Novartis Satellite Symposium

Multi-institutional, prospective, open labeled trial in ACE inhibitor intolerable patients with chronic heart failure to evaluate valsartan for the effects on surrogate markers of heart failure

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Background:

Usual treatment today has two aims

Aims of heart failure management

To improve symptoms

- Diuretics
- Digoxin
- ACE inhibitors

To improve survival

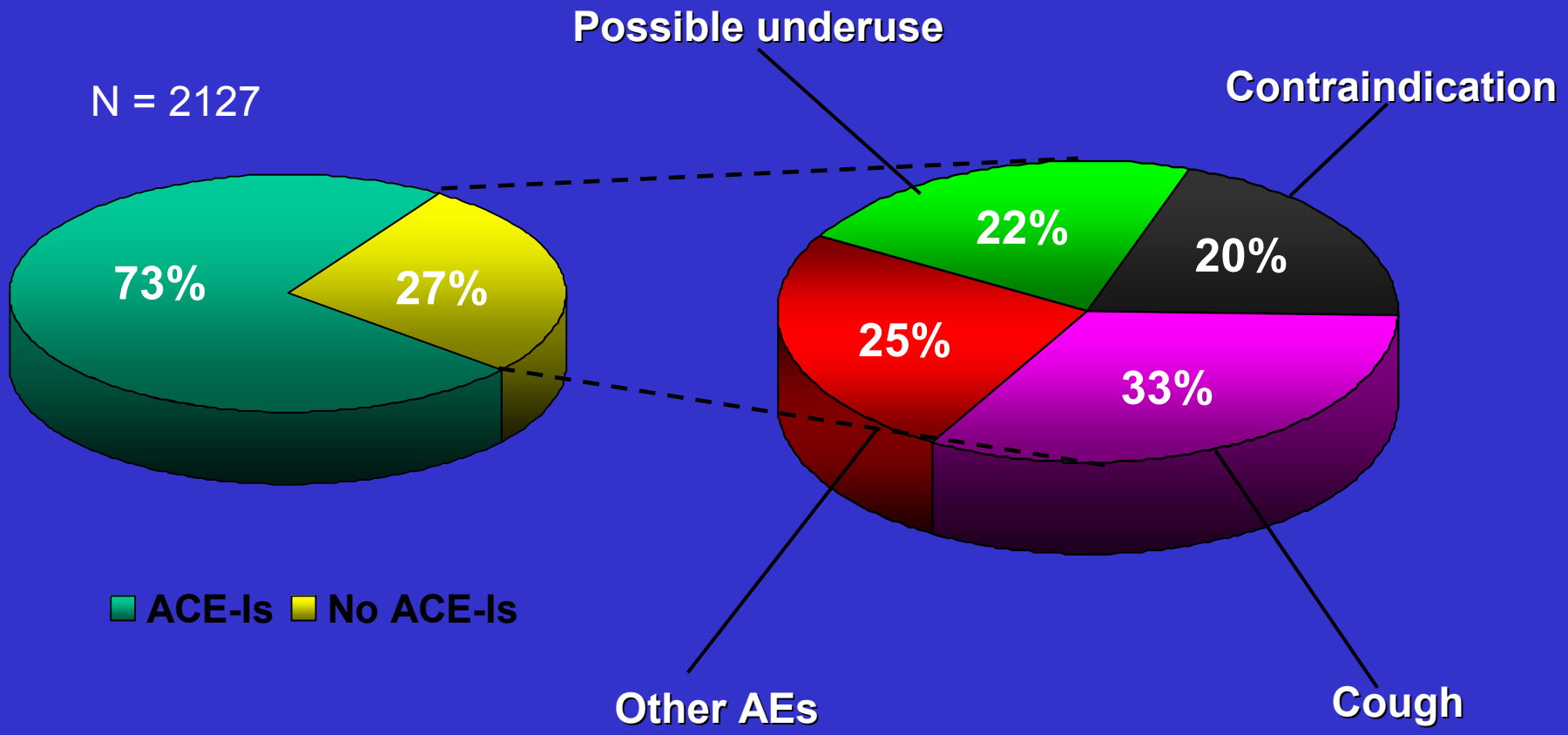
- ACE inhibitors
- β Blockers
- Oral nitrates plus hydralazine
- Spironolactone

Davies et al. BMJ 2000;320:428-431

Pharmacological Therapy

- ACE-inhibitors
  - Clear agreement : Cornerstone of the treatment for heart failure (evidence level of A and a class I recommendation)
  - ESC and CCS guidelines : particular ACE-inhibitors and doses shown to be effective in randomized, controlled, outcome trials.
  - ACC/AHA guideline : wider range of drugs
  - HFSA guideline : not specify drugs

Patients Not Receiving ACEIs



167 Cardiology and 250 Internal Medicine Clinics, Feb 14-25, 2000.
Data from TEMISTOCLE Registry, ANMCO.

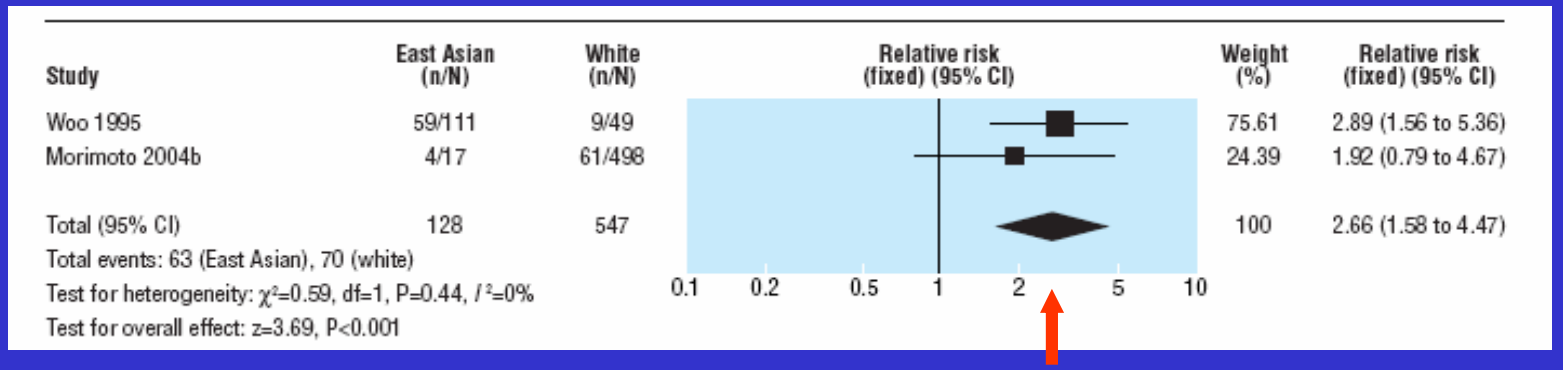
Patients Not Receiving ACEIs

- Old age, Female
- Oriental
- Korean; 40%,
  esp., female; 50%

TABLE III Incidence of ACE Inhibitor–Related Cough in Hong Kong Versus Auckland Patients

	Chinese (Hong Kong)	Caucasian (Auckland)
Captopril	32/59 (54%)	5/26 (19%)
Enalapril	27/52 (52%)	4/23 (17%)
Combined ACE	59/111 (53%)*	9/49 (18%)*†
Control	23/222 (10%)*	4/82 (5%)†
Odds ratio	5.1	3.8

Am J Cardiol. 1995 May 1;75(14):967-8

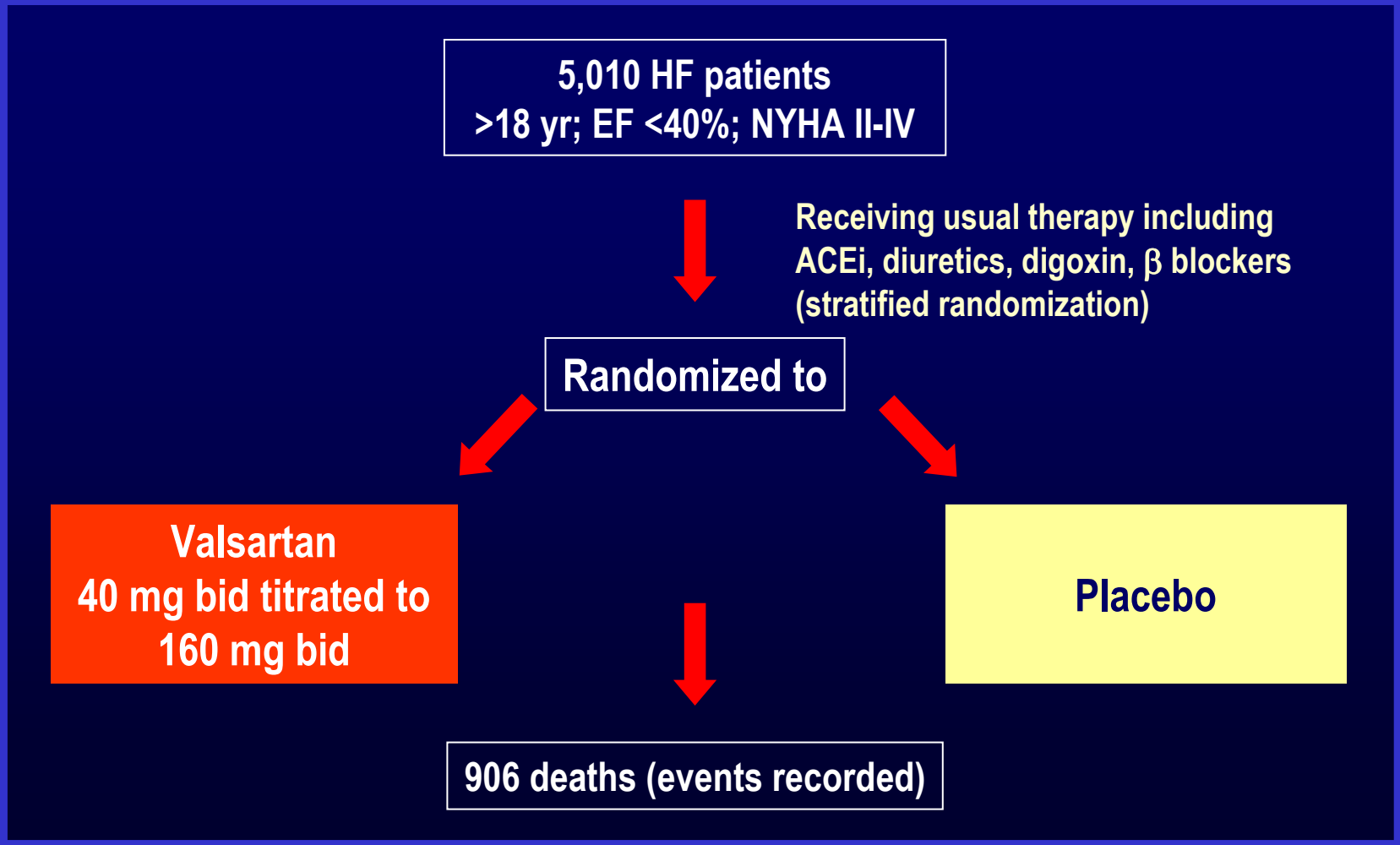


BMJ. 2006 May 20;332(7551):1177-81.

Angiotensin Receptor blockers

- **Patient intolerant of an ACE-inhibitor**
  - ESC guideline : evidence level of B
    - –The ESC guidelines :only one specific trial in the patients intolerant of ACE-inhibitors i.e. CHARM-Alternative trial.
  - Other three guidelines : evidence level of A
    - -The North American guidelines appear to have accepted the separate publication of a retrospective subgroup analysis of the effect of valsartan on ACE-inhibitor untreated patients as equivalent to a prospective randomized trial.
  - all : class I recommendation

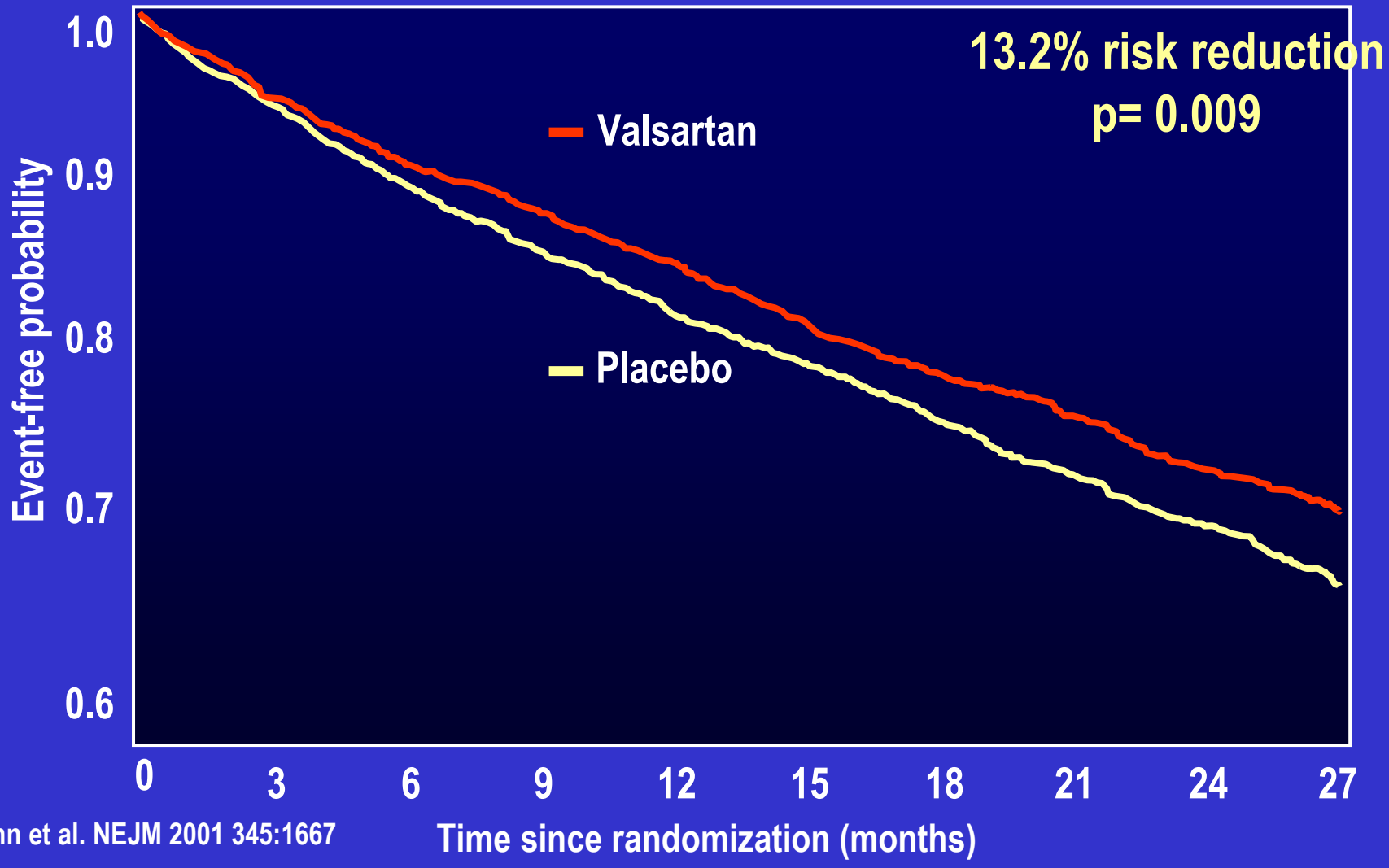
Val-HeFT Study:
Valsartan added to usual therapy for HF



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

Val-HeFT:

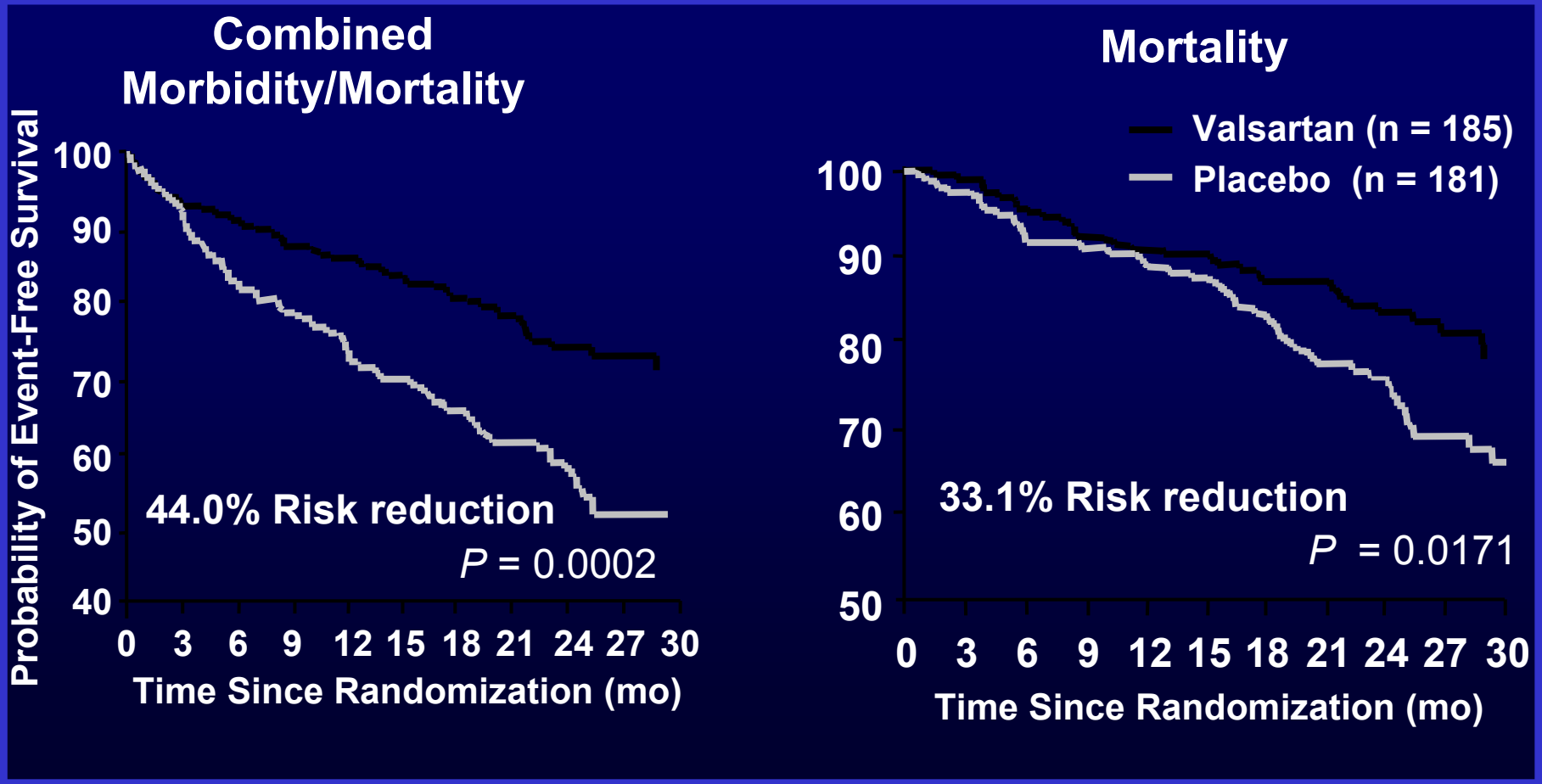
Significant benefits on combined mortality / morbidity endpoint



Cohn et al. NEJM 2001 345:1667

Val-HeFT:

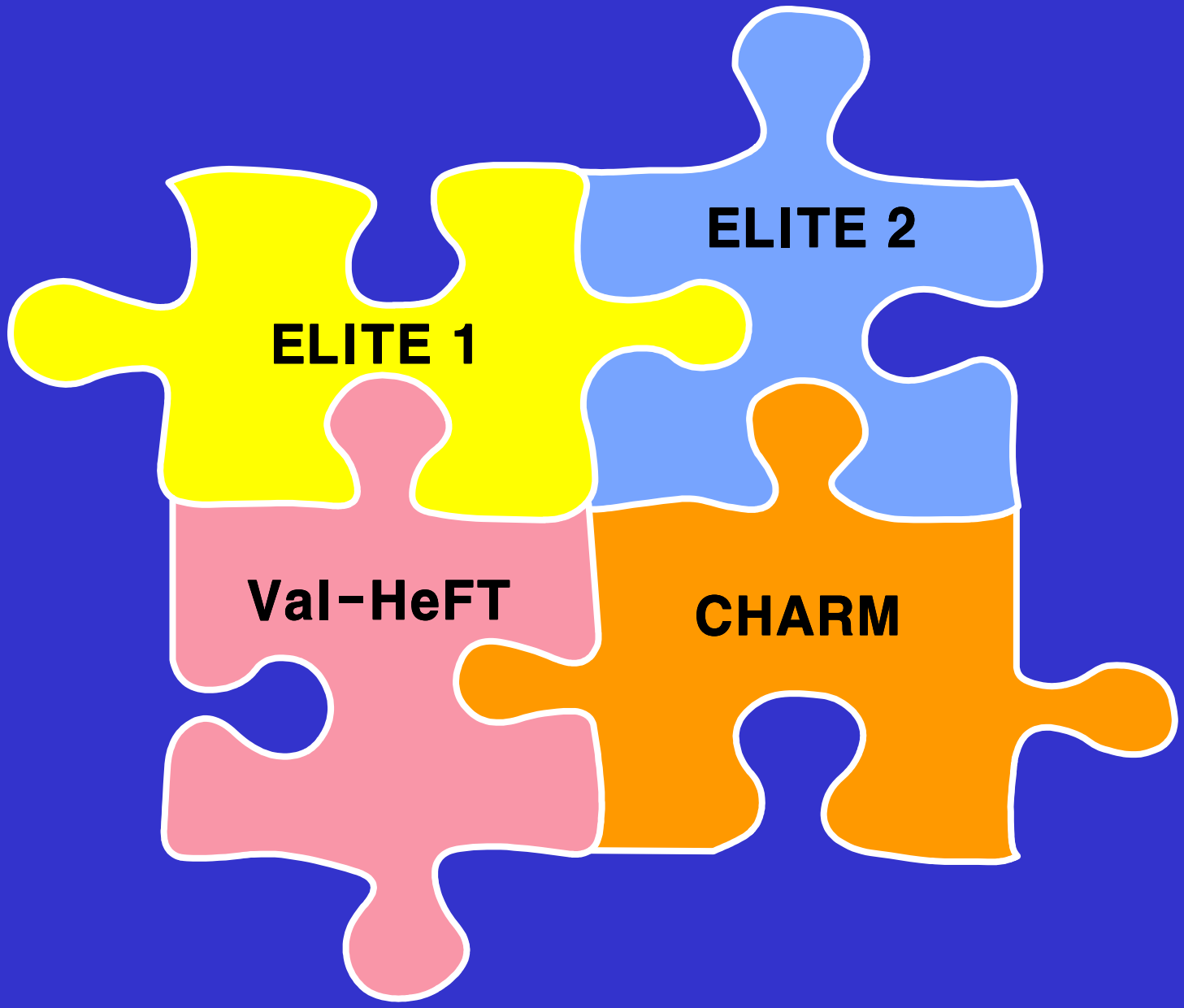
Reduction in Combined Morbidity/Mortality* and Mortality With Valsartan (No ACE-I)



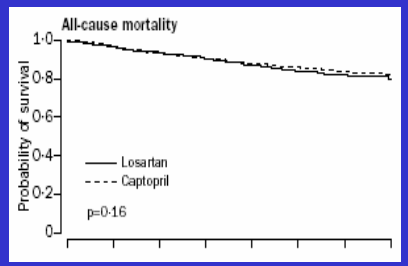
*First morbid event, including death or hospitalization

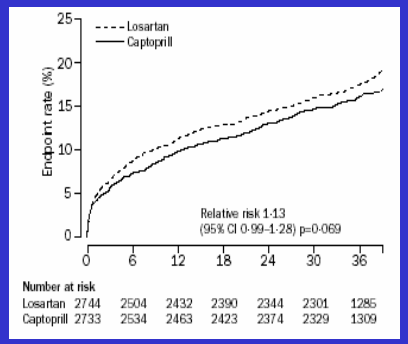
Adapted from Maggioni AP et al. *J Am Coll Cardiol*. 2002;40(8):1414-21.

The final piece of the ARB CHF jigsaw



ARBs: Important Differences In Effect According to Agent and/or Dose

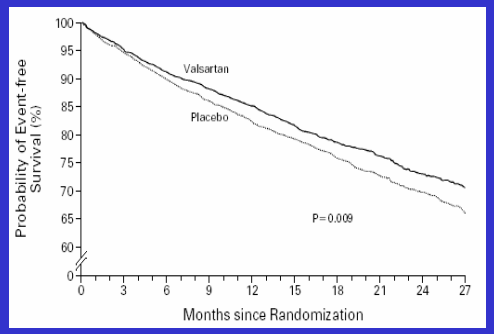


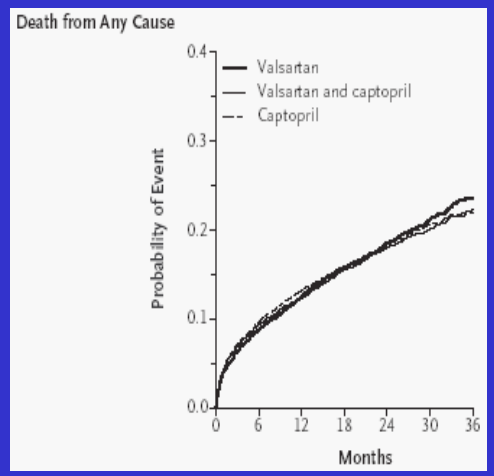


ELITE II, OPTIMAAL

Losartan 50 mg

Trend worse than captopril

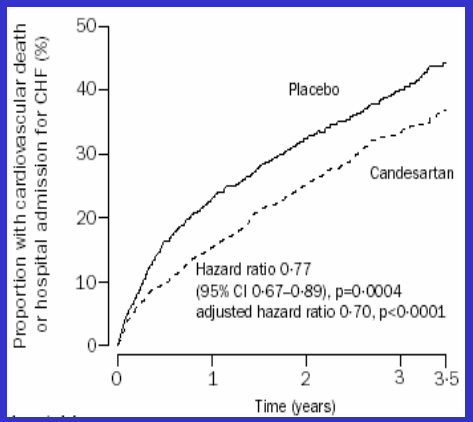


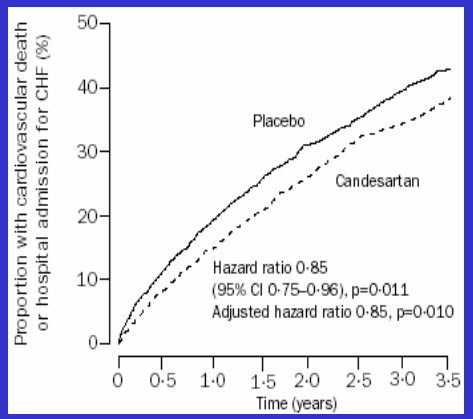


Val-HeFT, VALIANT

Valsartan 160 bid

Better than placebo, equal to captopril





CHARM

Candesartan 32 mg

Better than placebo for sxs and survival

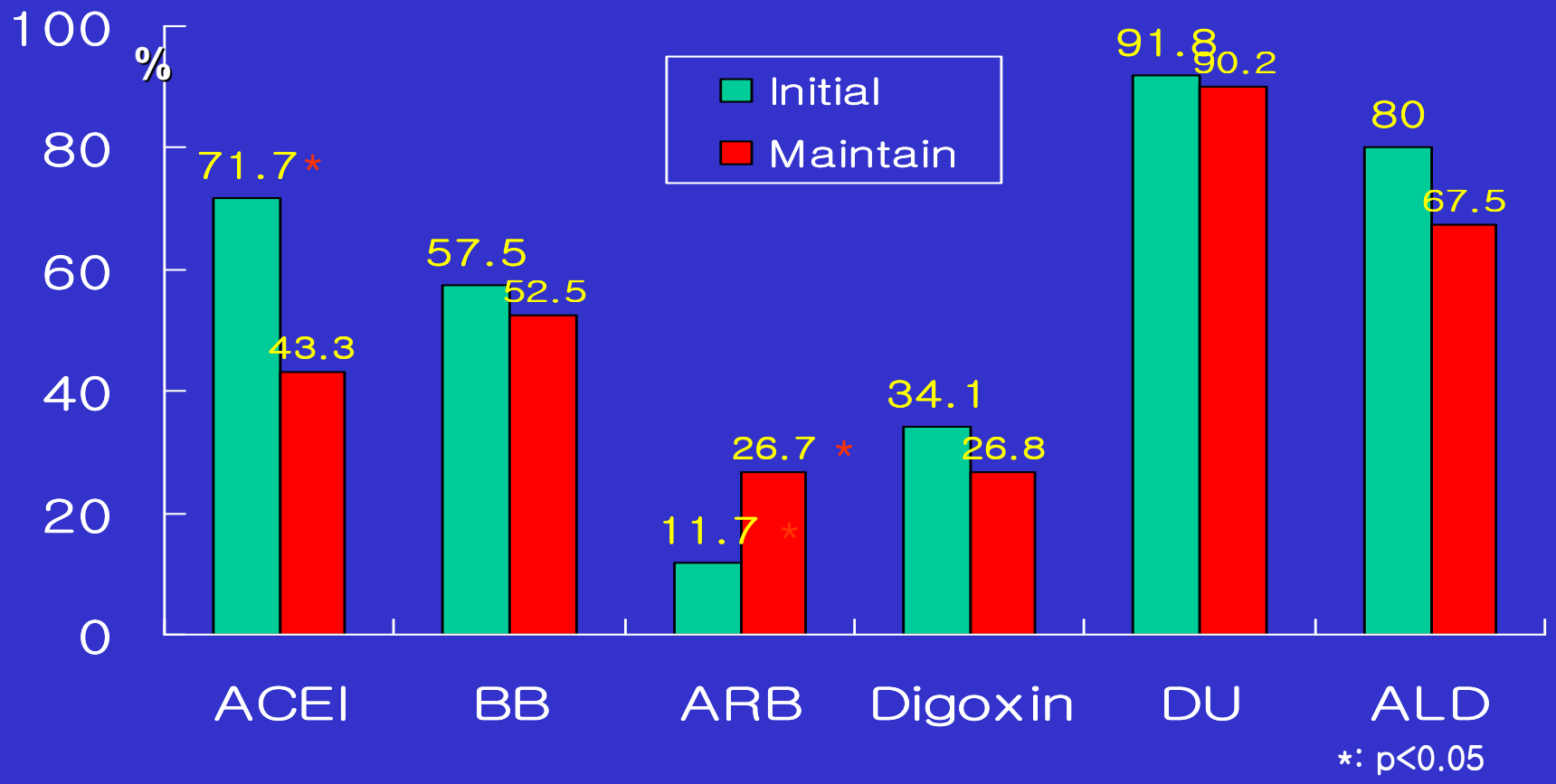
Polypharmacy in CHF

Portions of Target dosage in CHF

- Real practice : 17.2 % for optimal Tx (ESC)
- Study Practice : 55 % of BB in Charm trial, 82 % of ACEI in COMET

Real Practice :

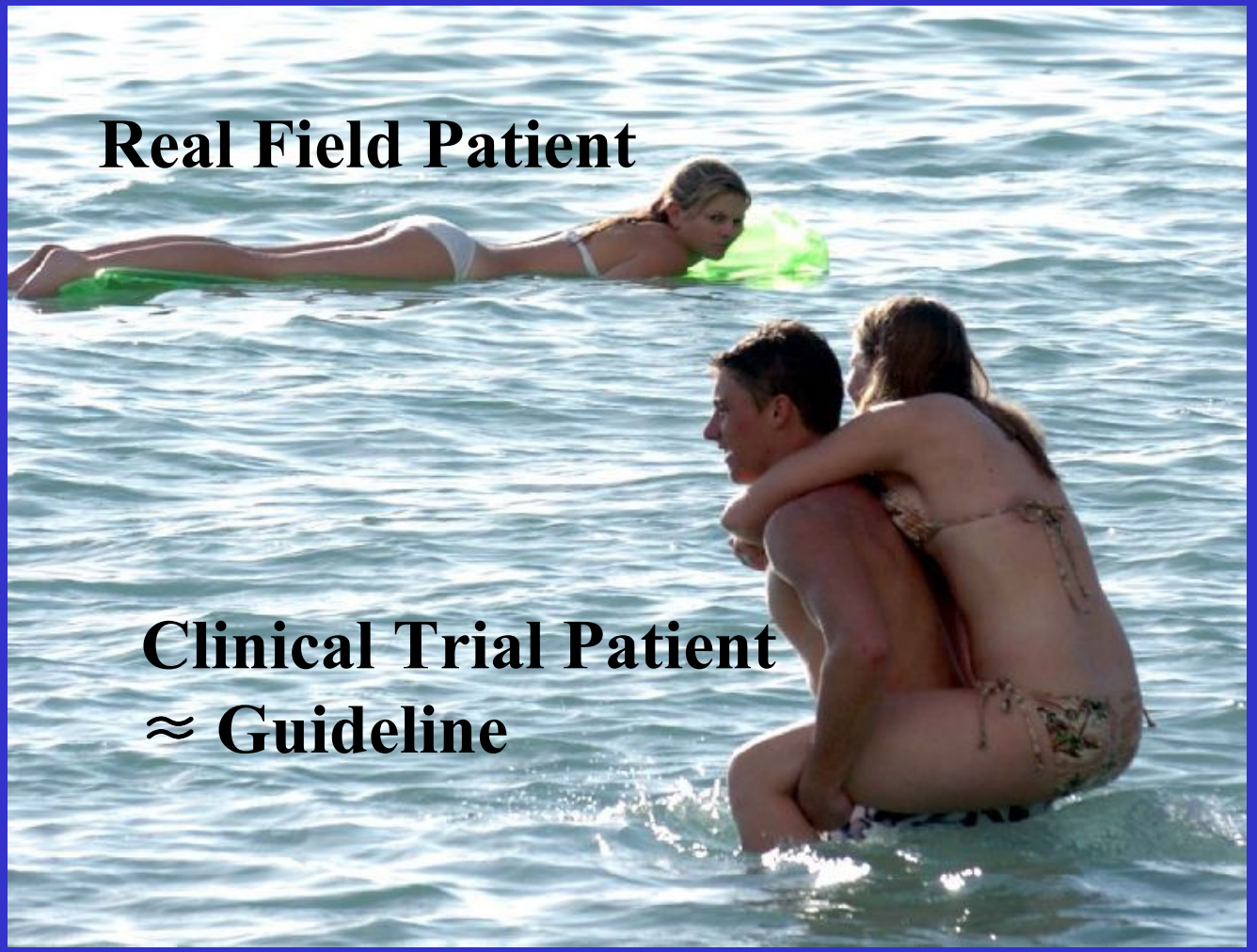
Patients Not Receiving Target Dose



The patients with not approaching target dosage of any drugs was 82.5%

Yoo BS et al. *Euro. H Failure.* 2006

Current Guideline vs. Real Practice



But I Was Following the Guidelines

‘NOT MY JOB’

Objectives

- To evaluate valsartan for the effects on surrogate markers of symptoms, sign, exercise tolerance and prognosis in ACE inhibitor intolerable patients with chronic heart failure (NYHA Class II – IV).
- To evaluate valsartan for tolerability in Korean patients

Study Investigators

시험총괄조정자	서울의대 내과 오병희 교수
시험연구자	건국의대 병원 내과 유규형 교수 서울대학교 병원 내과 강현재 교수 울산의대 서울 아산 병원 내과 김재중 교수 연세의대 신촌 세브란스 병원 내과 하종원 교수 원주의대 원주기독병원 내과 유병수 교수 이화의대 목동병원 내과 박성훈 교수

Multi-institutional, prospective, open labeled trial

Method : Inclusion criteria

- ACEIs intolerable patients or not using current medication
- Age ≥ 18 years
- Heart failure (NYHA Class II to IV) for at least 3 months before screening
- Ejection fraction < 40% and LV end-diastolic internal diameter > 2.9 cm/m^2 in initial echocardiography (Val-HeFT)
- Pt's written permission

Method : Exclusion criteria

- Pregnant or breast-feeding female
- Rt. Side heart failure
- Postpartum cardiomyopathy Hx.
- Acute exacerbation of heart failure
- Acute or recent myocardial infarction
- PTCA or cardiac surgery within 3 months
- Cardiac transplantation Hx.
- Unstable angina or coronary artery disease needed PTCA or CABG

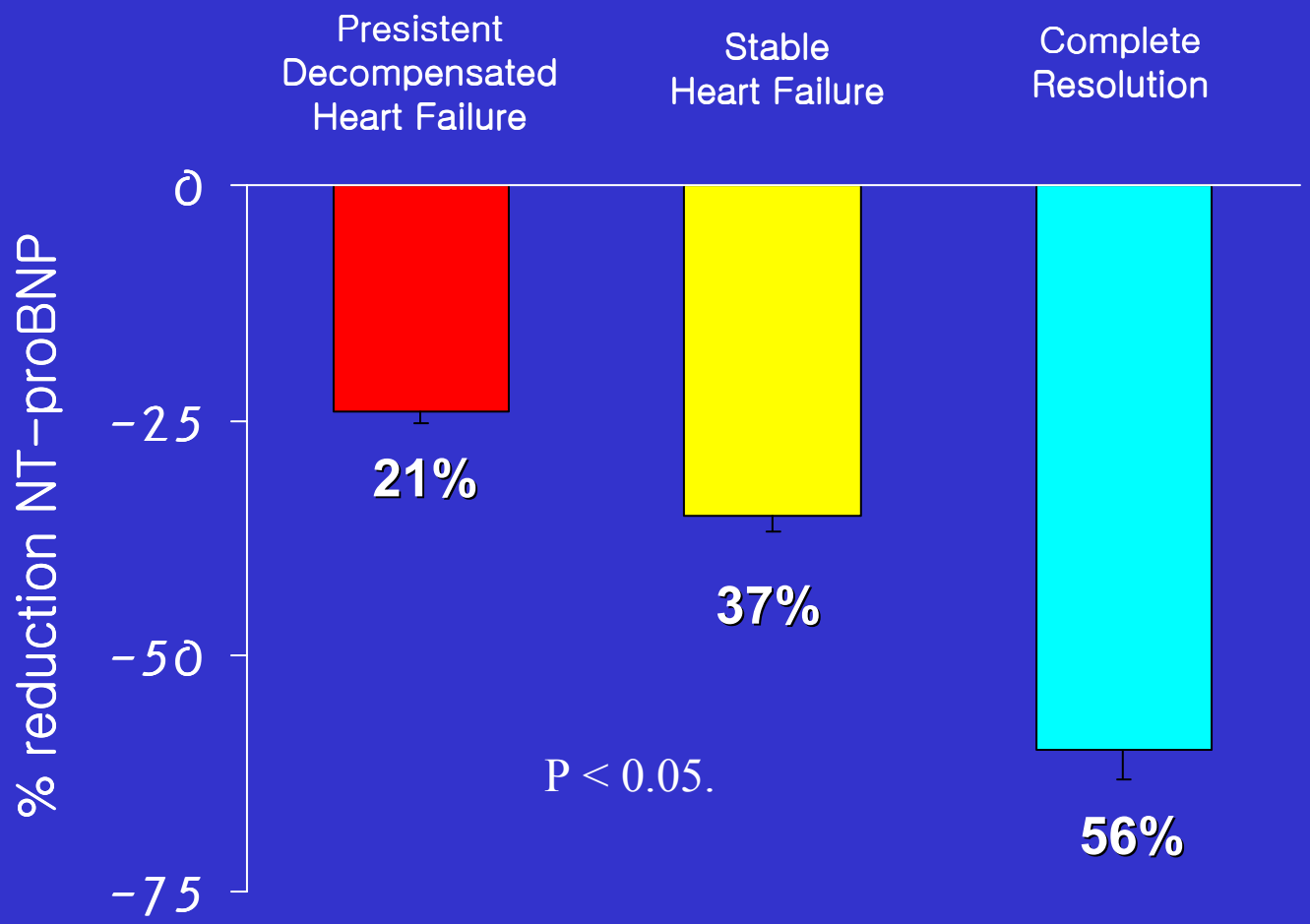
Method : Exclusion criteria

- Persistent ventricular arrhythmia in existence of syncopal attack within 3 months
- Mitral stenosis or mitral regurgitation (except secondary mitral regurgitation due to LV dilatation)
- Aortic stenosis
- Standing systolic blood pressure < 90 mm Hg
- CVA within 3 months
- Life-threatening hepatic disease
- Severe kidney disease or Cr > 2.5 mg/dl
- Contraindication of angiotensin II receptor blocker
- Administraion of class IC antiarrhythmic agent

Method : Study End-points

- Primary
  - Change of BNP from baseline
- Secondary
  - Echocardiographic parameter : LV end- diastolic internal diameter, EF
  - Heart rate variability : SDNN, pNN50, RMSSD
  - KASI idex
  - Exercise ability : total exercise time of treadmill test by naughton protocol
  - Major adeverse cardiovascular event
    - Death
    - Readmission due to exacerbation of HF
    - IV administration of vasodilator or inotropics
    - Resuscitation of sudden cardiac death
  - CT ratio of chest X-ray

BNP changes according to the clinical course



Lopez L. et al. EJHF 2004:301

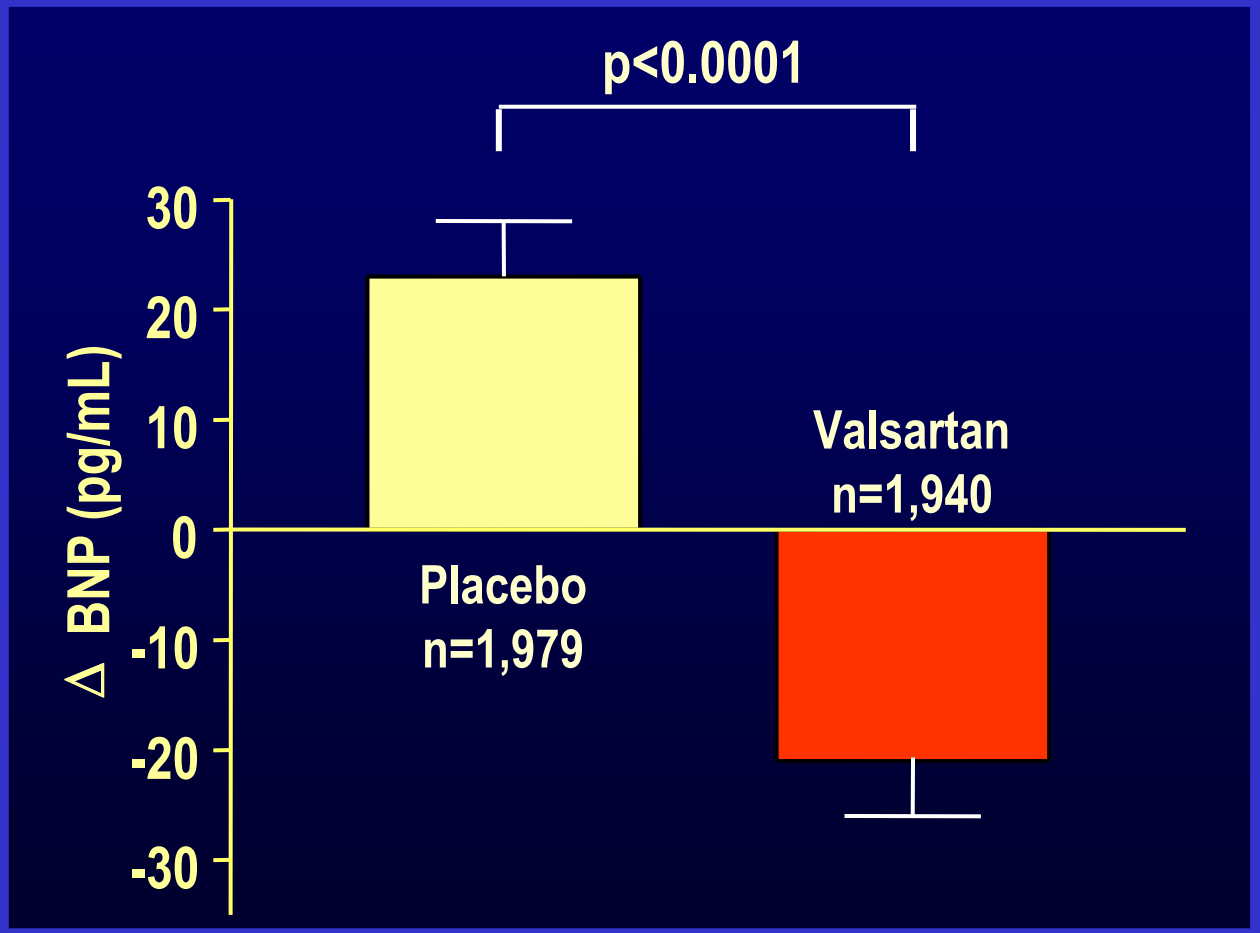
Val-HeFT: Baseline BNP values

- IRMA BNP-32 Shionogi

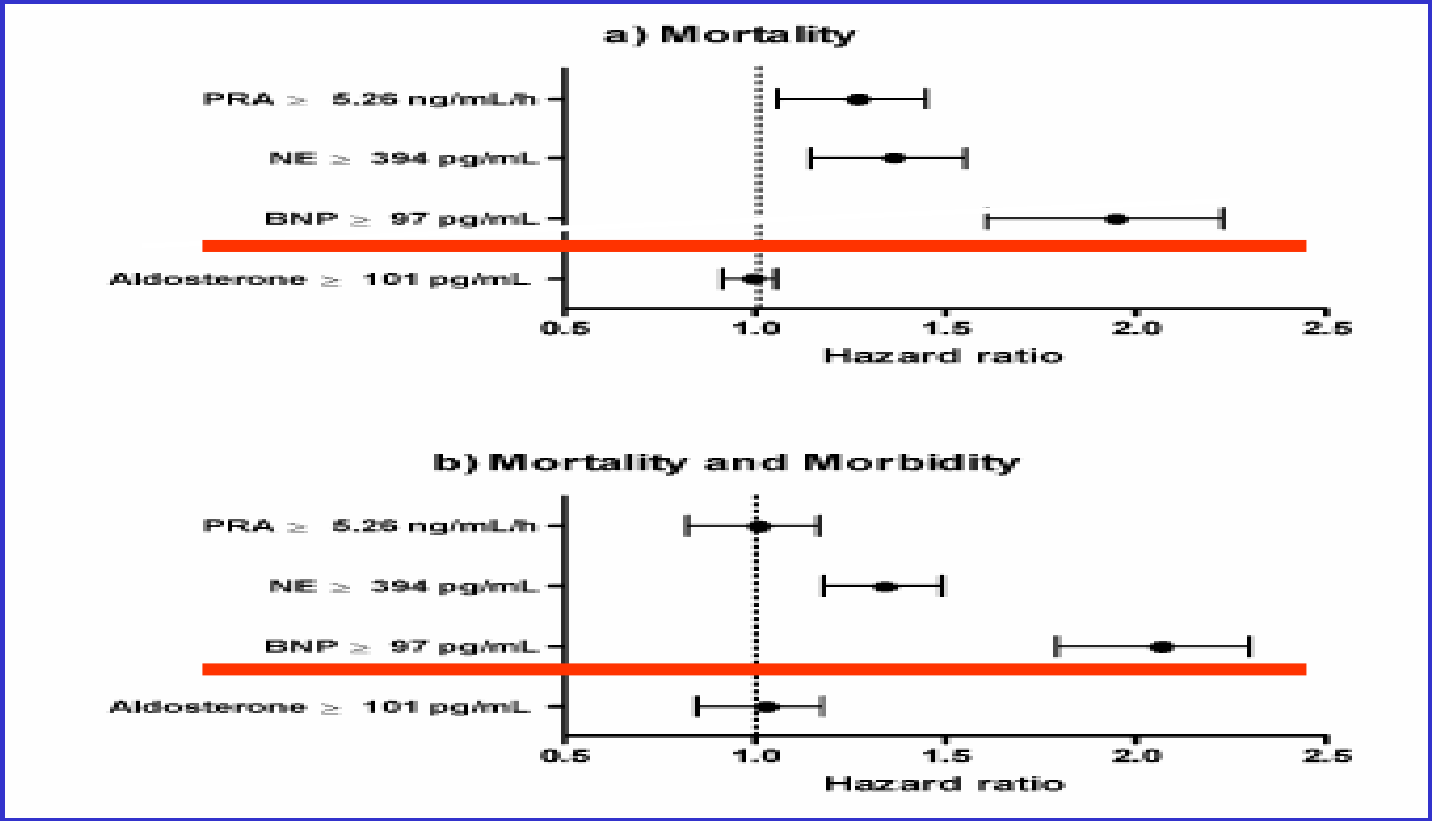
N	4,305
Mean	181 pg/mL
SD	230
Median	97
Minimum	2
Maximum	2162
BNP change	21±5

The largest neurohormonal database in an HF trial

BNP changes from baseline at end-point visit: Valsartan vs. placebo



Hazard ratios for all-cause mortality & morbidity according to neurohormones



R. Latini et al.EHJ, 2004: **25;** 292

Method : Study End-points

- Primary
  - Change of BNP from baseline
- Secondary
  - Echocardiographic parameter : LV end- diastolic internal diameter, EF
  - NYHA Class
  - KASI idex
  - Exercise ability : total exercise time of treadmill test by naughton protocol
  - Major adeverse cardiovascular event
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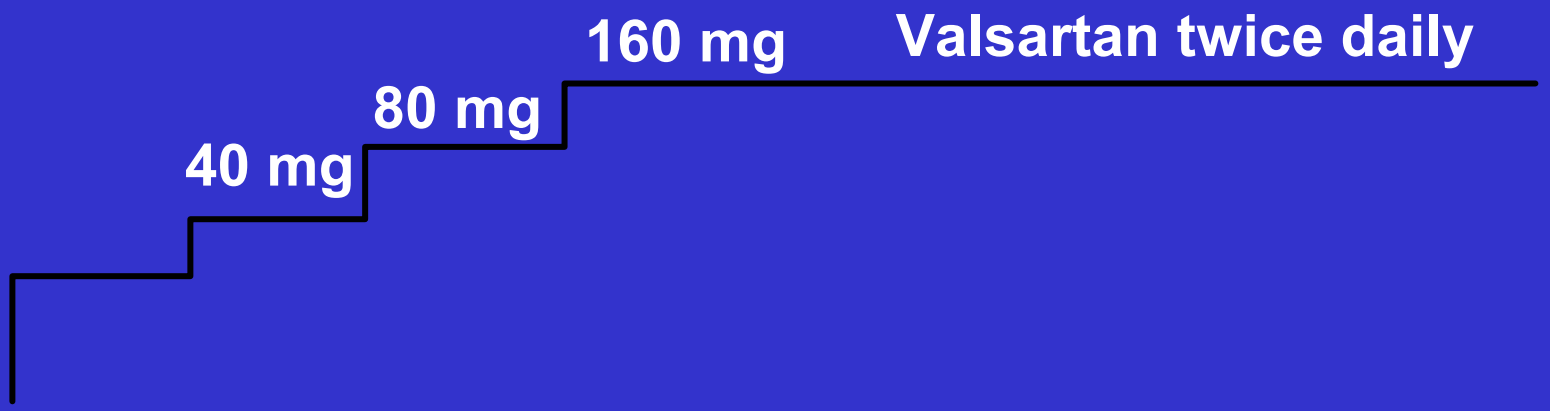
  - CT ratio of chest X-ray
  - Heart rate variability : SDNN, pNN50, RMSSD

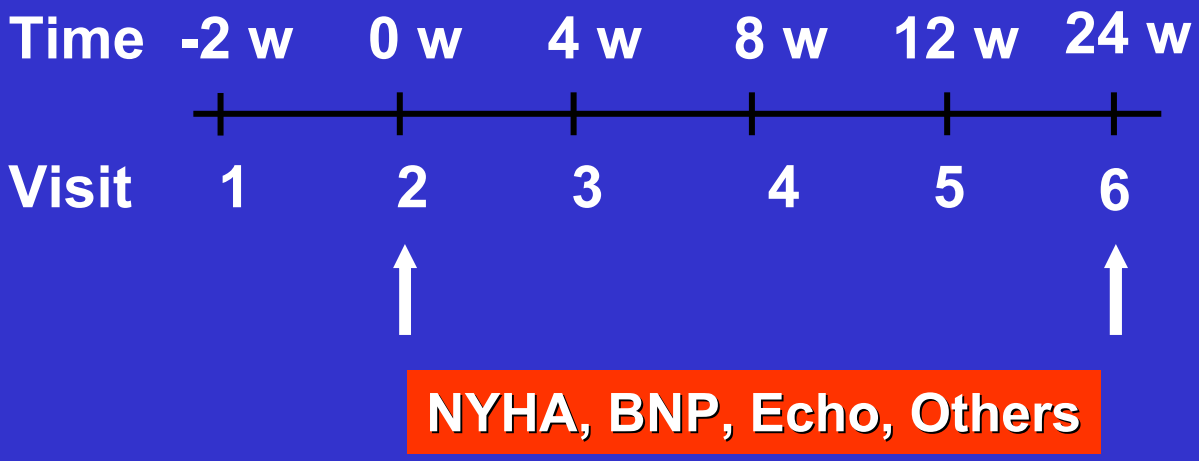
KASI index ; Korean Activity Scale
Index questionnaire

	문항			가중치
1	층계 걸어내려가기 (한 층 정도)	가능	불가능	4.5
2	짧은 언덕길 올라가기	가능	불가능	5.5
3	평지에서 천천히 걷기	가능	불가능	1.7
4	평지에서 보통 속도로 걷기	가능	불가능	3.5
5	평지에서 빠른 속도로 걷기	가능	불가능	6
6	무거운 물건(가구 등, 약 30-40 kg 정도) 들어 나르기	가능	불가능	8
7	등산 (가파른 산길)	가능	불가능	8
8	달리기 (빠른 속도)	가능	불가능	8
9	샤워하기	가능	불가능	3.6
10	집안 일 (예: 마루 쓸기, 빨래 널기, 창문 닦기 등)	가능	불가능	3.7
11	성행위	가능	불가능	5.5
12	가벼운 운동 (예: 맨손 체조, 볼링, 당구, 양궁 등)	가능	불가능	3
13	보통 정도의 운동, 예를 들면, 테니스, 배드민턴, 탁구, 골프(직접 걸으면서 클럽 운반) 등	가능	불가능	5
14	격렬한 운동 (예: 축구, 농구, 스쿼시, 핸드볼 등)	가능	불가능	9
15	옷 입고 벗기	가능	불가능	2

KASI = ∑ W * K (Maximum : 77), K = 1 (if response = Yes), 0 (if response = No), 0.4 if ambiguous or no response, W : 가중치
KASI functional class, I : KASI ≥ 46, II : 46 > KASI ≥ 24, III : 24 > KASI ≥ 4, IV : KASI < 4

Method : Dose-titration & visit schedule





Every 1 months
until study end

Method : Forced drug titration with no dose adjustment of other drugs

- Dose Up
  - Persistent standing SBP ≥ 90 mm Hg
  - No Sx. of hypotension at current dose medication (syncope, LOC, dizziness at standing up)
  - No increase of Cr (more than 50 % from basal level)
- Dose down
  - Persistent standing SBP < 80 mmHg
  - Sx. of hypotension at current dose medication (syncope, LOC, dizziness at standing up)
  - increase of Cr (more than 50 % from basal level)

Method : Drug titration

- Dose maintain
  - 80mm Hg ≤ standing SBP < 90 mm Hg
  - No Sx. of hypotension at current dose medication (syncope, LOC, dizziness at standing up)
  - No increase of Cr (more than 50 % from basal level)

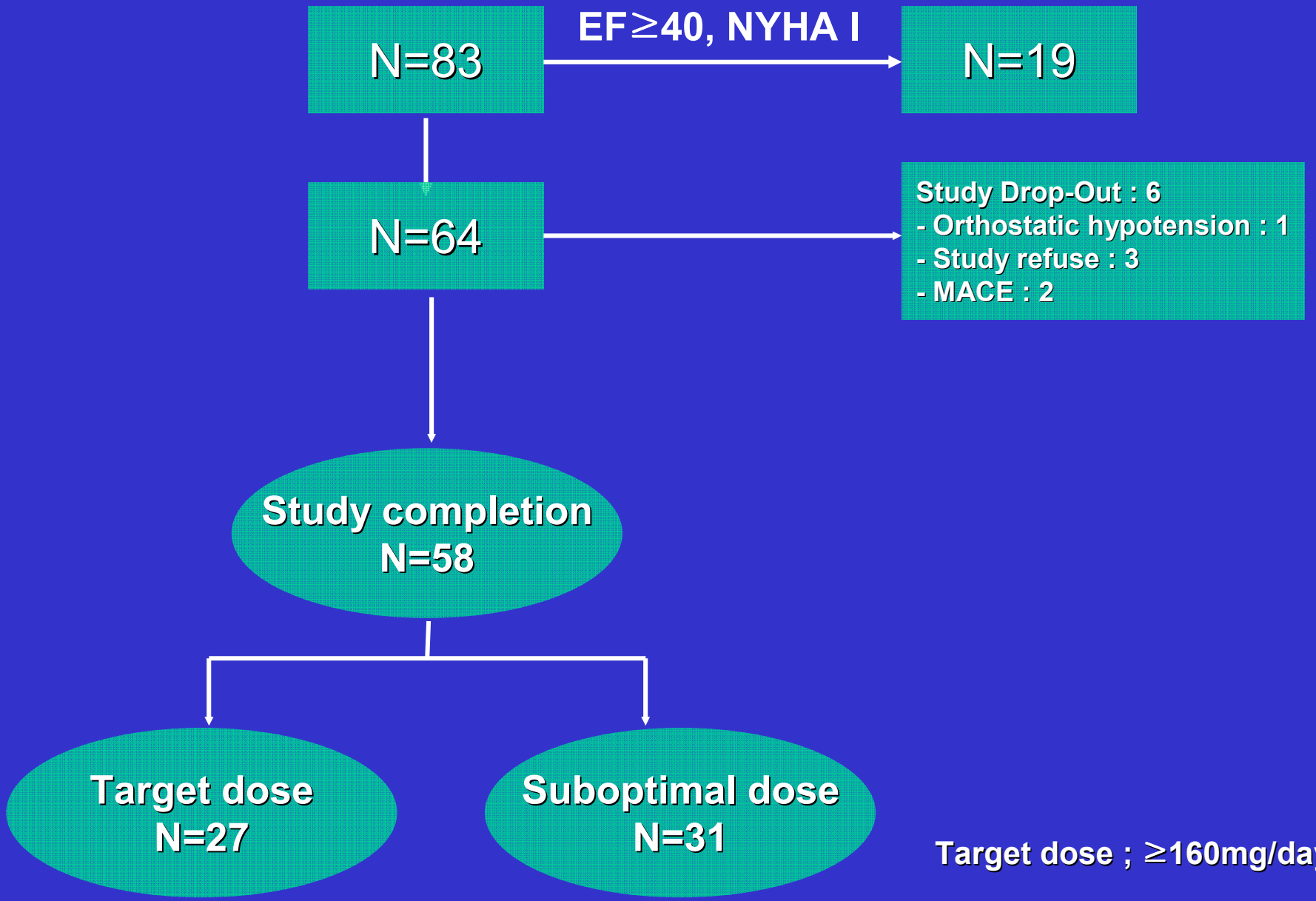
Method : Statistical Analysis

- Overall significance level : 0.05
  - continuous variables : t-test
  - categorical variables : χ^2-test
- Efficacy : PP (per protocol)
- Safety : ITT (intention to treat)

Results : Enrollment

- Enrollment No. : 83 persons
- Period : Feb. 2005 – Apr. 2007
- Hospital (Total : 83 cases)
  - Asan Medical Center
  - Ehwa Womans University Hospital
  - Konkuk University Hospital
  - Seoul National University Hospital
  - Wonju Coll. of Med., Wonju Christian Hospital
  - Yonsei University Severance Hospital

Results: Patients Flow



Target dose ; ≥160mg/day

Results : Baseline Characteristics

	K-Val-HeFT	Val-HeFT	CHARM (alternative)
Age*	59.5±10.1	62.2±10.4	67
Sex (male %)	59.4 %	71.3 %	68 %
HTN Hx. (%)	17.2 %	16.7%	50 %
DM Hx. (%)	21.9 %	25.9 %	27 %
CVA Hx. (%)	3.2 %		
MI Hx. (%)	10.9 %		61 %
CAD Hx	33.3 %*		67 %
BWt. (kg)	63.9±9.8		
Ht. (cm)	163.7±8.3		
NYHA (2/3/4) (%)	73/20/7	62.1/36.1/1.7	48/49/3
A-fib (%)	12.8 %	12.0 %	25 %
LBBB (%)	21.3 %		

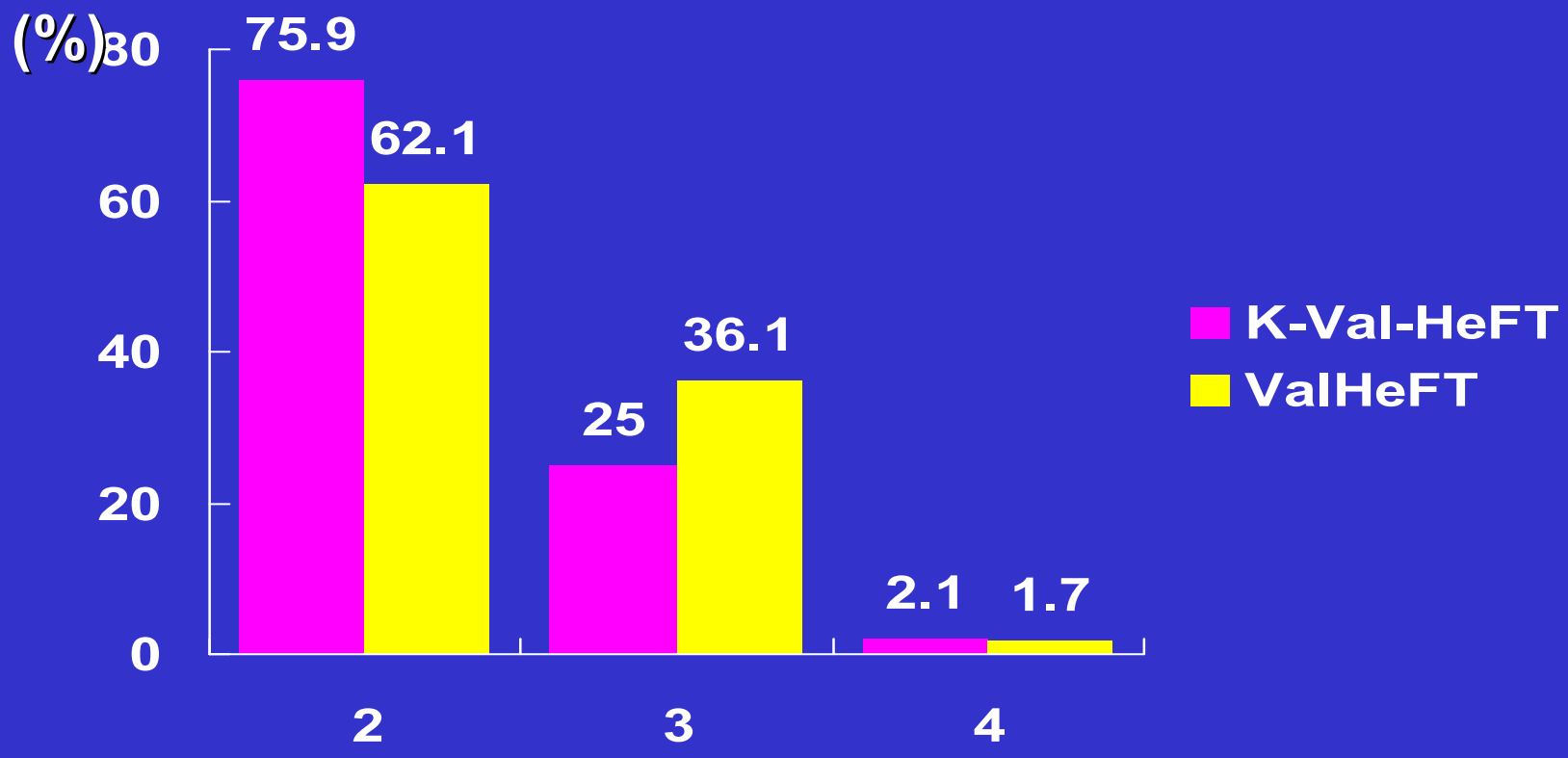
ARB CHF trials

Baseline Characteristics

Characteristic Number	Val-HeFT (4/97 - 3/99) 5010	ELITE-II (6/97 - 5/98) 3152	CHARM Alternative (3-11/99) 2028	K-Val-HeFT
Age (years)	63	71	67	59.5
Female (%)	20	31	32	40.6
NYHA Class II/III (%)	62/36	49/51	48/49	73/20
Mean LVEF (%)	27	27	33	29.0
Treatment (%)				
ACEI	93	0	0	
Diuretic	86	78	85	81.3
Digitalis	67	50	45	52.1
Beta-blocker	35	22	54	52.1
Spironolactone	5	na	24	60.4

McMurray et al, Eur J Heart Fail 2003

Results: NYHA Class



Results: Previous Medication Hx.

	% of patients
Beta blocker (%)	73.0 %
Aldosterone antagonist (%)	65.1 %
Digoxin (%)	47.6 %
Diuretics (%)	85.7 %
CCB (%)	1.6 %
Nitrate (%)	22.2 %
ARB (%)	6.3 %
ACEi (%)	14.3 %

Results : Previous Medication

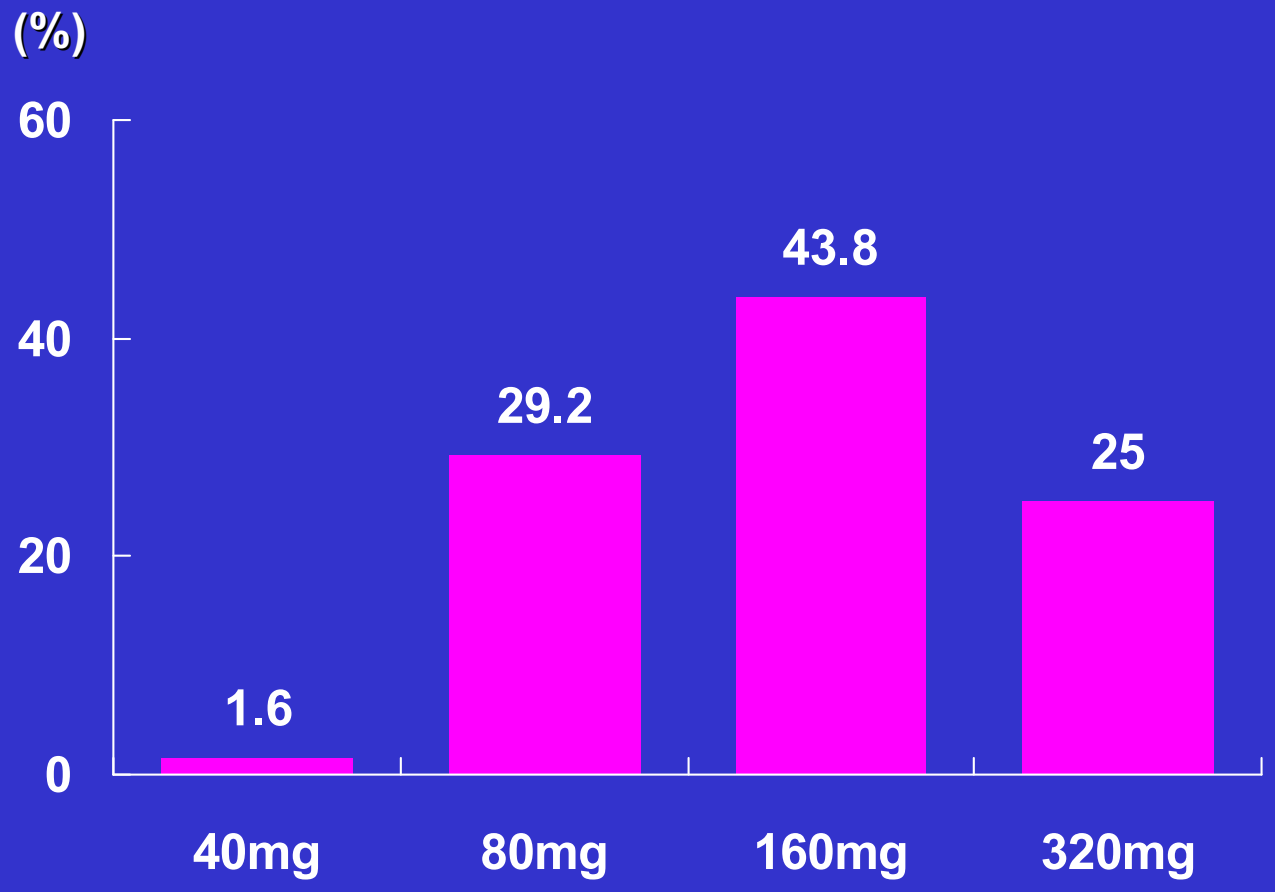
- Reasons for ACEi disuse
  - Judgment of investigator : 15.8 %
  - Cough : 52.6 %
  - Low BP : 31.6 %

Results:

Maintained combined Medication

	K-Val-HeFT	Val-HeFT	Charm
Beta blocker (%)	52.1 %*	34.5 %	55%
Aldosterone AT(%)	60.4 %	5%	46%
Digoxin (%)	52.1 %	67.1 %	24%
Diuretics (%)	81.3 %	85.8 %	86%
ACE inhibitor (%)	-	92.6 %	41 %*

Results: Maintain dose



Mean Dose : 174 mg /day in K-Val-HeFT

Results : Target Dose

Forced Titration Method : Same Method

- Korean Val-HeFT
  - 68.8 % : approaching dose of 160 mg/day
  - 25.0% : approaching dose of 320 mg/day
  - Mean : 174 mg
- Val-HeFT
  - Definition of Target dose: 160 mg twice (Total 320 mg/day),
  - 84%: approaching dose of 320 mg/day
  - Mean : 254mg

Result : Tolerability & Safety

- Reasons for failed up titration (75%)
  - Judgment of investigator : 25.2%
  - SBP (≤ 90 mmHg and > 80 mmHg) : 54.5%
  - Sx. of Dizziness : 20.3%

Results: F/U data

	Initial	6th month F/U	P value
EF (%)	29.0±7.5	34.2±11.5	0.000
LVDd (cm/m²)	3.97±0.72	3.83±0.80	0.002
LVDs (cm/m²)	3.34±0.73	3.09±0.78	0.000
CT ratio	0.559±0.057	0.540±0.068	0.011
SBP (rest)	117.0±16.0	115.5±20.7	0.541
DBP (rest)	73.5±12.3	70.6±11.9	0.079
SBP (stand)	114.0±18.4	115.5±21.7	0.491
DBP (stand)	73.7±12.1	70.8±14.5	0.069
HR (rest)	74.1±14.2	72.0±10.5	0.201
HR (stand)	74.3±13.5	74.3±12.0	0.959
NYHA class	2.29±0.50	1.94±0.48	0.000
BNP (pg/ml)	226.4±437.6	132.4±226.5	0.025
TMT (sec)	745.3±456.0	717.6±334.6	0.567
KASI score	42.5±17.3	45.0±18.6	0.211

Results: Framingham criteria (Major)

	Initial	6th month F/U
PND*	18.8 %	6.3 %
Neck vein distention	8.3 %	2.1 %
Rales	2.1 %	2.1 %
Cardiomegaly *	62.5 %	52.1 %
Acute pul. edema	2.1 %	0 %
S3 gallop	6.3 %	2.1 %
Increased venous pressure	2.1 %	0 %
Positive hepatojugular reflux	4.2 %	2.1 %
Wt. loss Criteria	0 %	0 %

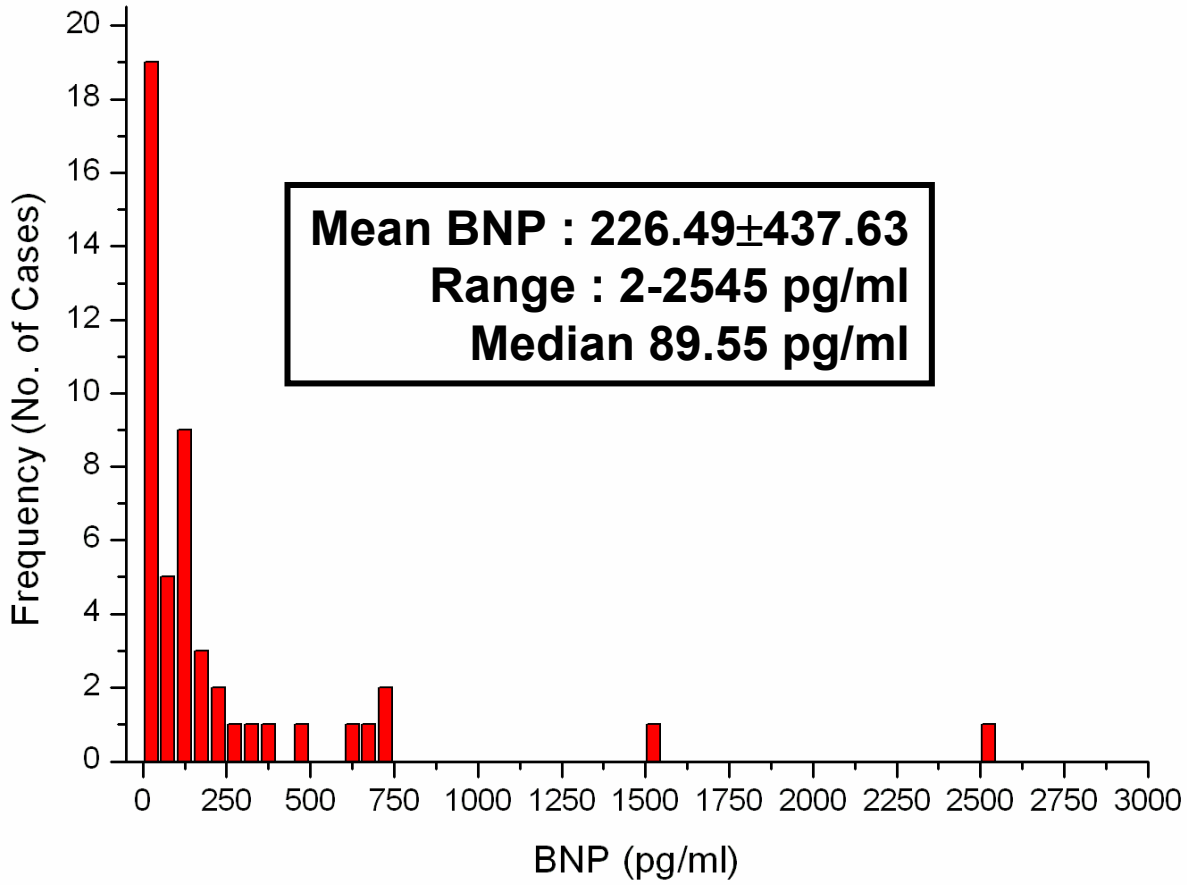
*: $p<0.05$

Results: Framingham criteria (Minor)

	Initial	6th month F/U
Ext. edema	14.2 %	10.1 %
Night cough*	10.4 %	0 %
DOE*	54.2 %	35.4 %
Hepatomegaly	4.2 %	2.1 %
Pleural effusion	2.1 %	0 %
Tachycardia	0 %	0 %
Decreased VC	0 %	0 %

*: $p<0.05$

Results: BNP distribution

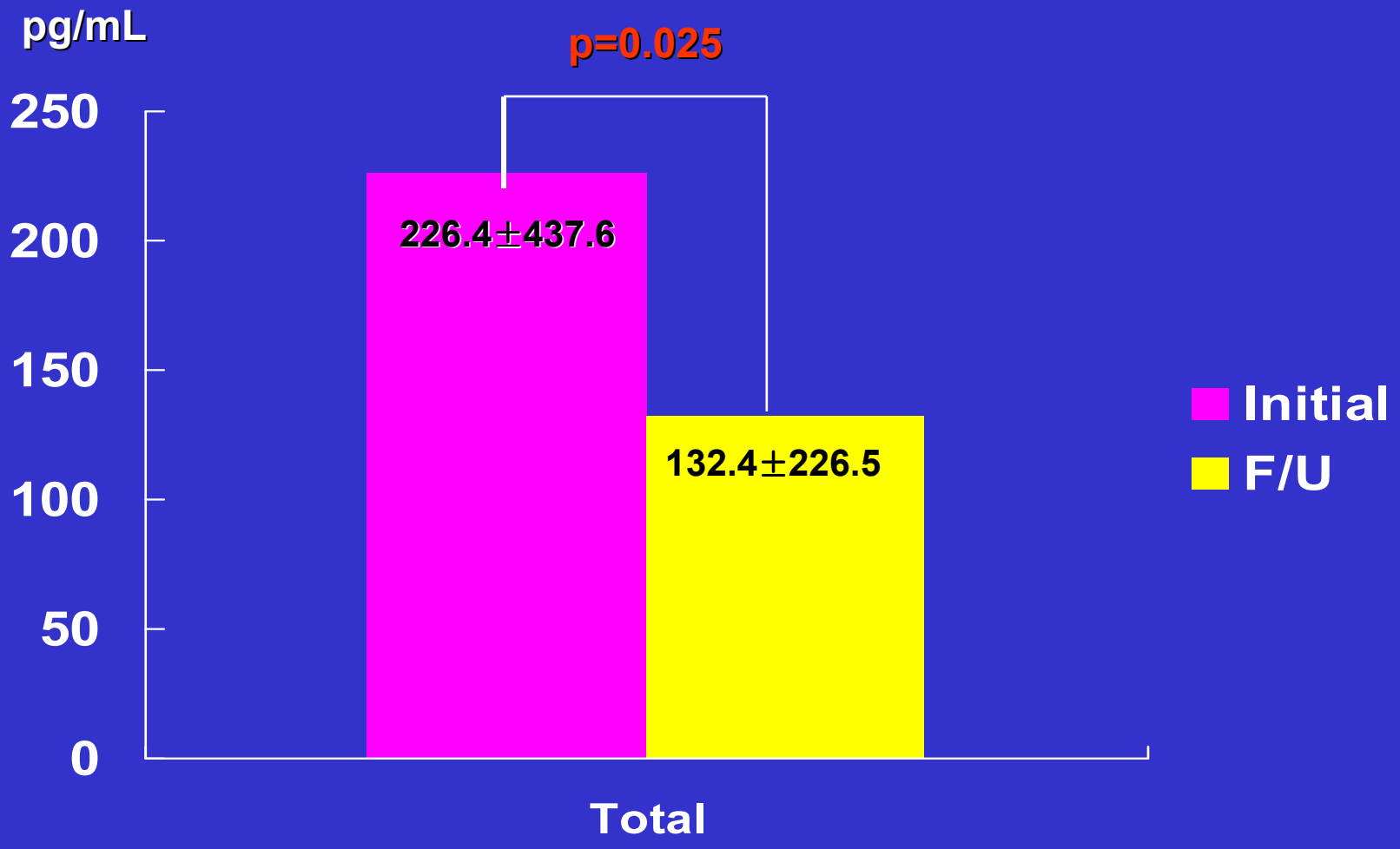


Results: Baseline BNP values

	K-Val-HeFT	Val-HeFT
BNP Kit	IFA, Bayer	IRMA, Shionogi
N	58	4,305
Mean	226 pg/mL	181 pg/mL
SD	437	230
Median	89	97
Minimum	2	2
Maximum	2545	2162
BNP change	-94 ± 230	-21 ± 5

Results:

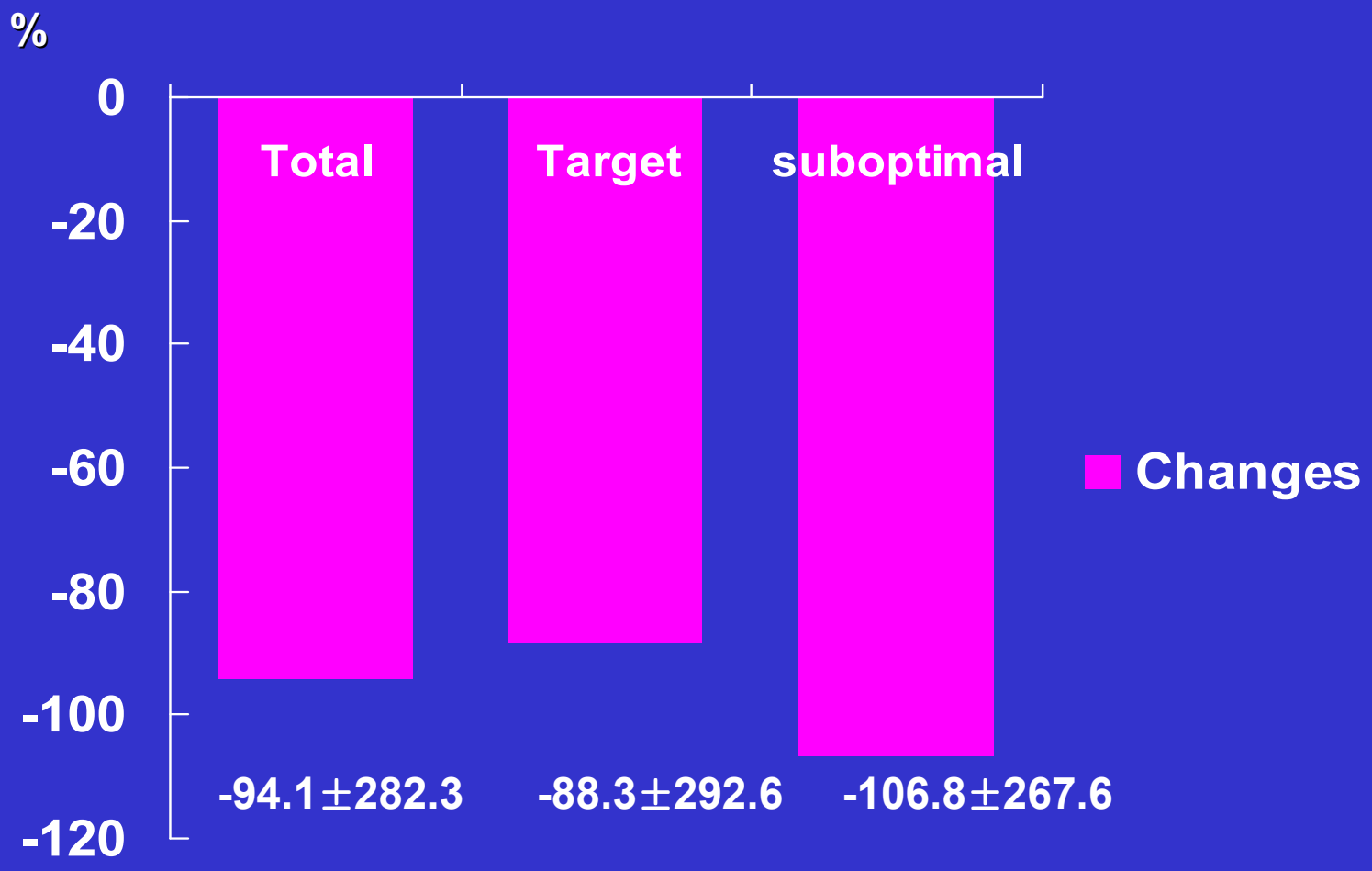
BNP change according to dose



paired t-test

Results:

BNP change according to dose



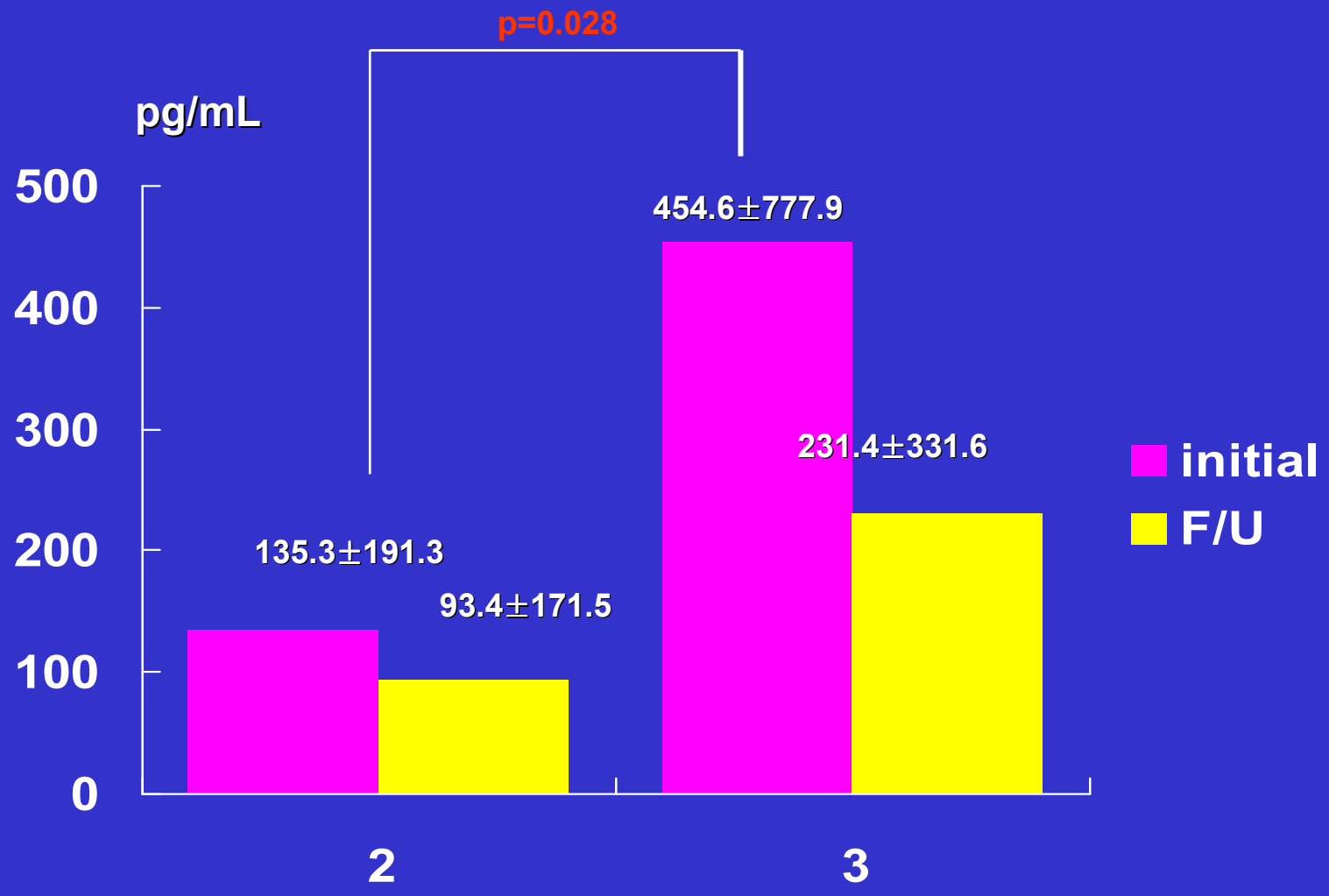
P=0.489

Indepedent t-test

Target dose ; ≥ 160mg/day

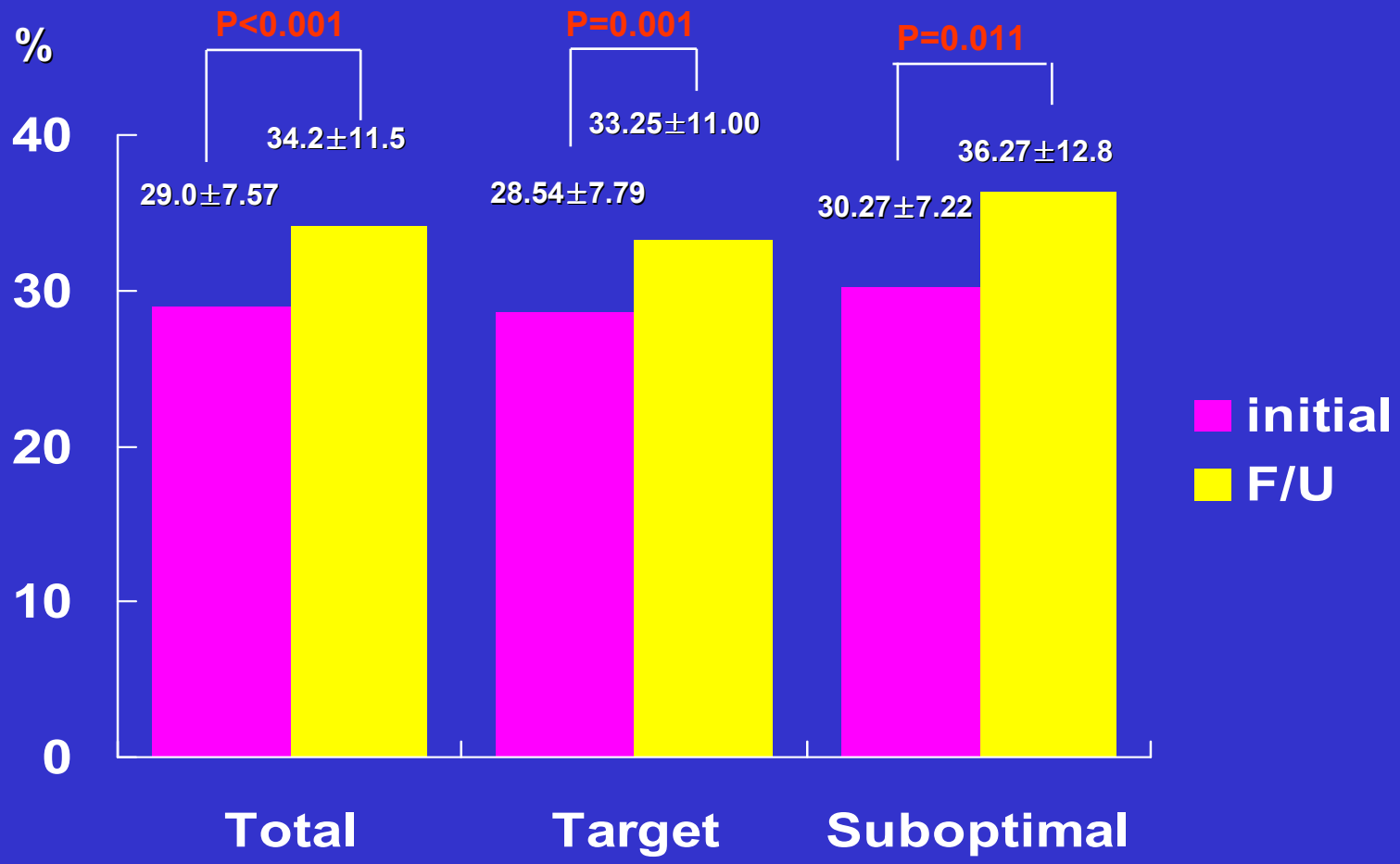
Results:

BNP change by NYHA Class



Results:

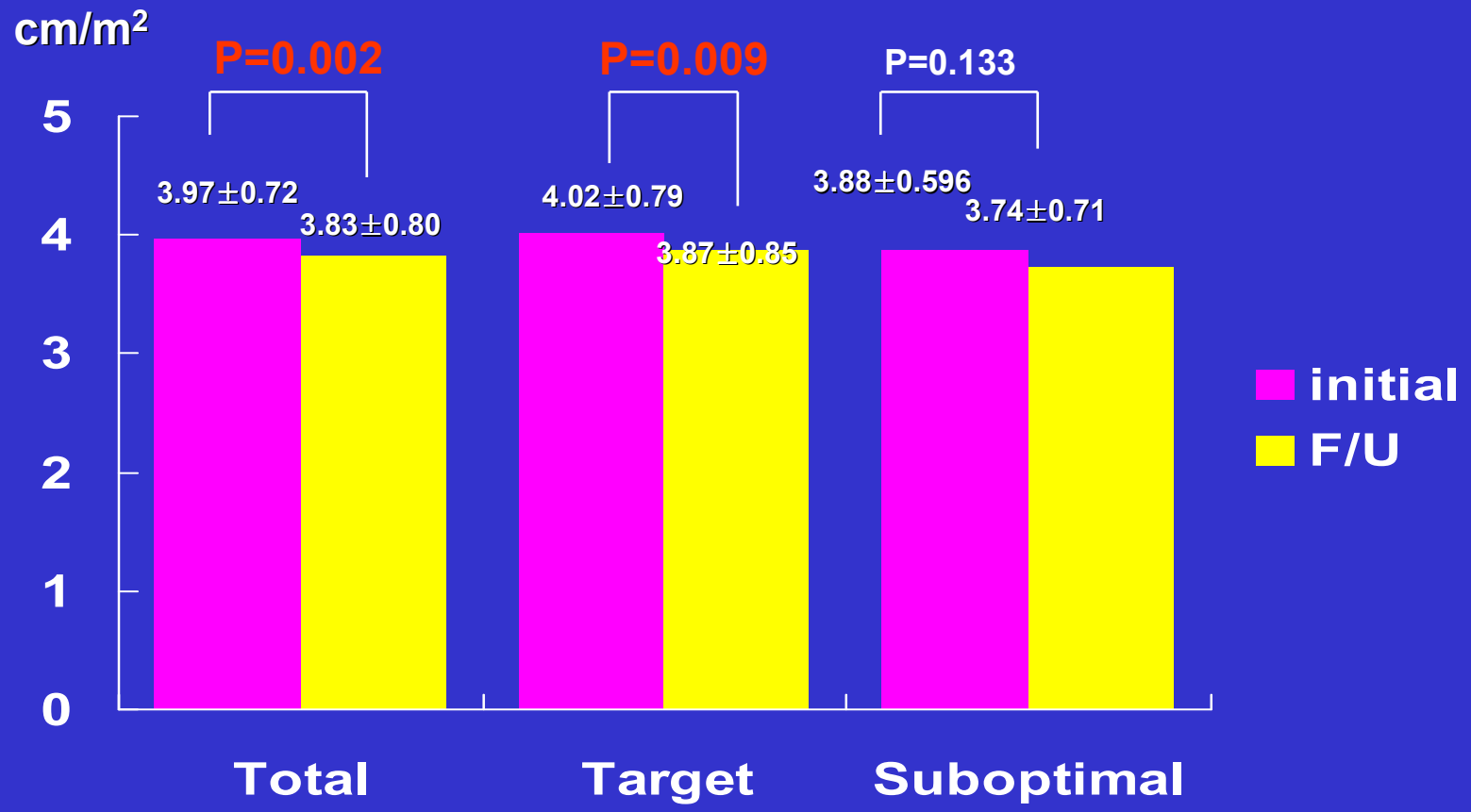
EF change according to dose



paired t-test

Results :

LV end-diastolic internal diameter



paired t-test

Result :

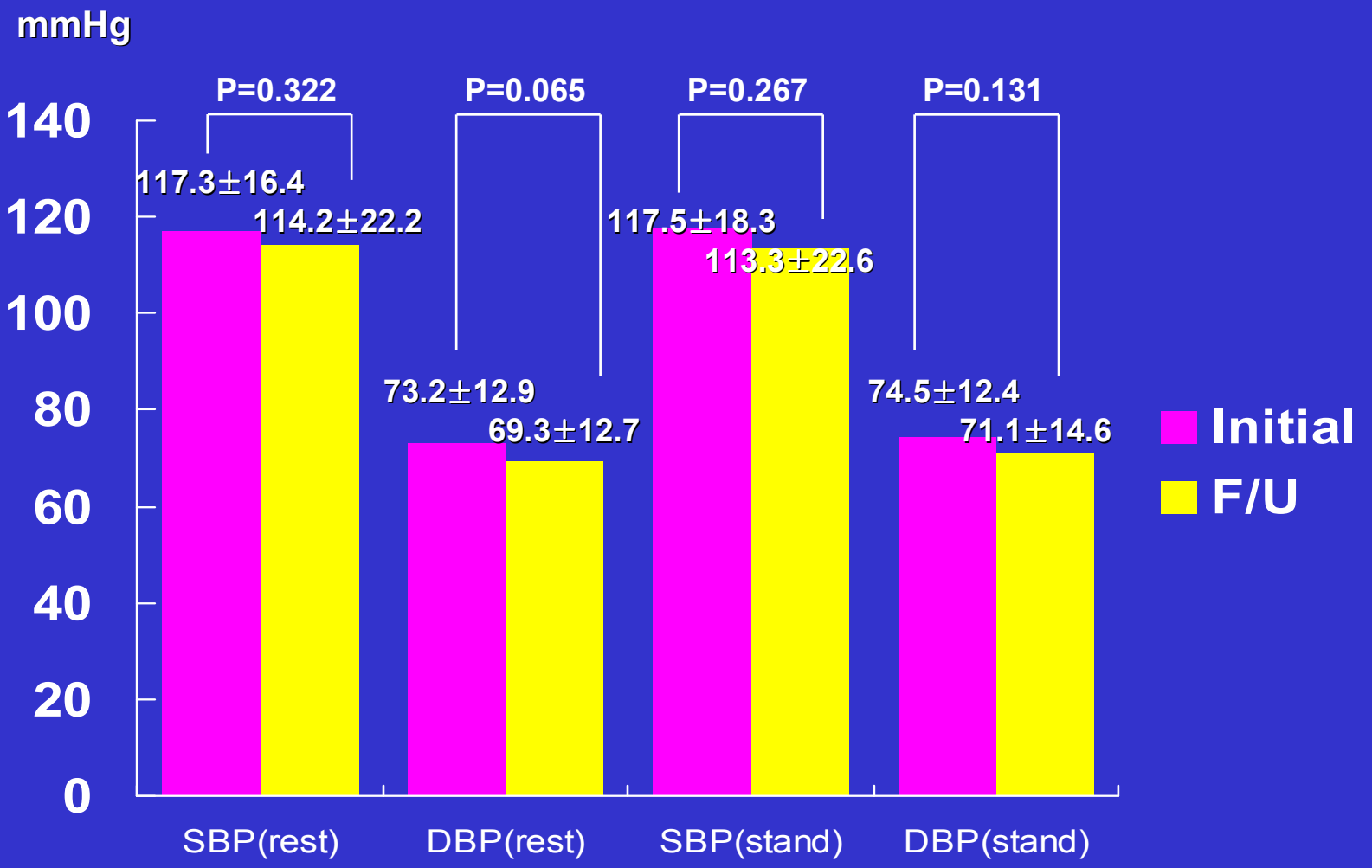
BP reduction (K-Val-HeFT vs. Val-HeFT)

	K-Val-HeFT (6 month)		Charm (Alt.)	Val-HeFT (4 month)	
Dose	174 mg (25%*)		27.8 mg (82.3%)	254 mg(84%*)	
	Rest	Stand		Valsartan	Placebo
Initial BP	118.1±16.1	114.3±18.9	130/77	123/76	124/76
Follow-up BP	113.4±19.3	108.9±19.9			
SBP Reduction	4.1±13.7	4.4±16.9		5.2±15.8	1.2±14.8
DBP Reduction	3.5±10.1	3.4±10.4			
HTN Hx	17.2%		50%	16.7%	

* ; Proportion of Target dose

Results :

BP Change in target dose

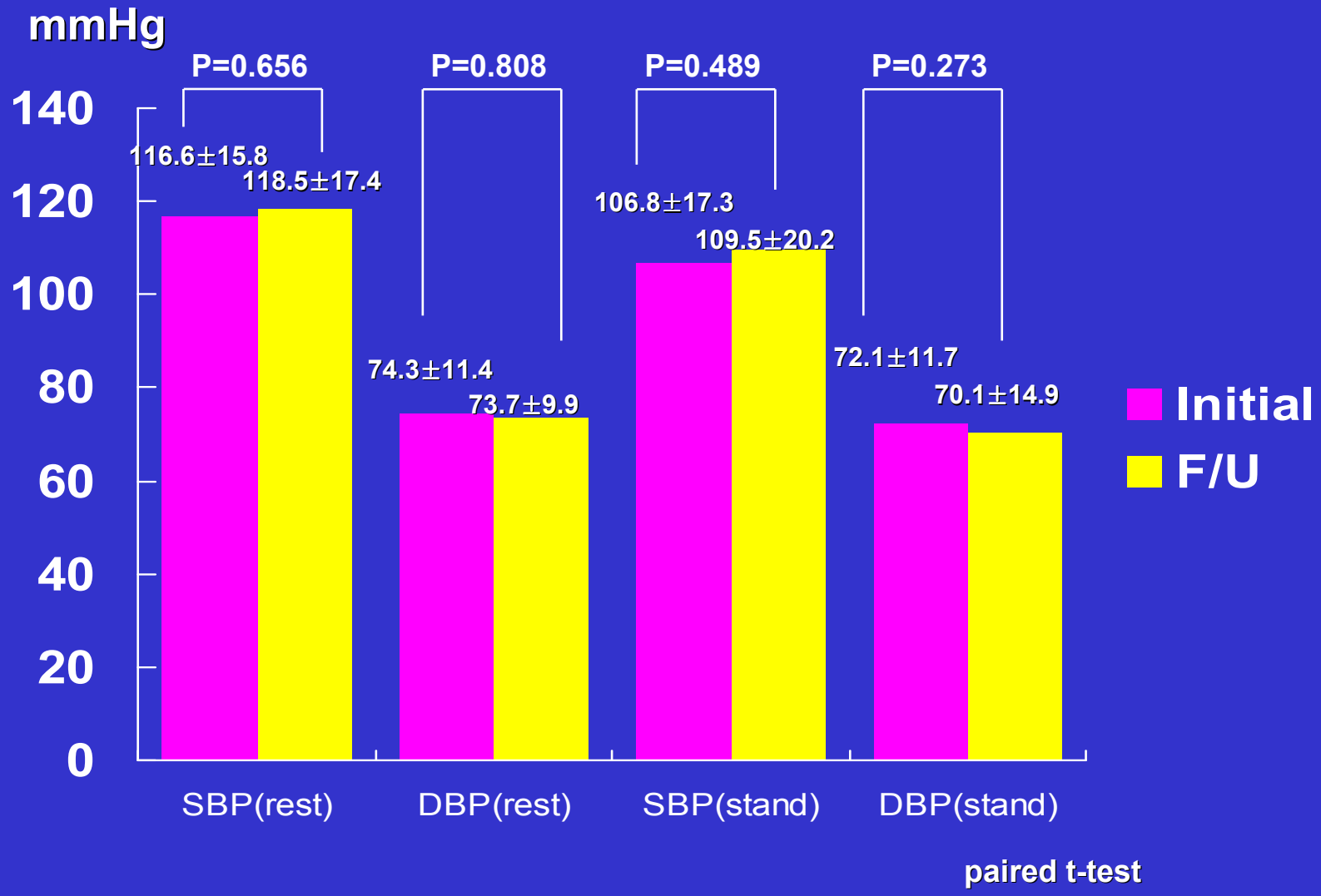


*; suboptimal dose < 160mg

paired t-test

Results :

BP Change in suboptimal dose



Result : Tolerability & Safety

- Direct drug related side effect (possible)
  - Peptic ulcer : 1 case
  - Dysarthria : 1 case
  - Tingling sensation : 2 cases
  - Death 2 cases : AMI Hx

    (1 case; Telephone contact d/t F/U loss : sudden death at home , 1 case : Sudden cardiac death at working : expired at ER)

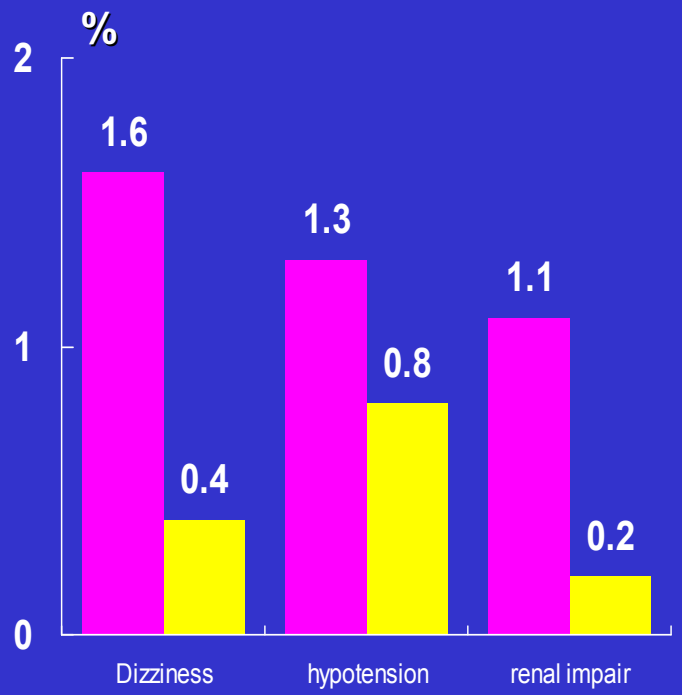
Result : Tolerability & Safety

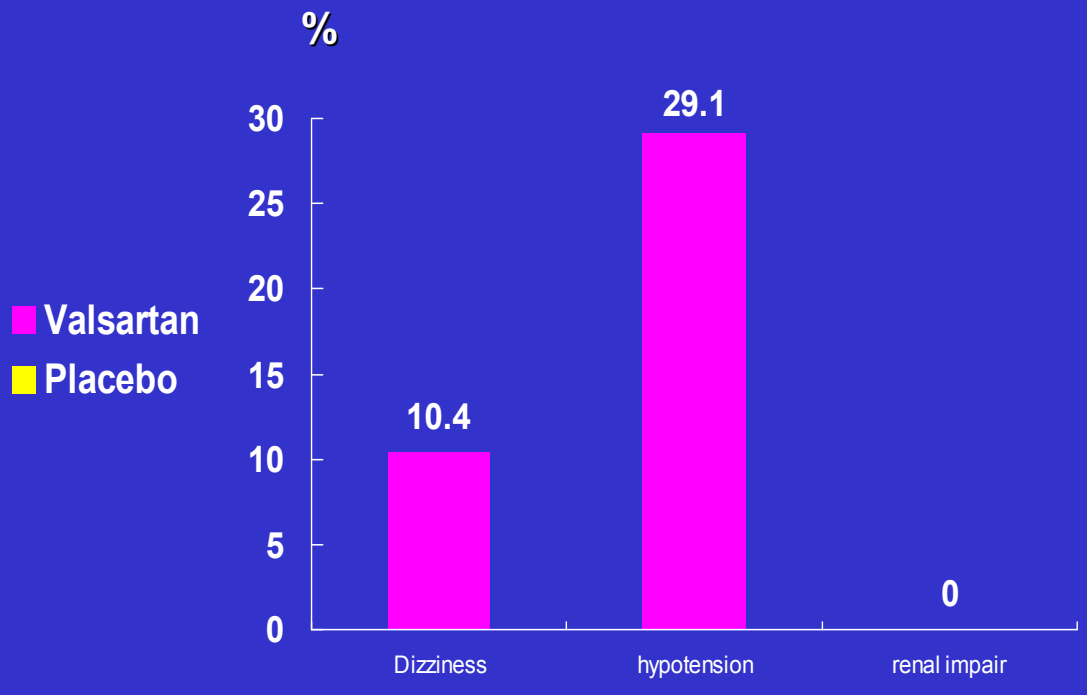
- Reasons for failed up titration (54.2%)
  - Judgment of investigator : 25.2%
  - SBP (≤ 90 mmHg and > 80 mmHg) : 54.5%
  - Sx. of Dizziness : 20.3%
- Study drug withdrawal or adjustment due to adverse events

Adverse Event	Valsartan (%)	Placebo (%)	K-Val-HeFT*
All disc due to AE	9.9	7.2	0
Dizziness	1.6	0.4	10.4
Hypotension	1.3	0.8	29.1
Renal impairment	1.1	0.2	0

- Study drug withdrawal due to adverse events (Val-HeFT)
- *: patients with adverse event, but without withdrawal

Result : Tolerability & Safety





Study drug withdrawal due to adverse events (Val-HeFT)

Failed up titration due to adverse events (K-Val-HeFT)

No drug withdrawal in K-Val-HeFT

Summary

- Clinical Characteristics: similar to Val-HeFT study
- Valsartan in ACE inhibitor intolerable patients with systolic HF: effective and tolerable, but relatively lower dose than other major clinical trials
- End-point difference : Significant
  - BNP, NYHA class
  - EF, LV end-diastolic internal diameter
  - CT ratio

Clinical Implications

- Important Clinical Experience
  - Prospective Clinical Study for CHF
  - Approaching Target Dose
  - Try to Useful Functional Test
  - Information for BNP Change, Echo Data, Other Clinical Parameters
  - Western vs. Korean

Study Limitations

- No placebo - active drug trial
- Incomplete Medical Record
  - Cause of HF
  - Medication History
  - BP Check
- Small sample size
- Inclusion bias
  - ACEI intolerance patient : ACEI Hx. (14.3%)
  - Forced Titration

Conclusions

- Valsartan significantly improves some composite endpoints (BNP, EF, NYHA) in patients with CHF and LVEF ≤40% when added to standard therapies including beta-blockers, diuretics and an aldosterone antagonist.
- Despite prior intolerance or not using to ACE inhibitor, valsartan was well tolerated.
- This approach offers the clinician an opportunity to make additional information in the treatment of CHF patients when left ventricular systolic dysfunction is present.

Thank You for Your Attention