months	0	6	12	18	24	30
Valsartan	2,511	2,287	2,136	1,623	1,076	381
Placebo	2,499	2,245	2,056	1,572	1,018	362

**P* value (log-rank): .00001; hazard ratio (Cox model): 0.725.

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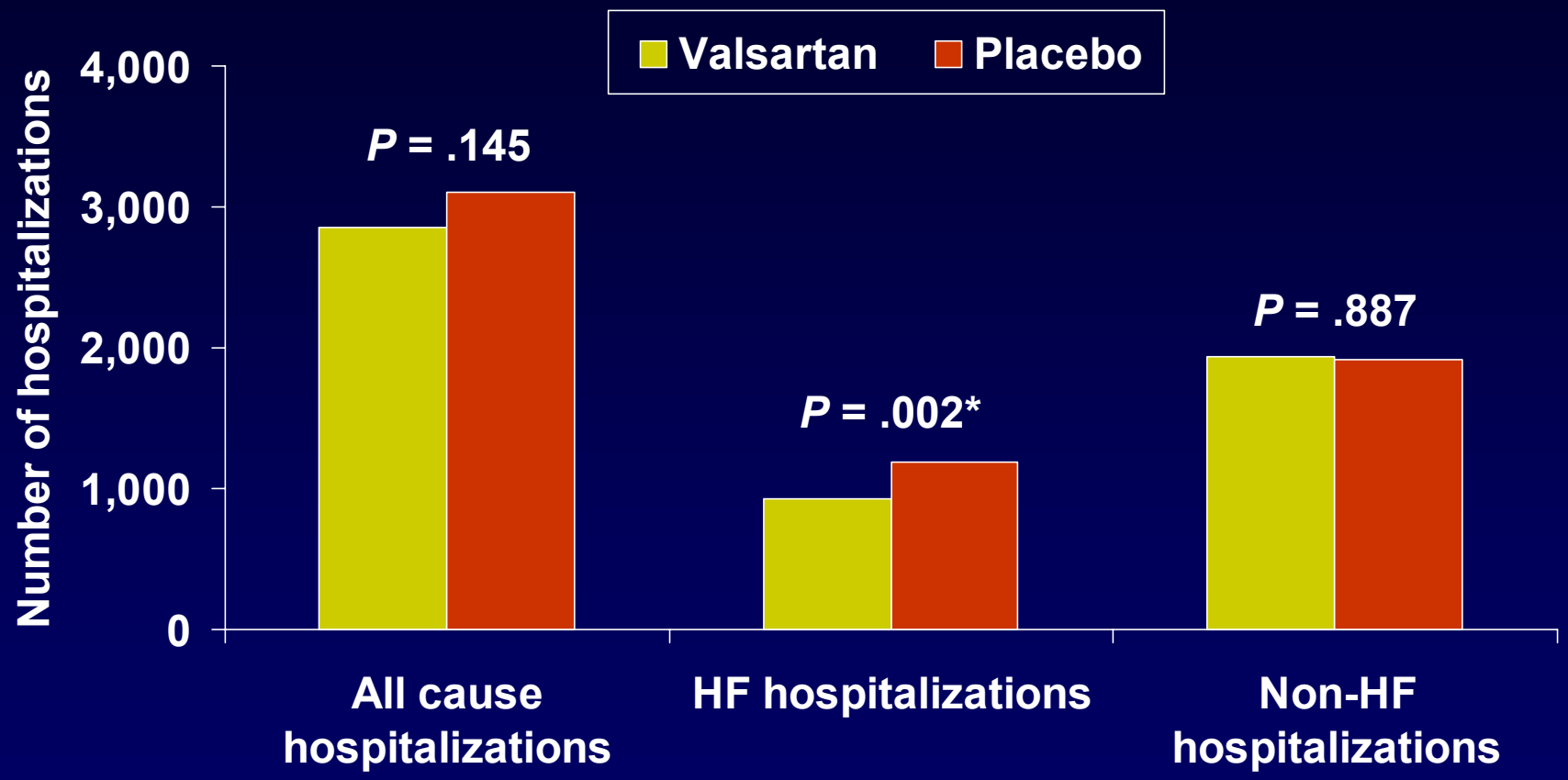
Total All Cause Heart Failure and Non-Heart Failure Hospitalizations§ (Val-HeFT)



	All cause hospitalizations	HF hospitalizations	Non-HF hospitalizations
Difference (%)	–250 (–8.0)	–266 (–22.4)	16 (0.8)

§Investigator assessment.
*Statistically significant.

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Days In Hospital (Val-HeFT)

Type of hosp.	Treatment	N	Mean days in hospital (SD)	*P* value
All-cause	Valsartan	2,511	9.8 (22.1)	.066
	Placebo	2,499	11.0 (22.2)	
HF	Valsartan	2,511	3.5 (11.4)	.001*
	Placebo	2,499	4.8 (15.3)	
Non-HF	Valsartan	2,511	6.3 (17.7)	.743
	Placebo	2,499	6.2 (14.1)	

*Statistically significant at $P < .05$; CMH test with rank scores.

Days In and Out of Hospital (Val-HeFT)

Type of hosp.	Treatment	N	Mean days in hospital (SD)	Mean days alive and out of hospital (SD)
All-cause	Valsartan	2,511	9.8 (22.1)	689.5 (246.1)
	Placebo	2,499	11.0 (22.2)	687.7 (246.9)
HF	Valsartan	2,511	3.5 (11.4)	695.8 (246.3)
	Placebo	2,499	4.8 (15.3)	693.8 (246.8)
Non-HF	Valsartan	2,511	6.3 (17.7)	693.0 (245.0)
	Placebo	2,499	6.2 (14.1)	692.5 (245.8)

Days Out of Hospital (Val-HeFT)

Type of hosp.	Treatment	N	Mean days alive and out of hospital (SD)	*P* value
All-cause	Valsartan	2,511	689.5 (246.1)	.795
	Placebo	2,499	687.7 (246.9)	
HF	Valsartan	2,511	695.8 (246.3)	.779
	Placebo	2,499	693.8 (246.8)	
Non-HF	Valsartan	2,511	693.0 (245.0)	.942
	Placebo	2,499	692.5 (245.8)	

Days Per Year§ In and Out of Hospital (Val-HeFT)

Type of hosp.	Treatment	N	Mean days per year in hospital (SD)	Mean days per year alive and out of hospital (SD)	*P* value
All-cause	Valsartan	2,511	6.9 (17.7)	358.3 (17.7)	.135
	Placebo	2,499	8.2 (21.1)	357.1 (21.1)	
HF	Valsartan	2,511	2.8 (11.7)	362.5 (11.7)	.002*
	Placebo	2,499	3.8 (14.7)	361.4 (14.7)	
Non-HF	Valsartan	2,511	4.1 (12.7)	361.1 (12.7)	.734
	Placebo	2,499	4.3 (13.5)	360.9 (13.5)	

*Statistically significant at $P < .05$; CMH test with rank scores.
§Days per year adjusted by patient's duration in the trial.

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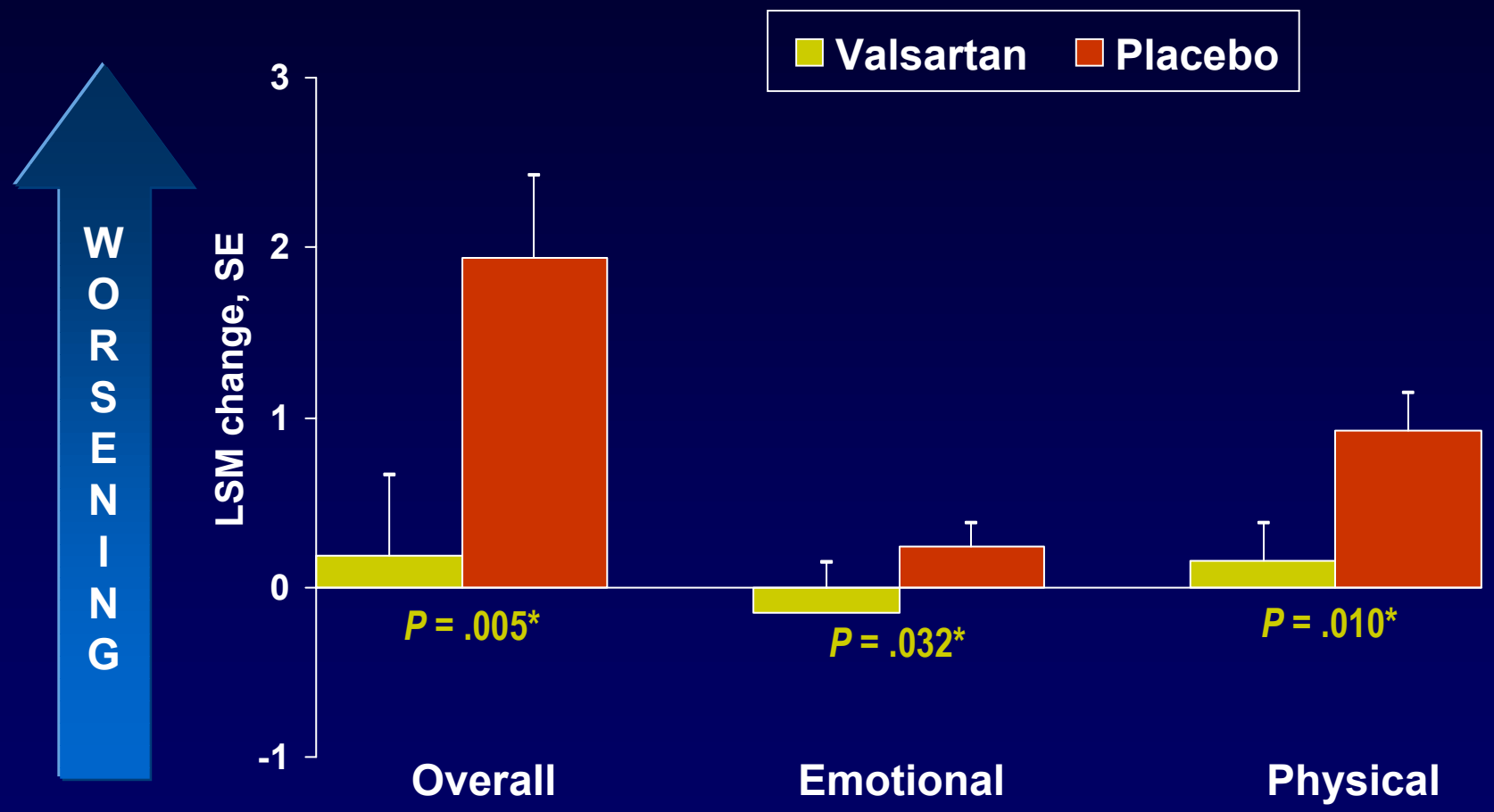
Patients With Signs and Symptoms of HF and NYHA Class at Endpoint (Val-HeFT)

	Patients, %				
	Valsartan		Placebo		
Variable	Improved	Worse	Improved	Worse	*P* value
NYHA class	23.1	10.1	20.7	12.8	< .001*
Jugular venous distension	8.0	5.5	7.6	7.2	< .001*
Edema	11.8	10.1	9.7	12.3	.003*
Rales	7.1	6.1	6.4	8.3	< .001*
Third heart sound	13.3	5.6	11.9	5.6	.195
Paroxysmal nocturnal dyspnea	6.6	4.9	5.7	7.0	.001*
Dyspnea at rest	4.3	6.4	3.6	7.4	.029*
Dyspnea on effort	34.2	18.8	31.6	21.3	.001*
Fatigue	31.7	21.6	29.4	25.3	.008*
Orthopnea	14.2	10.6	13.8	11.5	.109

*Statistically significant at $P < .05$.

From ISE Table 2-24 & 2-25

Minnesota Living With Heart Failure (LHFQ)—Least Square Mean Change From Baseline at Endpoint (Val-HeFT)



*Statistically significant at $P < .05$.

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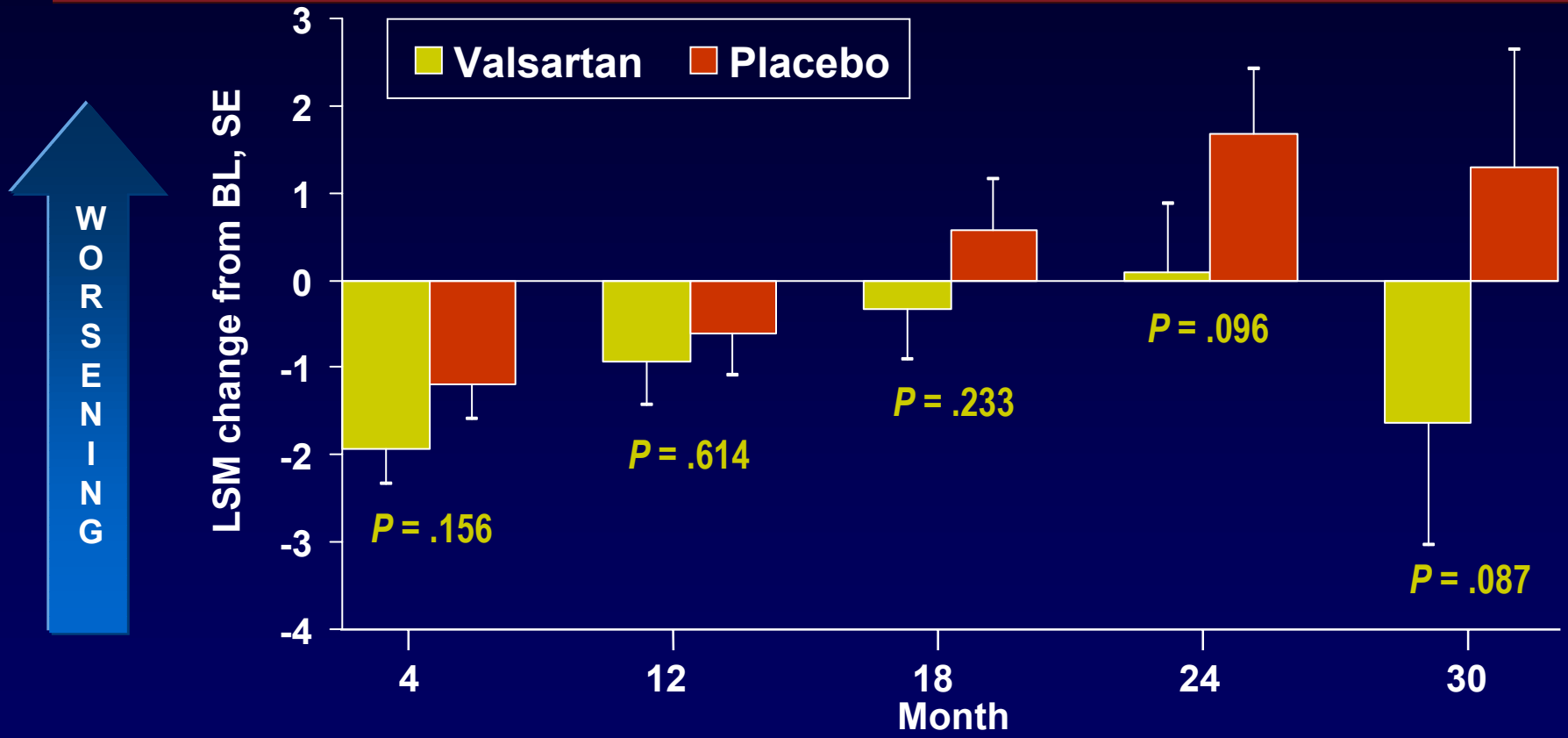
Minnesota LHFQ Overall Score Least Square Mean Change From Baseline by Month (Val-HeFT)



Valsartan, n	1,345	1,132	874	564	224
Placebo, n	1,369	1,204	907	586	232

*Statistically significant at $P < .05$.

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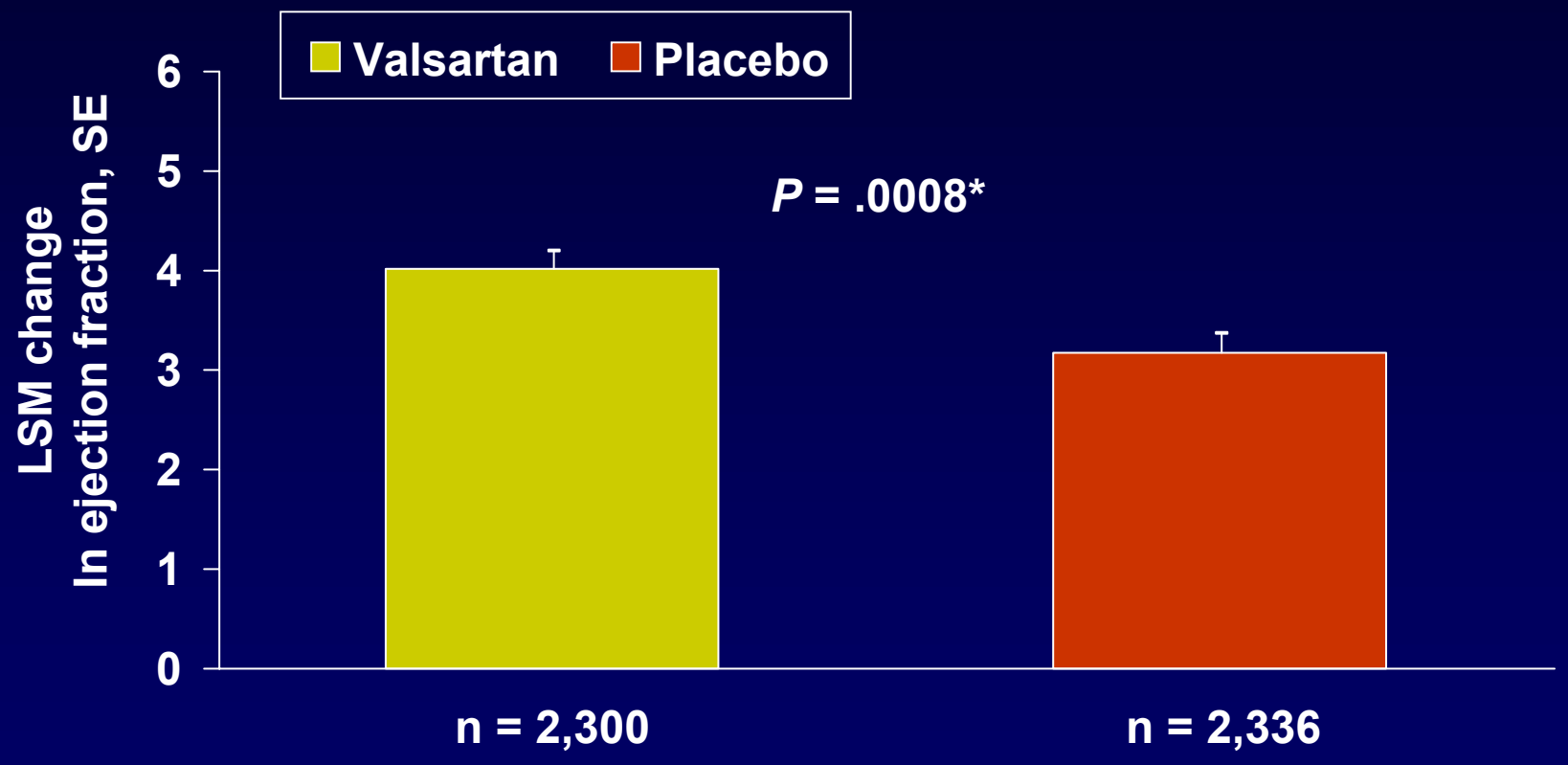
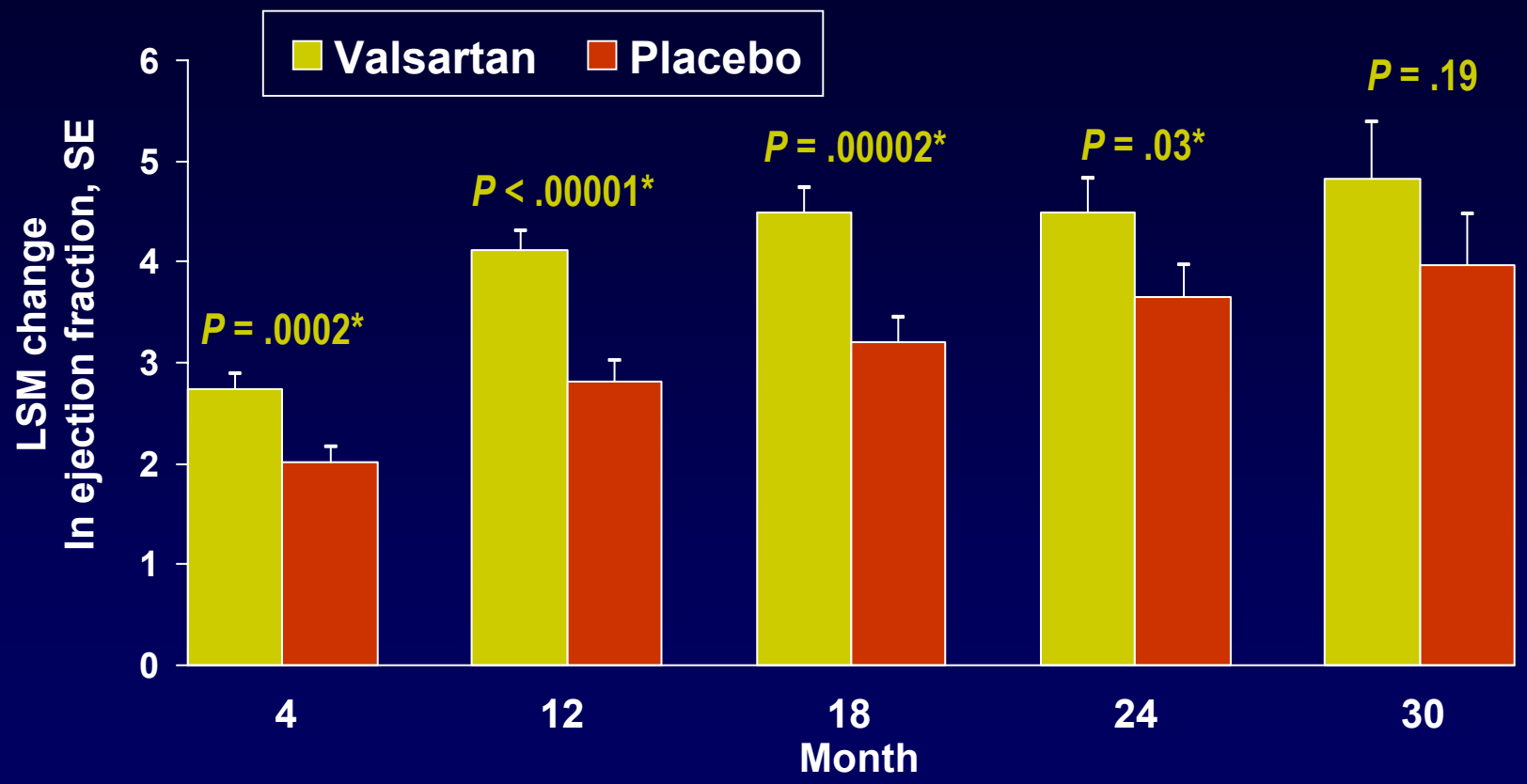
Left Ventricular Ejection Fraction Least Square Mean Change From Baseline at Endpoint (Val-HeFT)



Left Ventricular Ejection Fraction Least Square Mean Change From Baseline by Month (Val-HeFT)

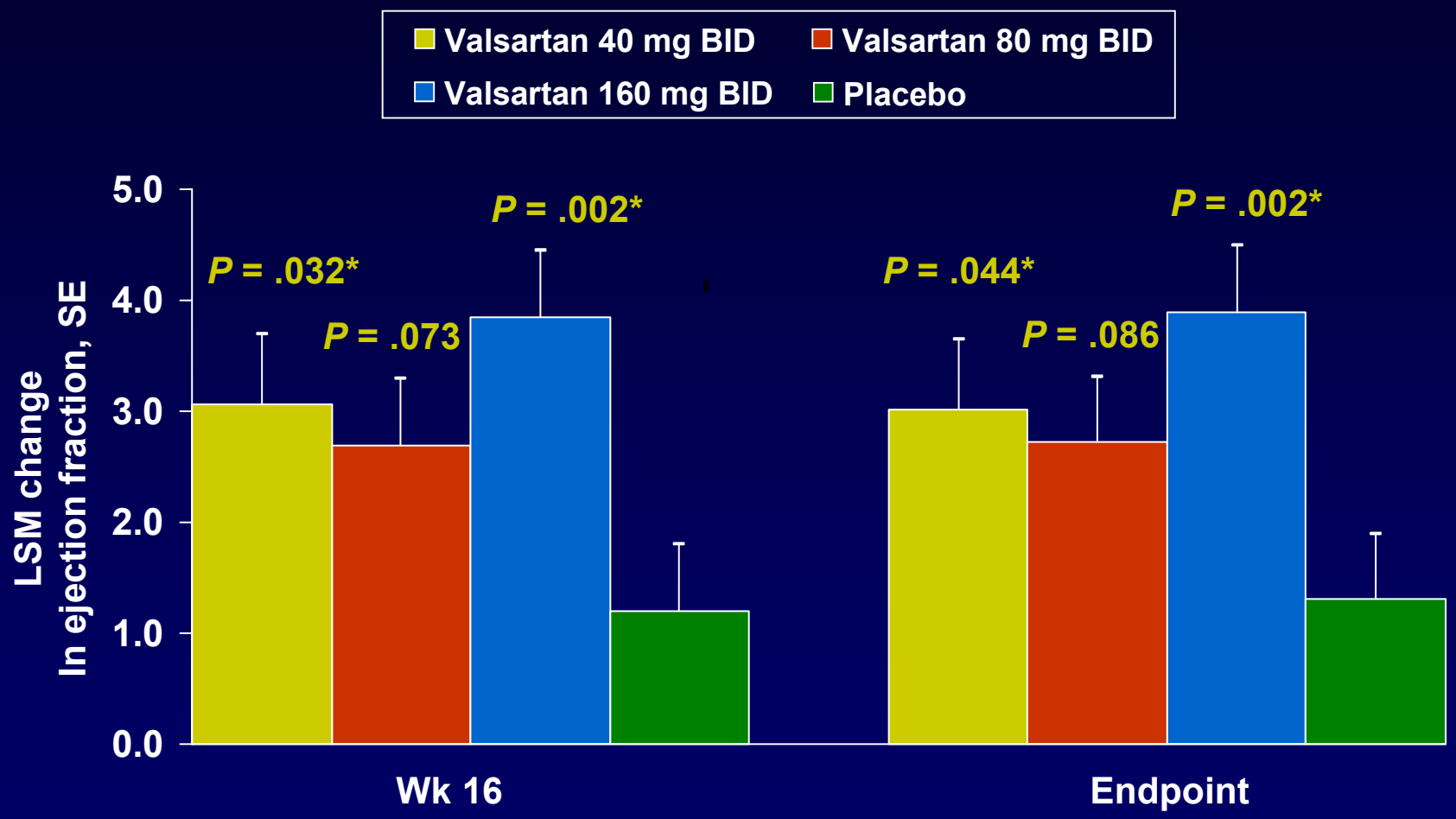


Valsartan, n	2,254	1,976	1,459	981	353
Placebo, n	2,302	2,038	1,559	1,010	366

*Statistically significant at $P < .05$.

NOVARTIS

Left Ventricular Ejection Fraction Least Square Mean Change From Baseline (106)



*Statistically significant at $P < .05$.

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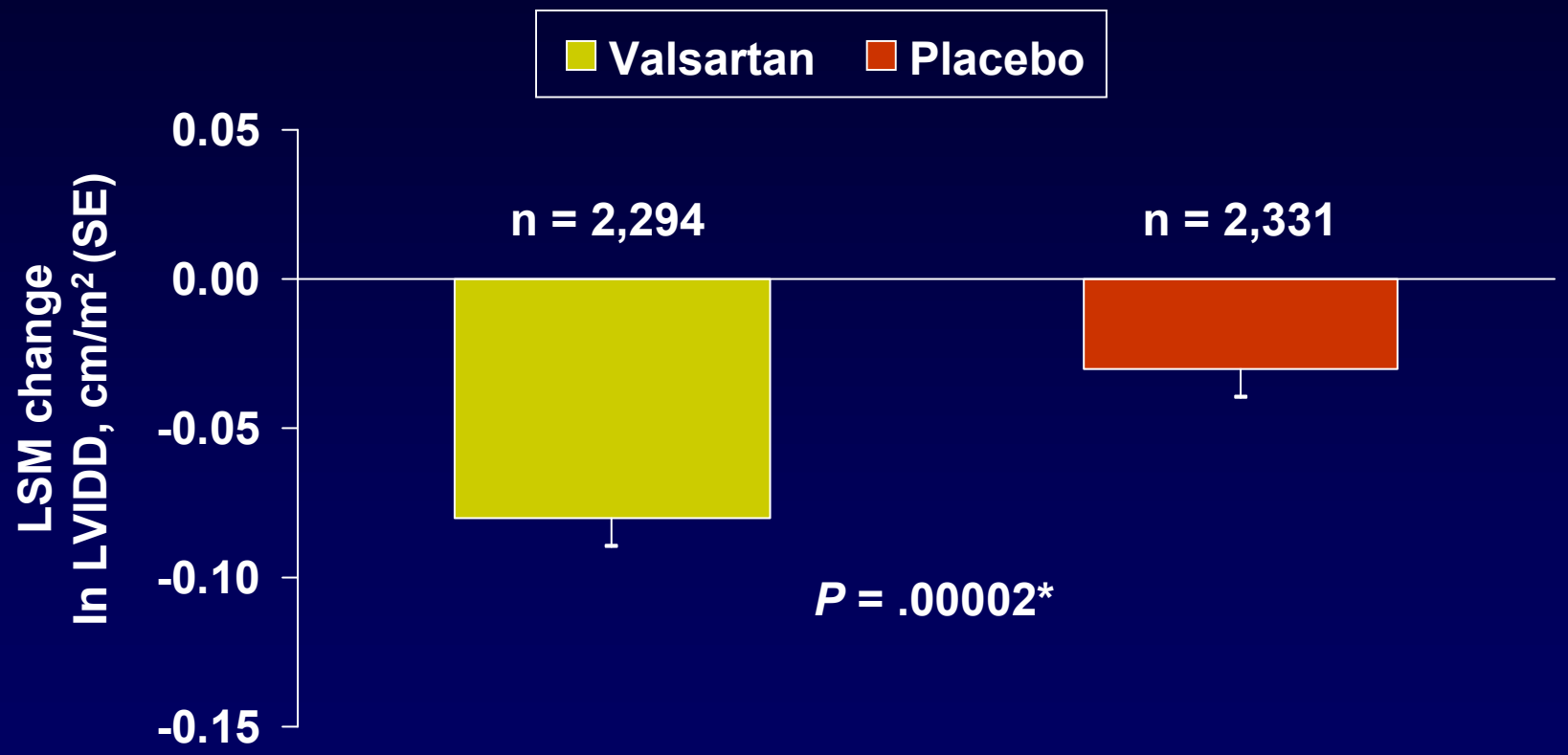
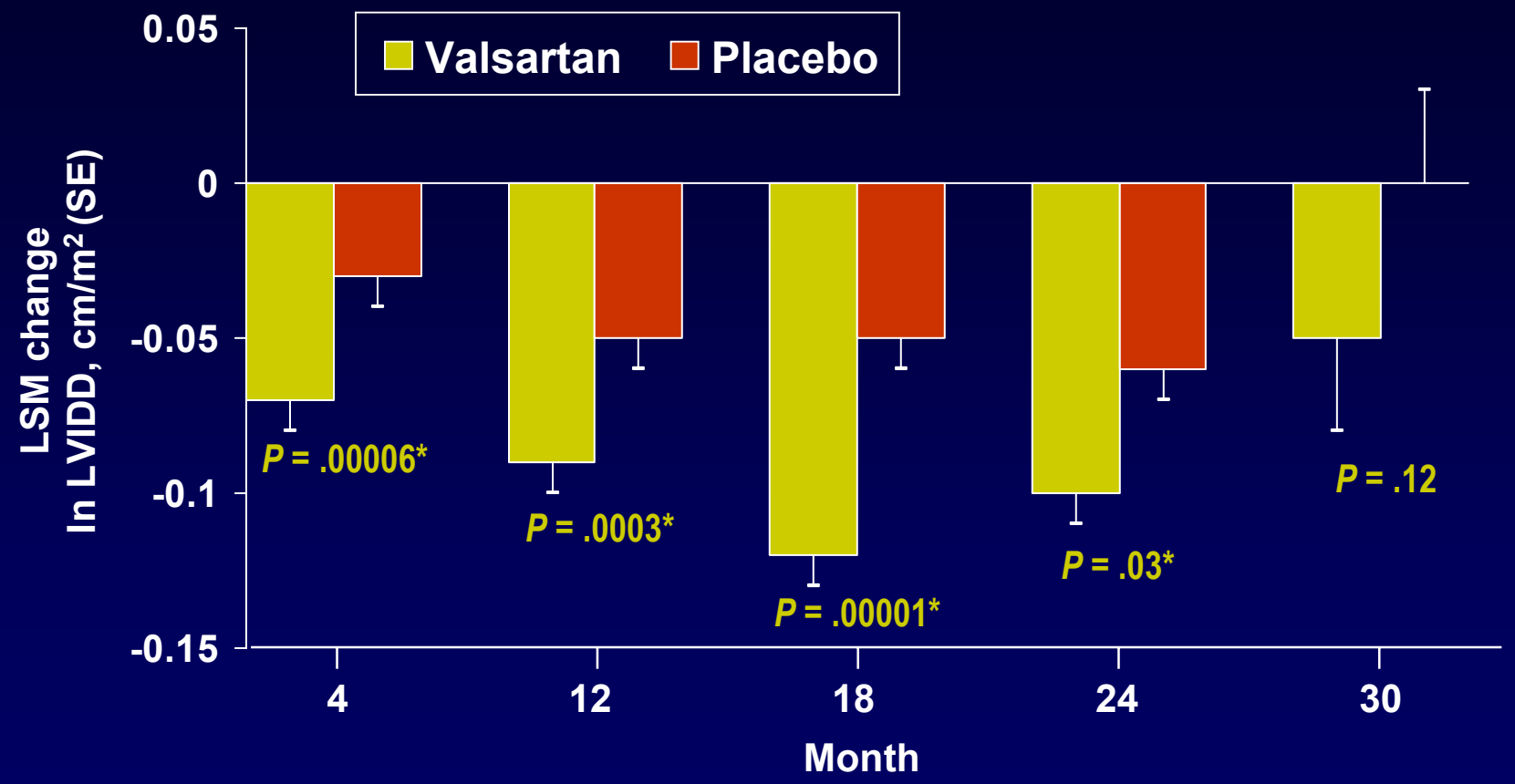
Left Ventricular Internal Diastolic Diameter Adjusted for BSA - Least Square Mean Change From Baseline at Endpoint (Val-HeFT)



Left Ventricular Internal Diastolic Diameter Adjusted for BSA - Least Square Mean Change From Baseline by Month (Val-HeFT)



Valsartan, n	2,244	1,954	1,440	967	351
Placebo, n	2,293	2,020	1,538	993	363

*Statistically significant at $P < .05$.

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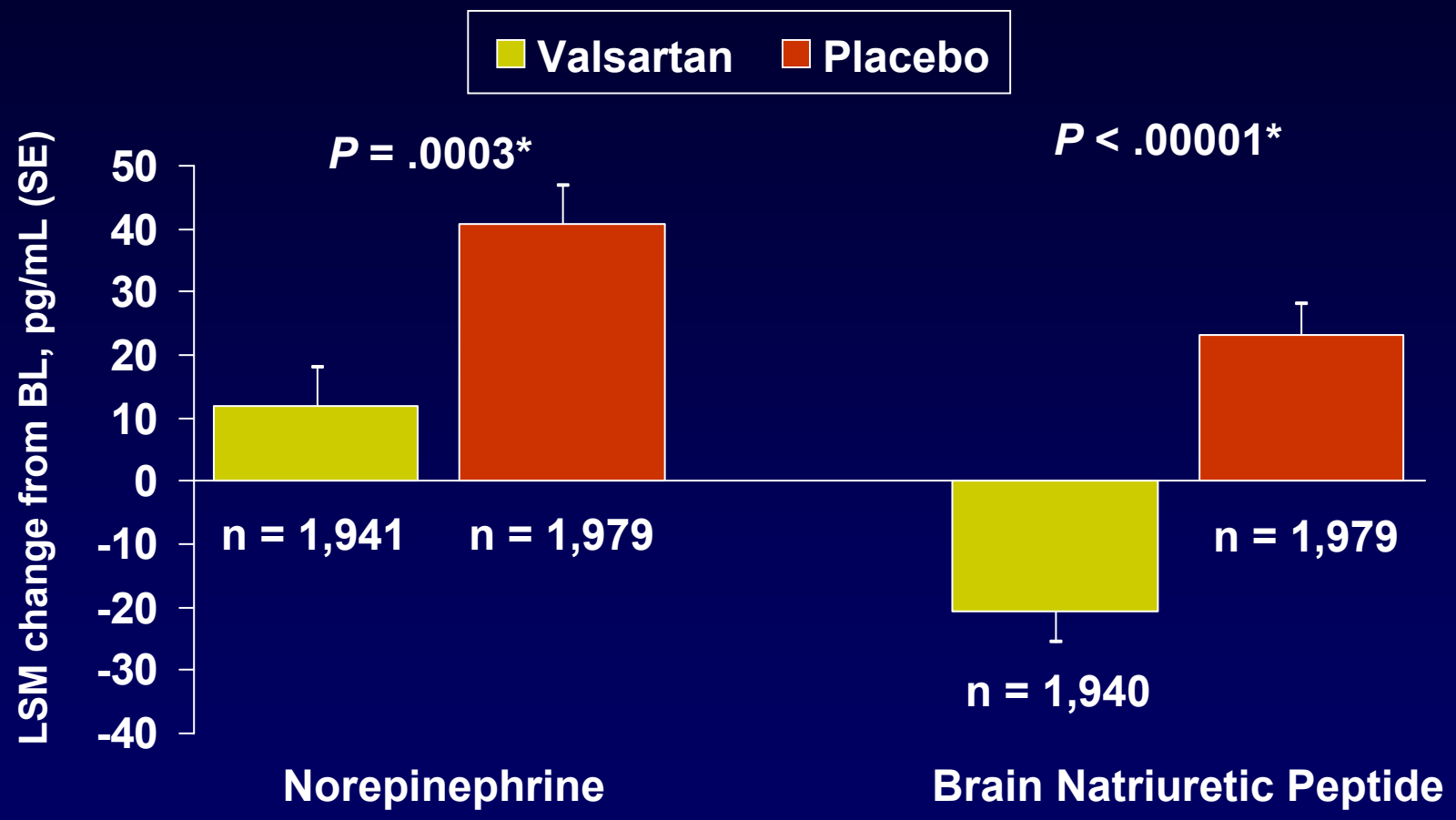
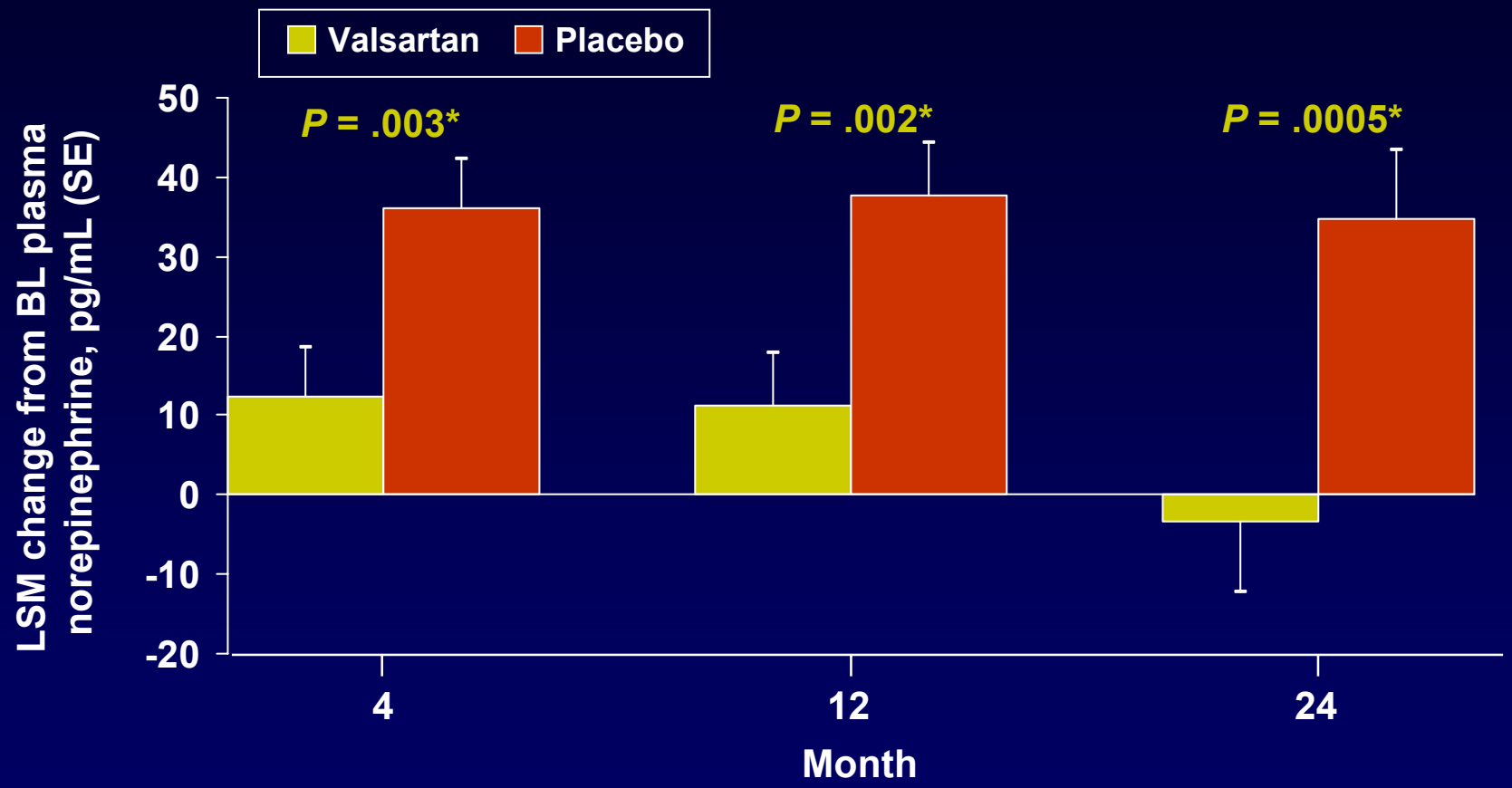
Norepinephrine and Brain Natriuretic Peptide Least Square Mean Change From Baseline at Endpoint (Val-HeFT)



*Statistically significant at $P < .05$.

Norepinephrine Least Square Mean Change From Baseline by Month (Val-HeFT)



Valsartan, n	1,855	1,635	816
Placebo, n	1,894	1,713	840

*Statistically significant at $P < .05$.

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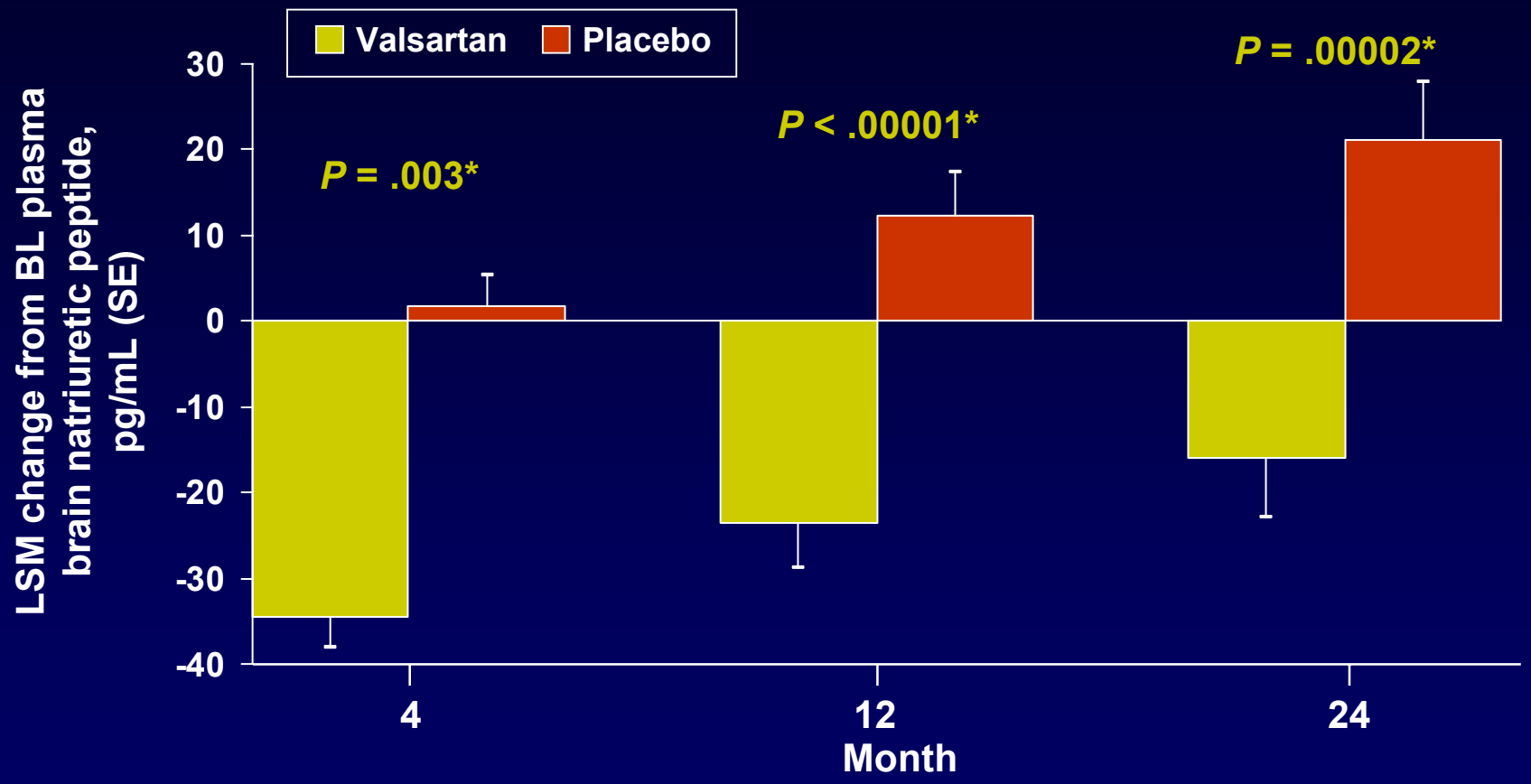
Plasma Brain Natriuretic Peptide Least Square Mean Change From Baseline by Month (Val-HeFT)



Valsartan, n	1,850	1,633	823
Placebo, n	1,890	1,710	844

*Statistically significant at $P < .05$.

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Val-HeFT: Summary of Results

- Valsartan reduced
  - Morbidity in patients receiving prescribed therapy for HF by 13.2% ($P = .009$)
  - Risk for time to first HF hospitalization by 27.5% ($P = .00001$)
- Valsartan improved
  - Heart failure signs and symptoms ($P < .05$)
  - Ejection fraction ($P = .001$)
  - LVIDD/BSA ($P < .001$)
  - Quality of life ($P = .005$)
  - Neurohormonal (NE, BNP) profile ($P < .001$)
- Mortality was similar between the 2 groups

Valsartan
Summary of Placebo-Controlled Results

Study	Hemo-dynamics	Exercise	Sign and symptoms	QOL	Neuro-hormones	Left ventricular function	Morbidity	Mortality
Val-HeFT	ND	I	+	+	+	+	+	I
103	+	ND	ND	ND	+	ND	ND	ND
104	+	ND	ND	ND	+	ND	ND	ND
106	ND	I	I	I	ND	+	ND	ND

ND = Not done; + = Positive results; I = Inconclusive results.