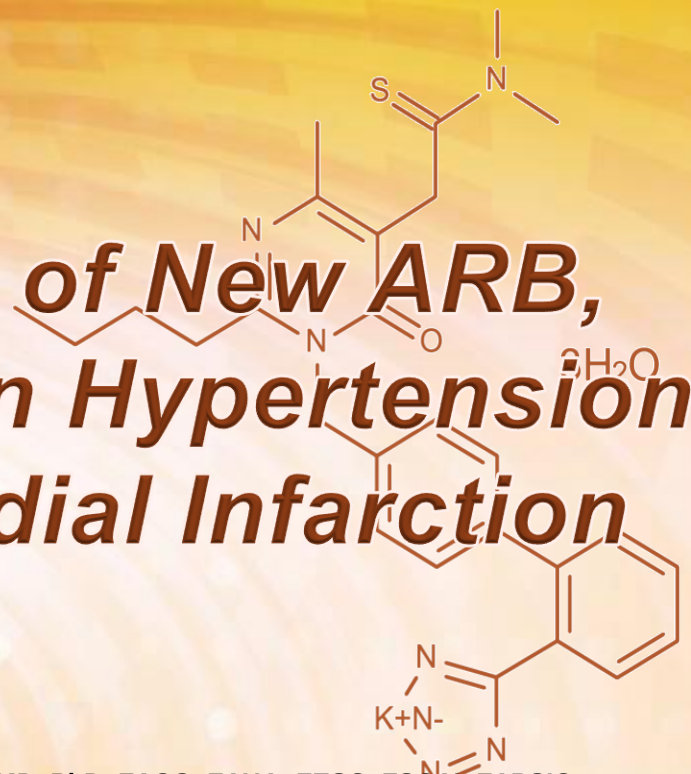
BORYUNG

Benefit of New ARB, Fimasartan, in Hypertension and Myocardial Infarction



Myung Ho Jeong, MD, PhD, FACC, FAHA, FESC, FSCAI, FAPSIC

Professor, Principal Investigator of Korea Acute Myocardial Infarction Registry,
Director of Heart Research Center Designated by Korea Ministry of Health and Welfare,
Director of Korea Cardiovascular Stent Research Institute,
Chonnam National University Hospital,
Gwangju, Korea

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Antihypertensives in RAAS

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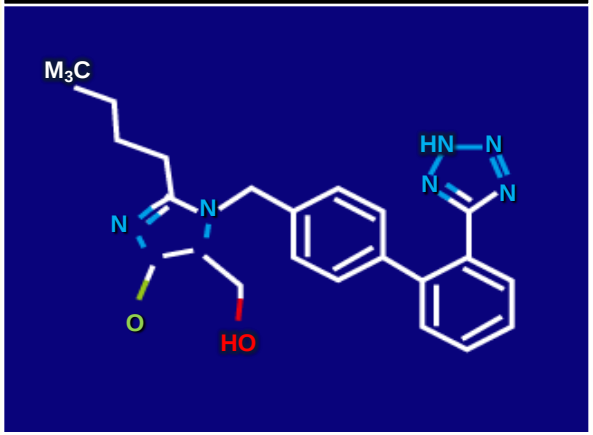
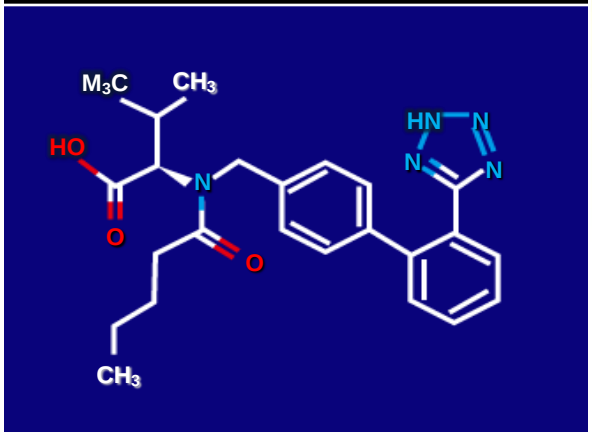
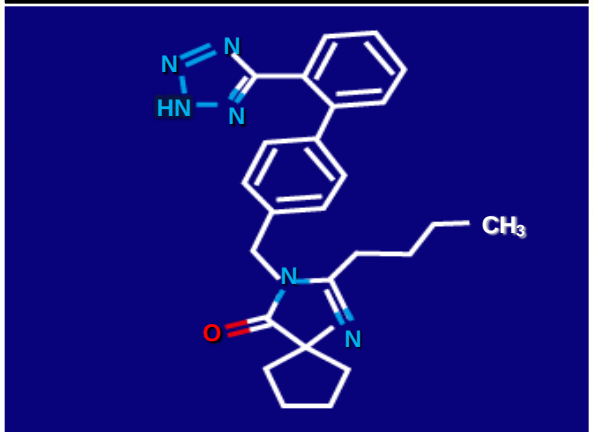
Losartan



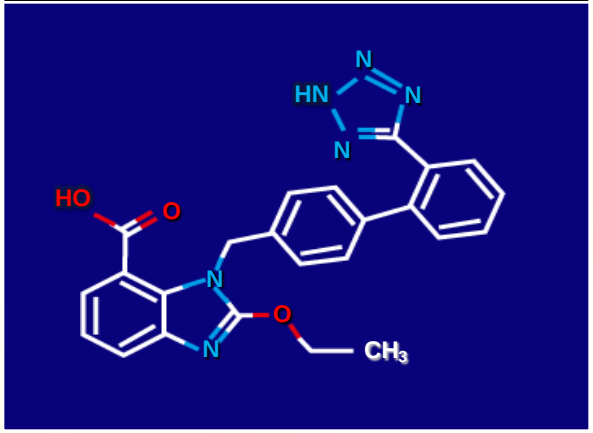
Valsartan



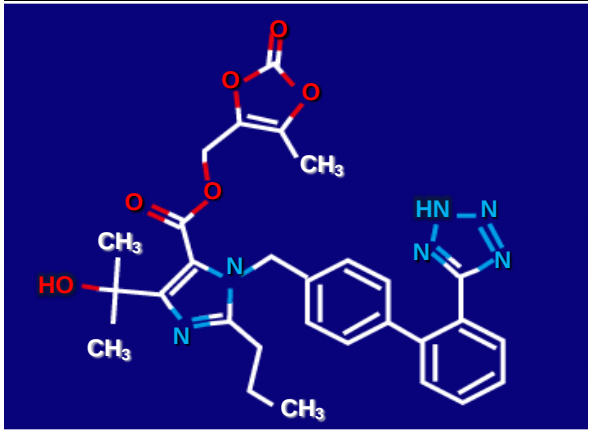
Irbesartan



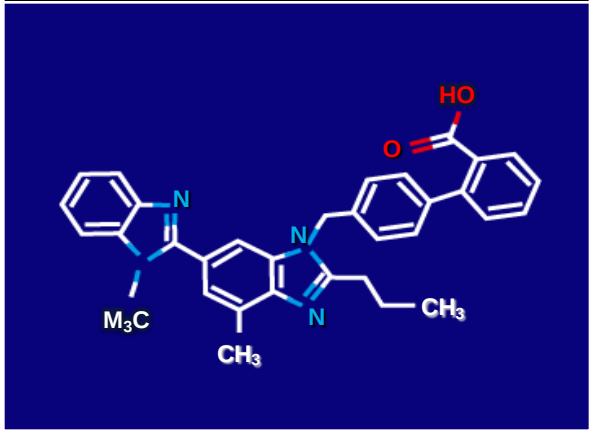
Candesartan



Olmesartan

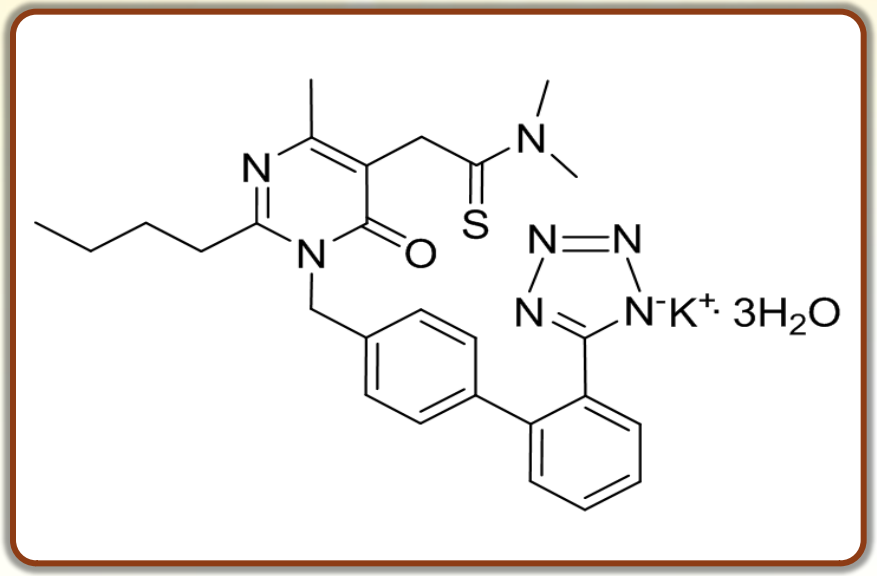


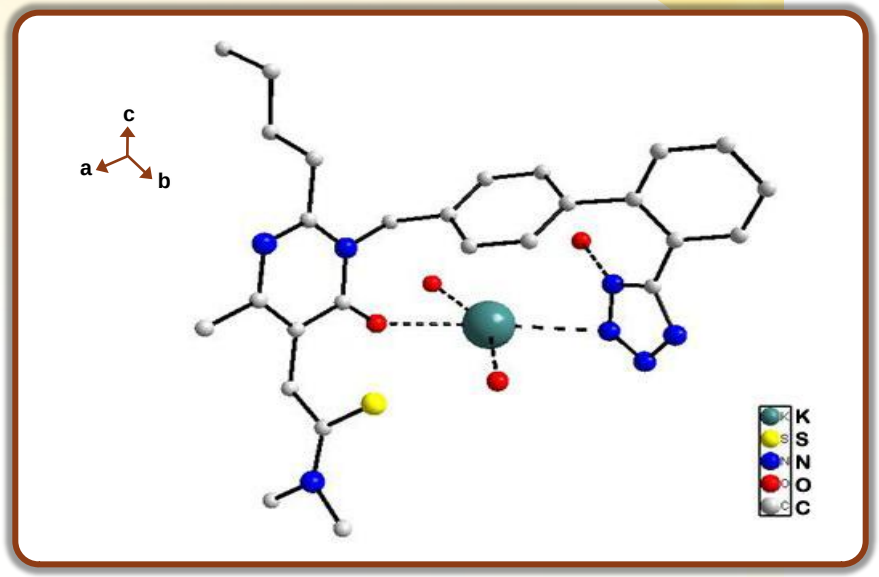
Telmisartan



Ries et al. J Med C

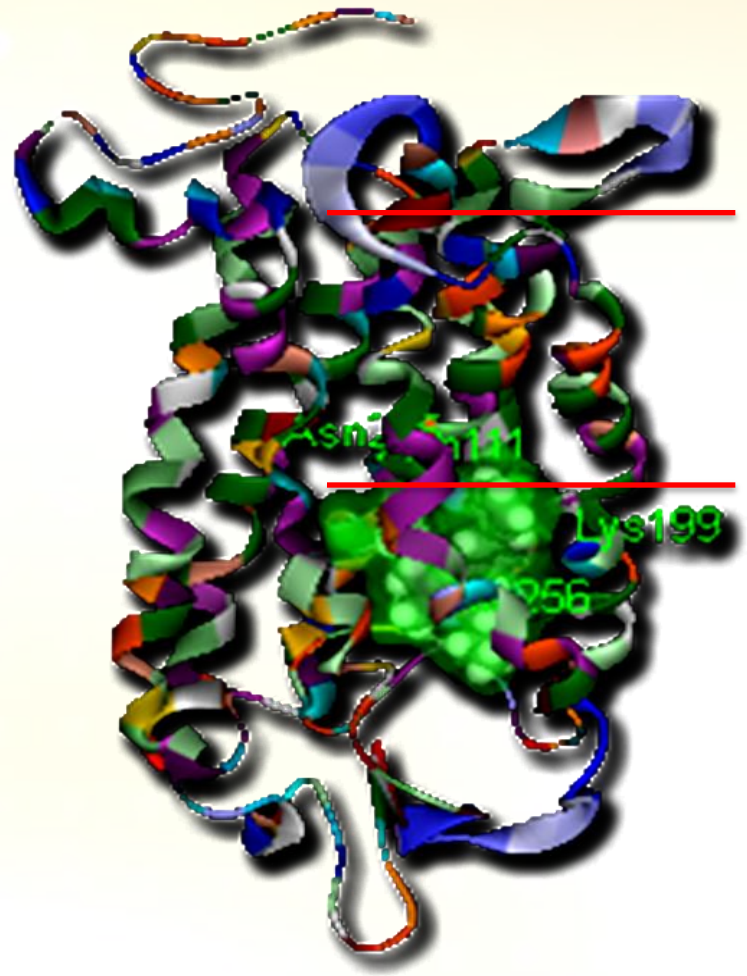
Fimasartan : a Novel Angiotensin Receptor Antagonist





- **Brand Name:** KANARB (KHAN of ARBs)
- **Active Pharmaceutical Ingredient:**
  Fimasartan potassium trihydrate, C27H30N7OS·K·3H2O
- **Molecular Weight** = 593.79
- **pH** = 6~8 (water, 50mg/10mL)
- **$T_{1/2}$(hr)** : 7-10
- **Solubility:**
  freely soluble in MeOH, soluble in EtOH, slightly soluble in water

Fimasartan and Angiotensin Type I (AT1) Receptor binding



By Discovery Studio 2.5, Accelys Inc., CA, USA

Pharmacological characteristics of ARBs

	Losartan	Valsartan	Irbesartan	Eprosartan	Telmisartan	Olmesartan	Candesartan	Fimasartan
Tmax (hr)	3-4	2-4	1.5-2	1-2	0.5-1	1-2	3-4	0.5~3
$T_{1/2}$ (hr)	2 (EXP3174: 6-9)	6-9	11-15	5-9	24	13	5-9	7-10
Active metabolite	EXP3174	None	None	None	None	None	None	None
Protein Binding (%)	99	95	90-92	98	99.5	99	>99	>97
Bioavailability (%)	33	10-35	60-80	13	42-58	26	15	30-40
Urinary Elimination (%)	35	13	20	7	<1	35-50	33-59	<3
Dose[*1] (mg)	25, 50, 100	40,80,60,320	75, 150,300	400, 600	20, 40, 80	5, (10[*2]), 20, 40	4, 8, 16, 32	60, 120
AT1 binding pattern	Competitive Surmountable	Competitive Surmountable	Competitive Insurmountable	Competitive Insurmountable	Non-competitive Insurmountable	Non-competitive Insurmountable	Non-competitive Insurmountable	Non-competitive Insurmountable

** 1 : Registration in the US*
** 2 : Additional registration in Korea and Japan*

Fimasartan Toxicological Data

Kanarb® Fimasartan

Ⅰ Not affect general behavior, respiratory rate or tidal volume

Ⅱ **MTD > 2,000mg/kg oral administration in mice, rats and Beagle dogs**

Ⅲ Safe in repeated administrations in rats(26weeks) and dogs(52weeks)

Ⅳ Not clastogenic (i.e., not causing mutation)

Ⅴ NOEL 10 mg/kg/day in 104 weeks carcinogenecity study ; 10 times human dose

Very favorable safety profile in preclinical studies

- MTD : Maximum tolerated dose
- NOEL : No observed effect level
- NOAEL : No observed adverse effect level

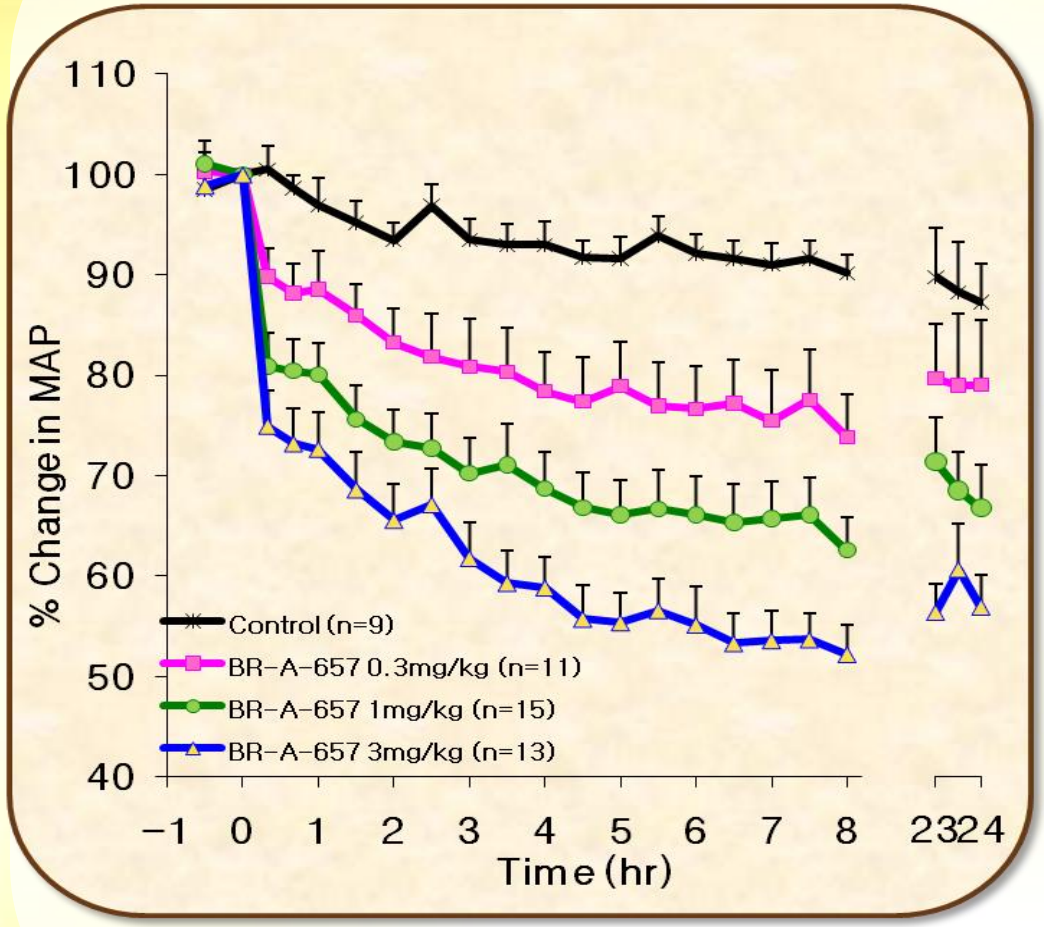
Blood Pressure Lowering Effect in Animal (I)

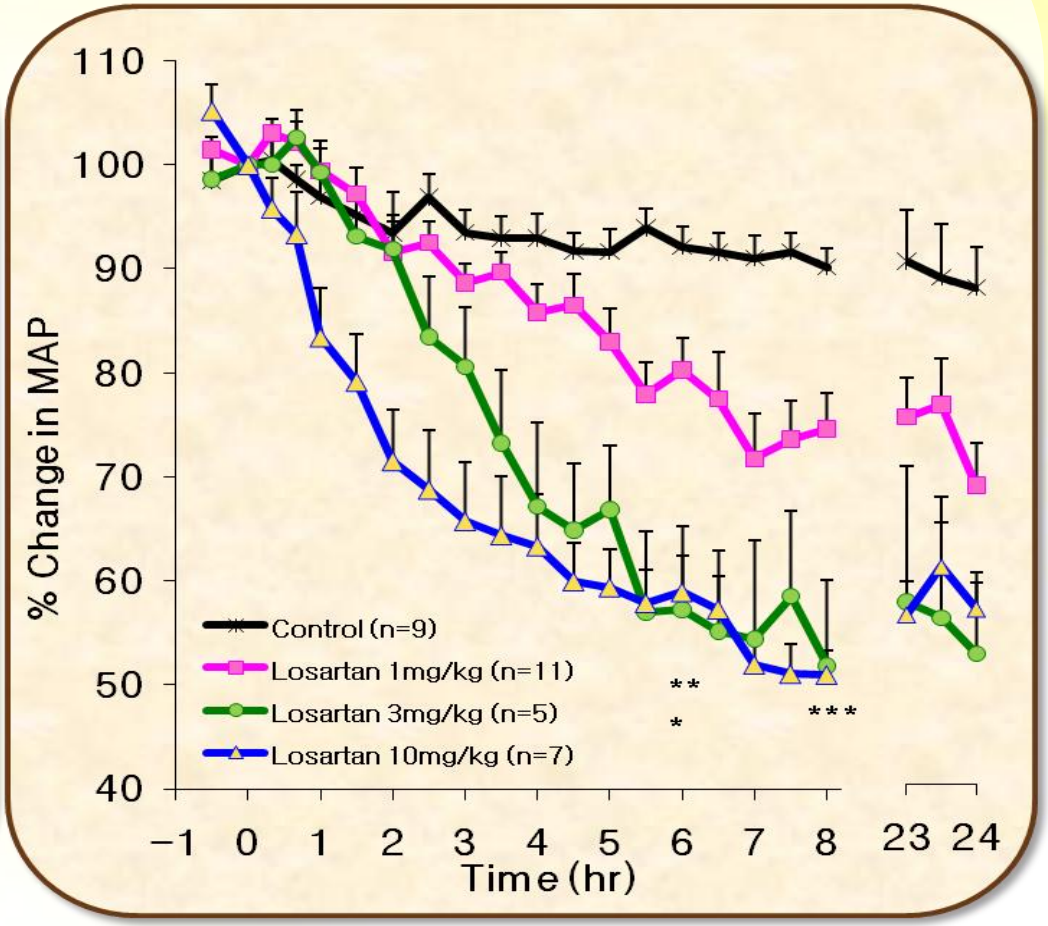
Kanarb® Fimasartan

- **Animal Model**
  - Renal Hypertension Rat models (RHR)
- **Object**
  - To determine mean arterial BP responsiveness
  - To determine BP lowering effect for 24 hours
- **Method**
  - Tail pressure monitoring
- **Fimasartan Dose**
  - Control : Vehicle (n= 9)
  - Fimasartan : 0.3 mg/kg (n=11), 1 mg/kg (n=15), 3 mg/kg (n=13)
  - Losartan : 1 mg/kg (n=11), 3 mg/kg (n=5), 10 mg/kg (n=7)

▪ Blood Pressure Lowering Effect in Animal (I)

Kanarb®
Fimasartan





Blood Pressure Lowering Effect in Animal (2)

Kanarb® Fimasartan

Animal Model

- Spontaneous Hypertensive Rat (SHR)

Object

- To determine mean arterial BP responsiveness over a month
- To determine BP lowering effect comparing to valsartan

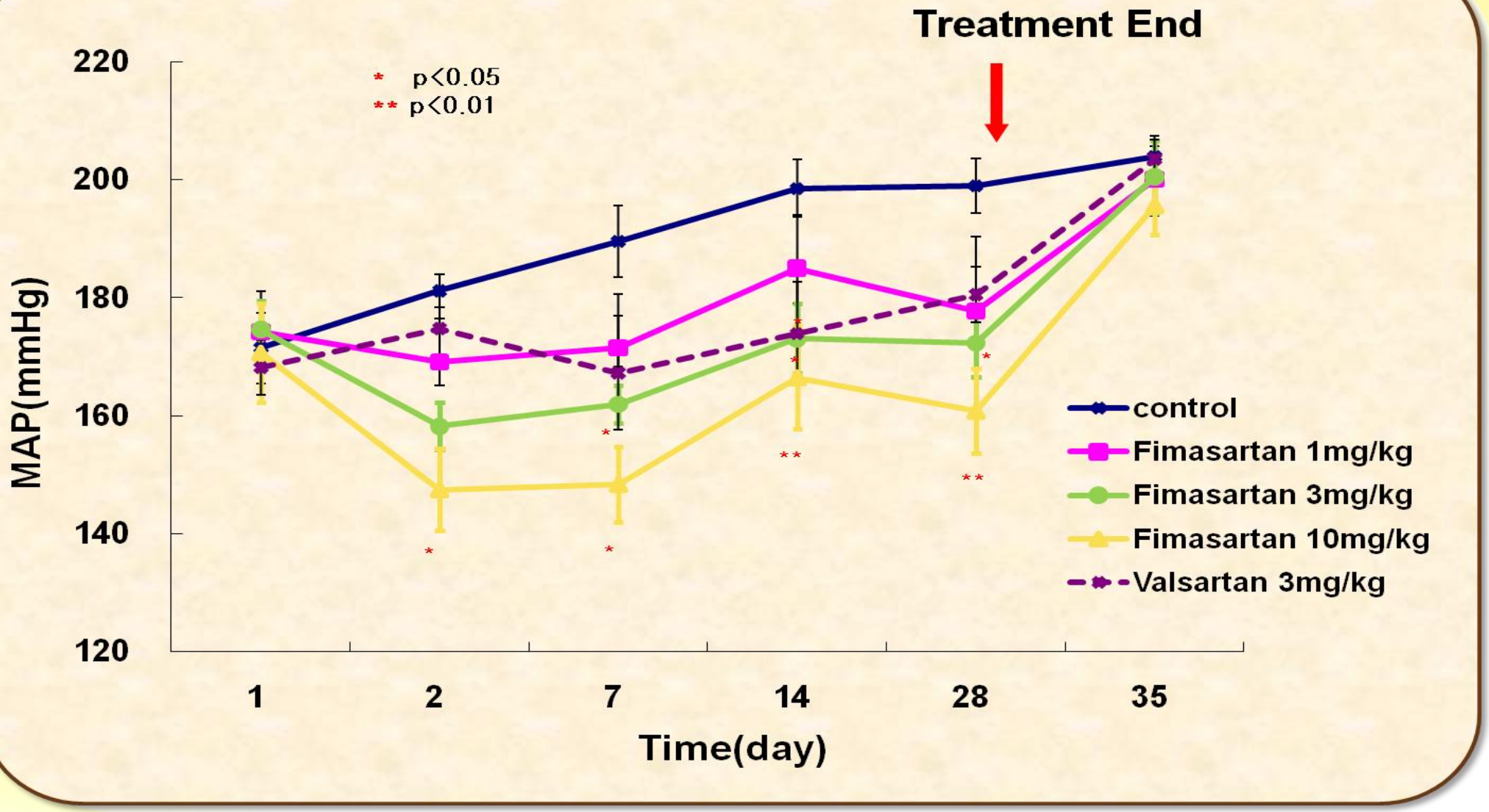
Method

- Tail pressure monitoring

Fimasartan Dose

- Control : Vehicle (n= 9)
- Fimasartan : 1 mg/kg , 3 mg/kg, 10 mg/kg
- Valsartan : 3 mg/kg

Blood Pressure Lowering Effect in Animal (2)

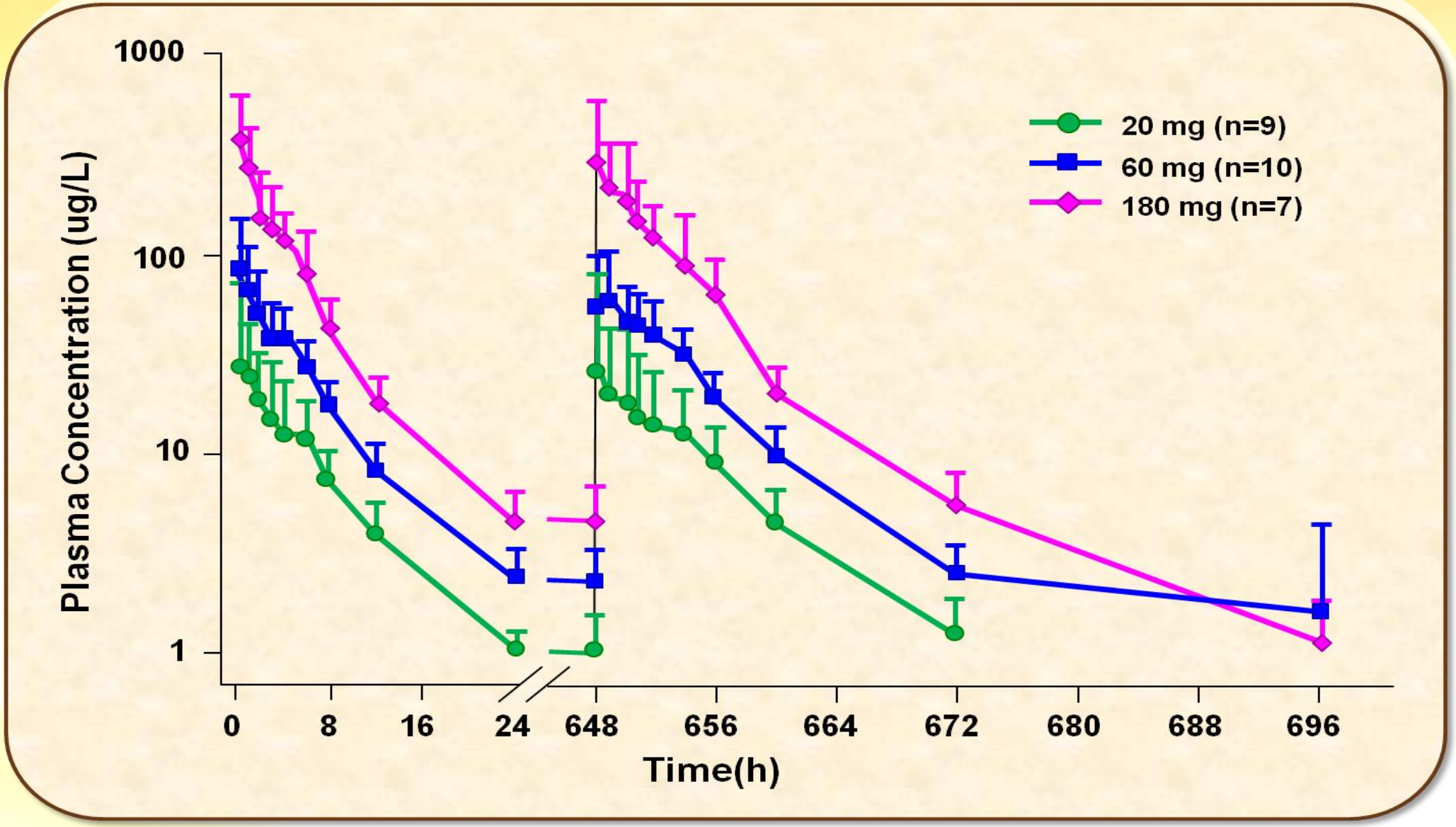


Fimasartan Clinical Studies

Kanarb® Fimasartan

- Ⅰ Phase Ⅰ study
- Ⅱ Drug interaction study
- Ⅲ Phase Ⅱa & Ⅱb study
- Ⅳ Phase Ⅲ study
- Ⅴ Subgroup analysis

▪ Plasma concentration profiles in hypertensive patients



▪ Plasma concentration profiles in hypertensive patients

Combination drug	Rationale of selection	Ratio of geometric mean (Combination/Mono)	
		C_{max}	AUC
Ketoconazole Rifampicin	Ketoconzole (CYP3A4 inhibitor) Rifampicin (CYP3A4 inducer)	K+F: 2.47 R+F: 10.33	K+F: 2.03 R+F: 4.60
HCTZ	Combination therapy for hypertension	Fimasartan : 1.30 HCTZ: 0.94	Fimasartan: 1.17 HCTZ: 0.88
Amlodipine	Combination therapy for hypertension	Fimasartan : 1.10 Amlodipine : 1.03	Fimasartan: 1.16 Amlodipine: 0.97
Atorvastatin	Co-administration with fimasartan Substrate of CYP3A4 & ATP1B1	Atorvastatin: 1.89 A lactone: 1.32 O-A: 2.45 O-A lactone: 1.45	Atorvastatin: 1.19 A lactone: 0.85 O-A: 1.42 O-A lactone: 1.10
Wafarin	Narrow therapeutic window	R-Wafarin: 1.06 S-Wafarin 1.02	R-Wafarin: 1.07 S-Wafarin: 0.99
Digoxin	Narrow therapeutic window	Digoxin: 1.31	Digoxin: 1.09

**** HCTZ : Hydrochlorothiazide, F: Fimasartan, K: Ketoconazole, R: Rifampicin, A: Atrovastatin, O-A: Orthohydroxy-Atorvastatin***

Weak interaction with ketoconazole and rifampicin
No interaction with other drugs tested → can be prescribed safely

Inclusions

- Mild-to-moderate (stage 1 or 2) essential hypertension
- Male or female
- Age : 18~65 year-old
- Blood pressure

  mean sitting DBP ≥ 90 mmHg and <110 mmHg at baseline

Endpoints for phase II study

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Primary endpoint

- Sitting DBP change from baseline at the study end

Secondary endpoints

- Sitting DBP and SBP change from baseline at each visit
- Responder rate/control rate

Phase II studies

Kanarb® Fimasartan

Clinical trials	Control	Group	N	Baseline	4 wks	8 wks	12 wks	24wks
Phase IIa	Placebo	Placebo F 20mg F 60mg F 180mg	15 16 15 15	→	→			
Phase IIb	Placebo	Placebo F 20mg F 60mg F 120mg F 240mg	41 41 38 38 37	→	→	→		

* P; Placebo, F; fimasartan

▪ Phase IIa : efficacy

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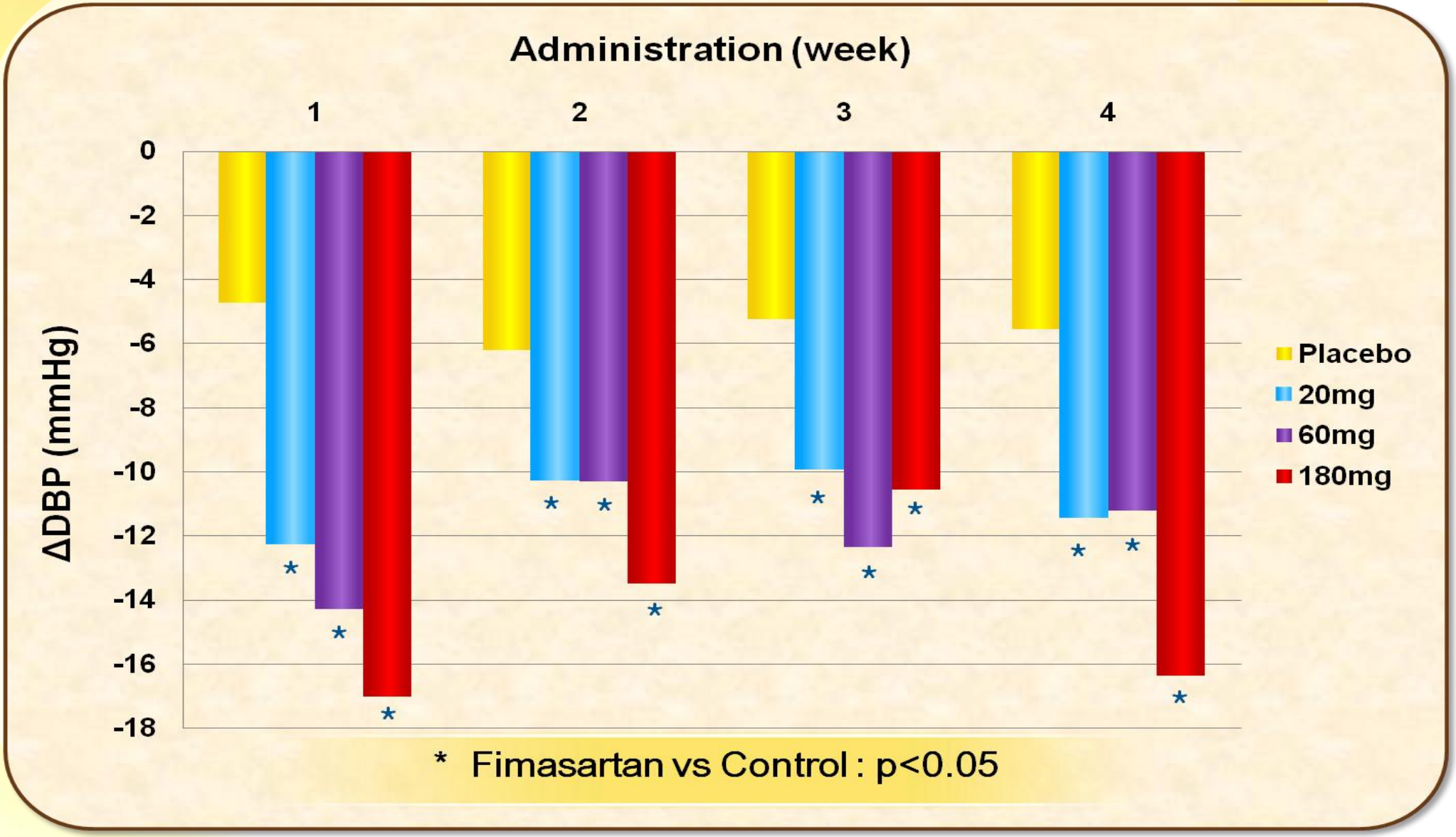
Fimasartan



Phase IIb : efficacy

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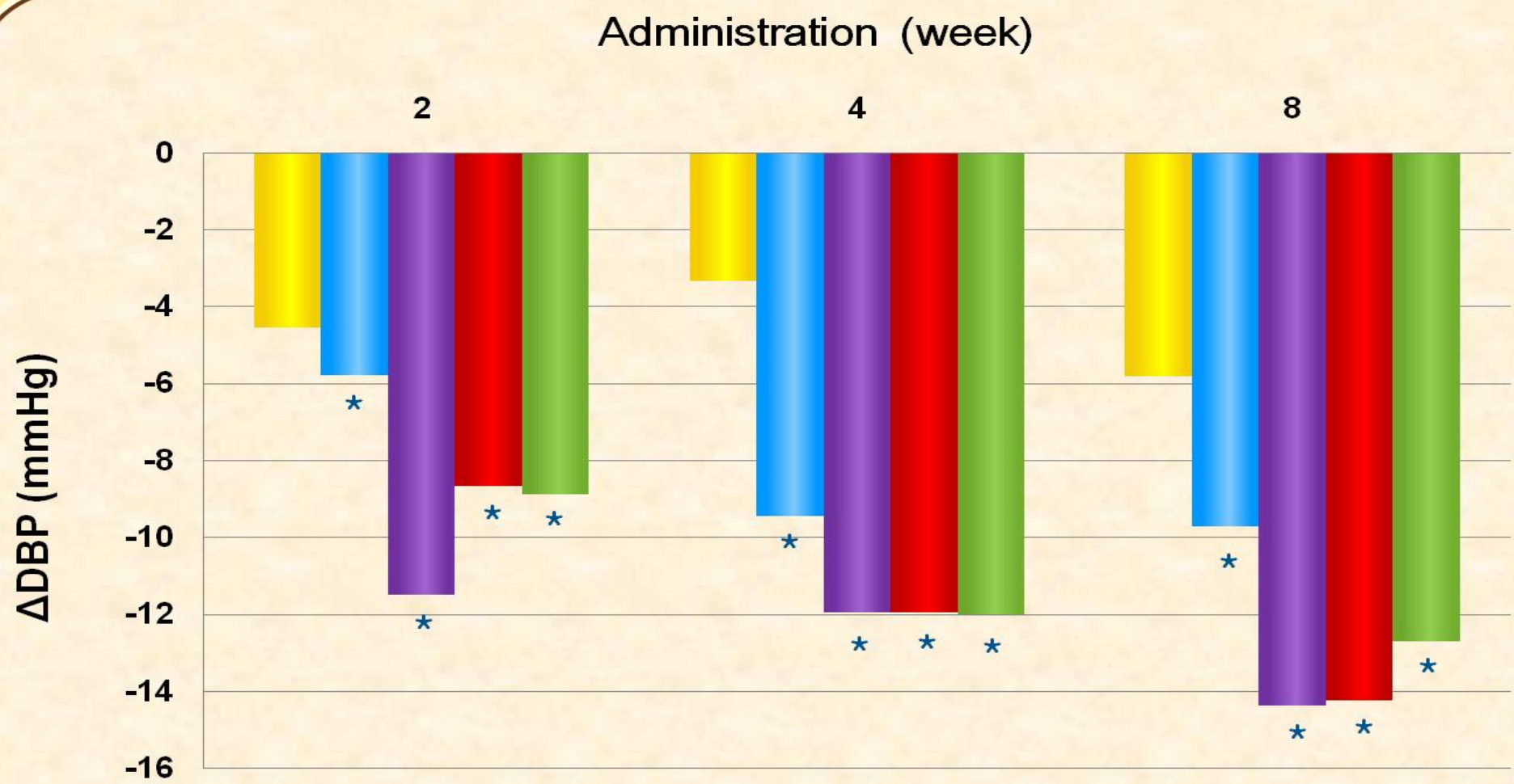

Endpoints for ABPM study

Kanarb®
Fimasartan

Primary endpoint

- 24 hour ABPM change from baseline after 8 week medication at the study end

Secondary endpoints

- Comparison of ABPM changes with valsartan
- Determine the T/P ratio and Smoothness index

Ambulatory BP Monitoring

Kanarb® Fimasartan

Clinical trials	Control	Group	N	Baseline	4 wks	8 wks	12 wks	24wks
ABPM	Valsartan	F 60mg F 120 mg V 80mg	32 30 30	→	→	→		
				ABPM 1		ABPM 2		

ABPM study efficacy_(1)

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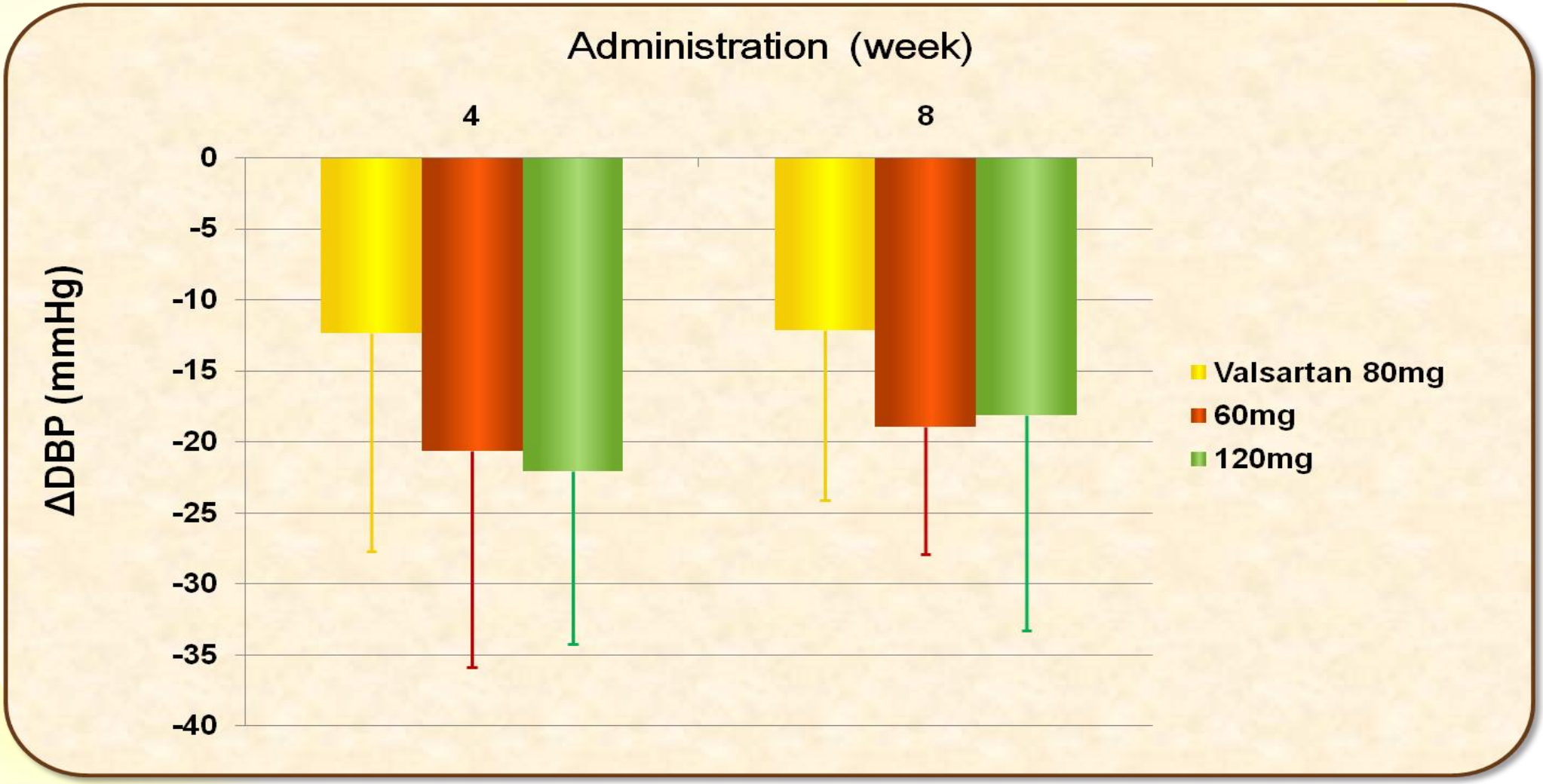
Sitting BP



Efficacy Analysis of 24hrs ABPM (Phase II)

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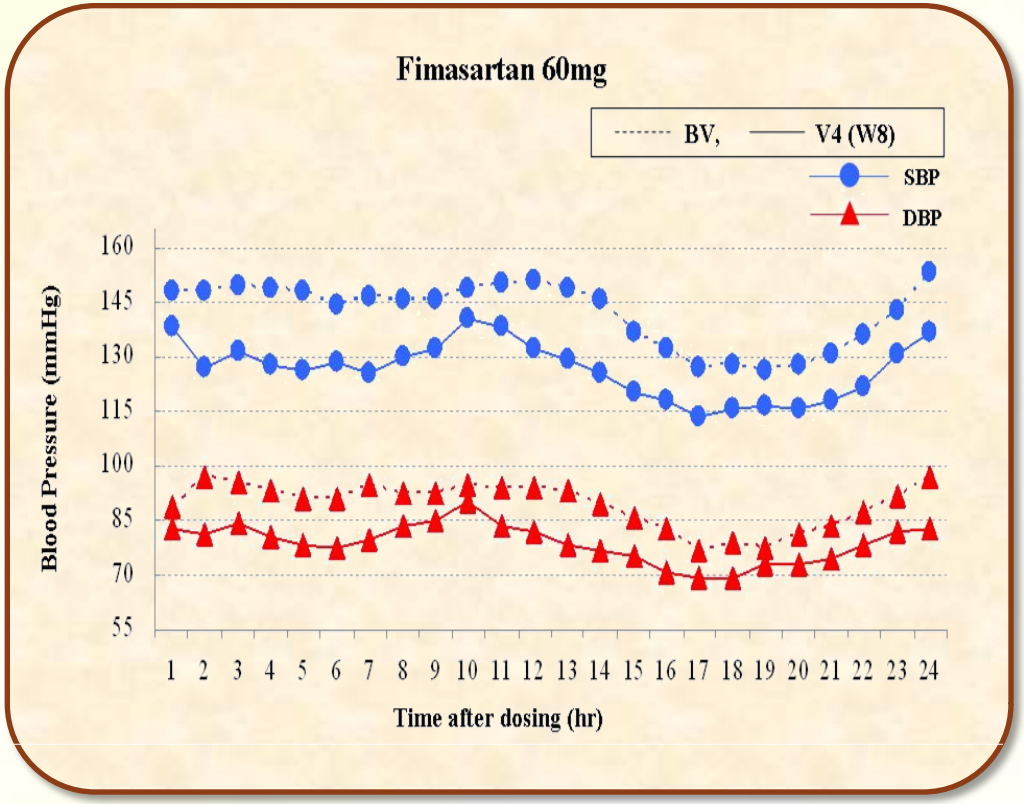
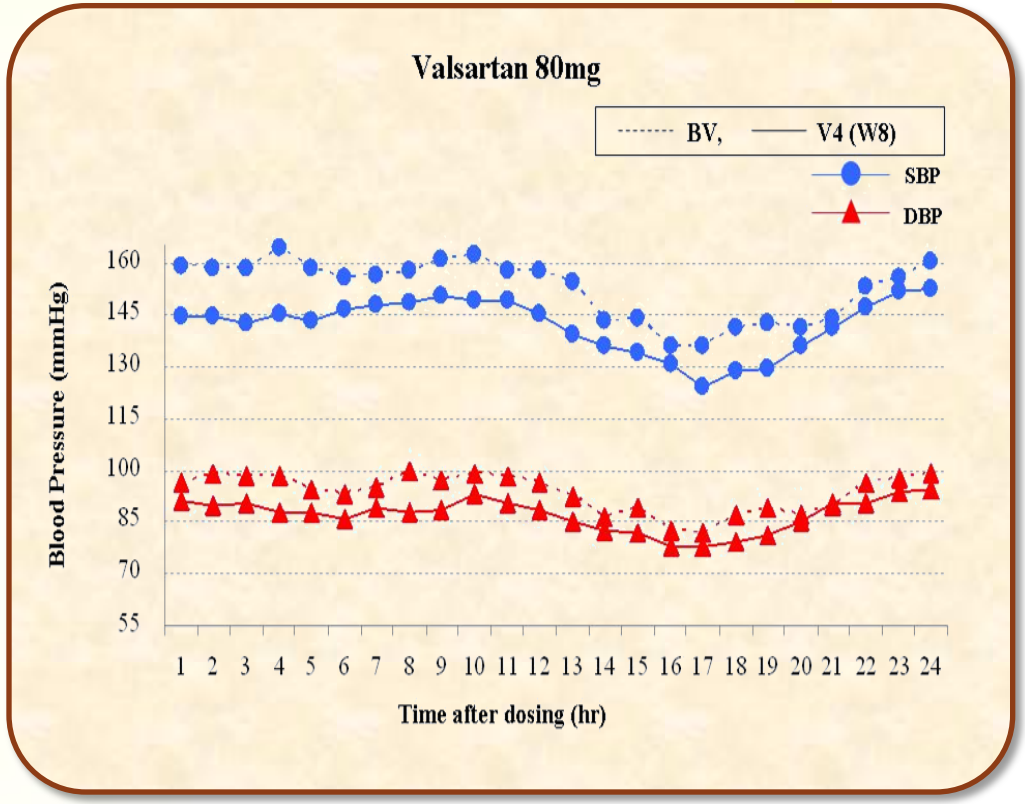




Endpoints for phase III study

Kanarb® Fimasartan

Primary endpoint

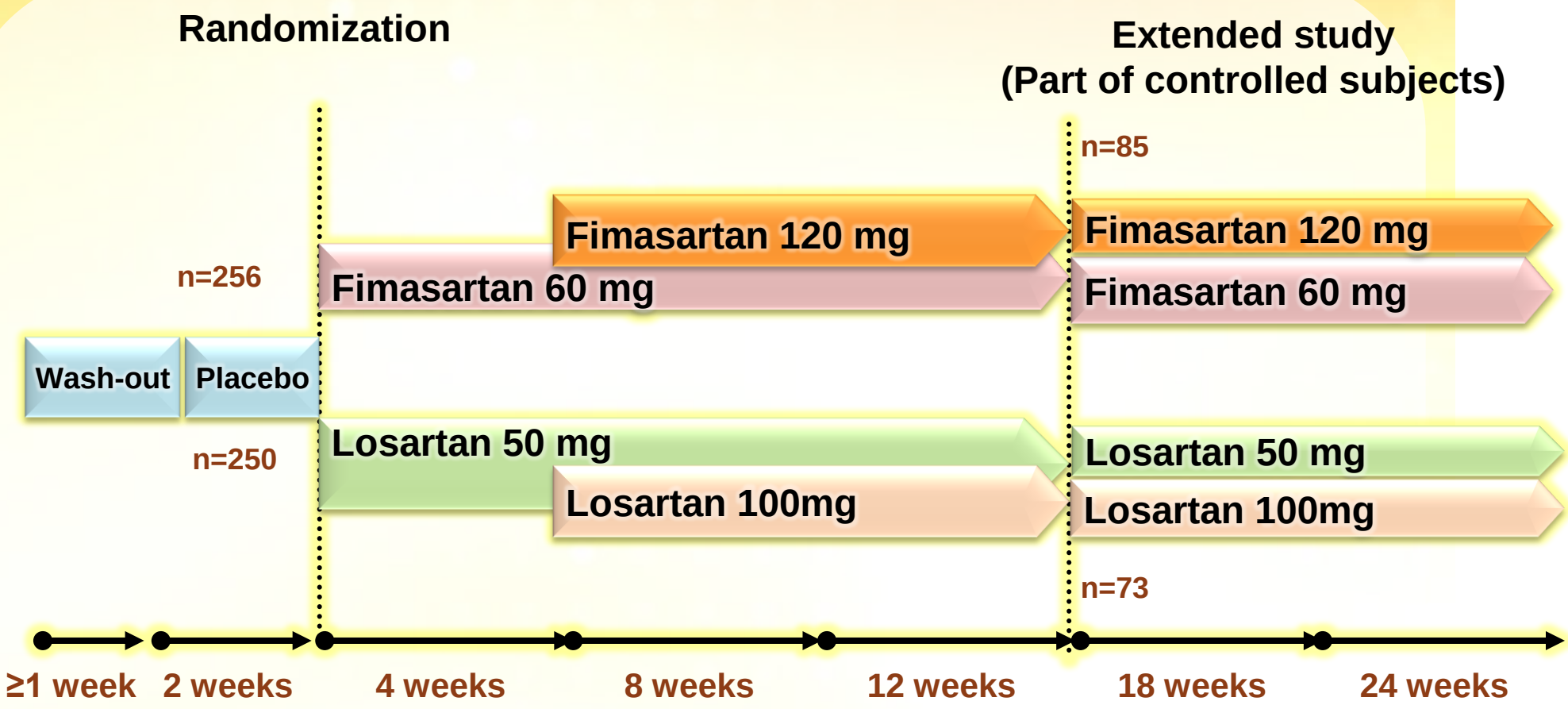
- Sitting DBP changes from baseline at 12 weeks of medication compared with losartan

Secondary endpoints

- Sitting SBP changes from baseline at 12 weeks of medication compared with losartan
- Sitting DBP and SBP changes from baseline at extended period, 24 weeks of medication compared with losartan
- DBP changes in subjects controlled with low dose, or subjects treated with low and high doses
- Safeties at 12 weeks of medication compared with losartan

Phase III Study design

Kanarb® Fimasartan



†Optional up-titration of fimasartan or losartan

Phase III efficacy_(I)

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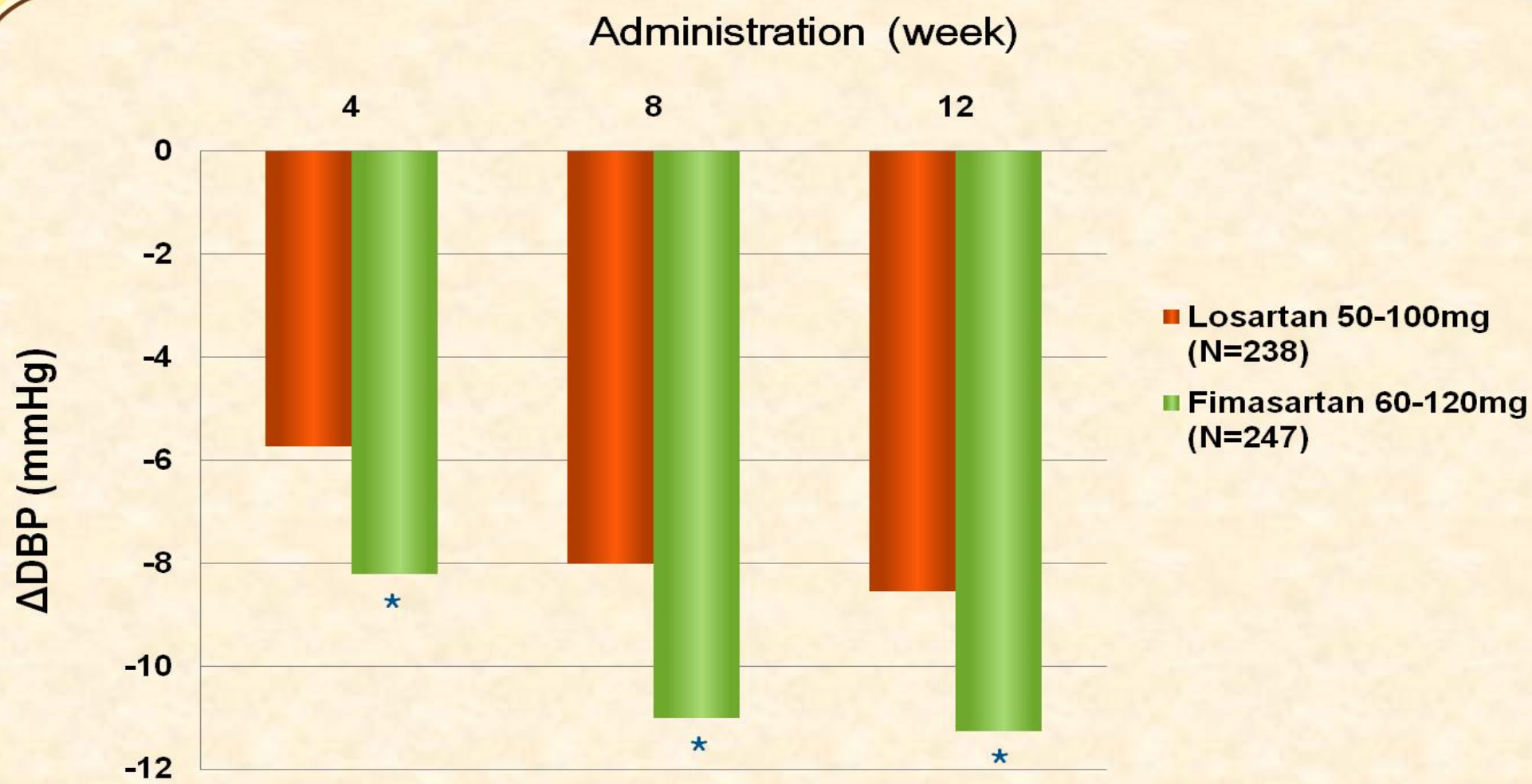
Fimasartan



* Fimasartan vs Control : p<0.05

Phase III efficacy_(2)

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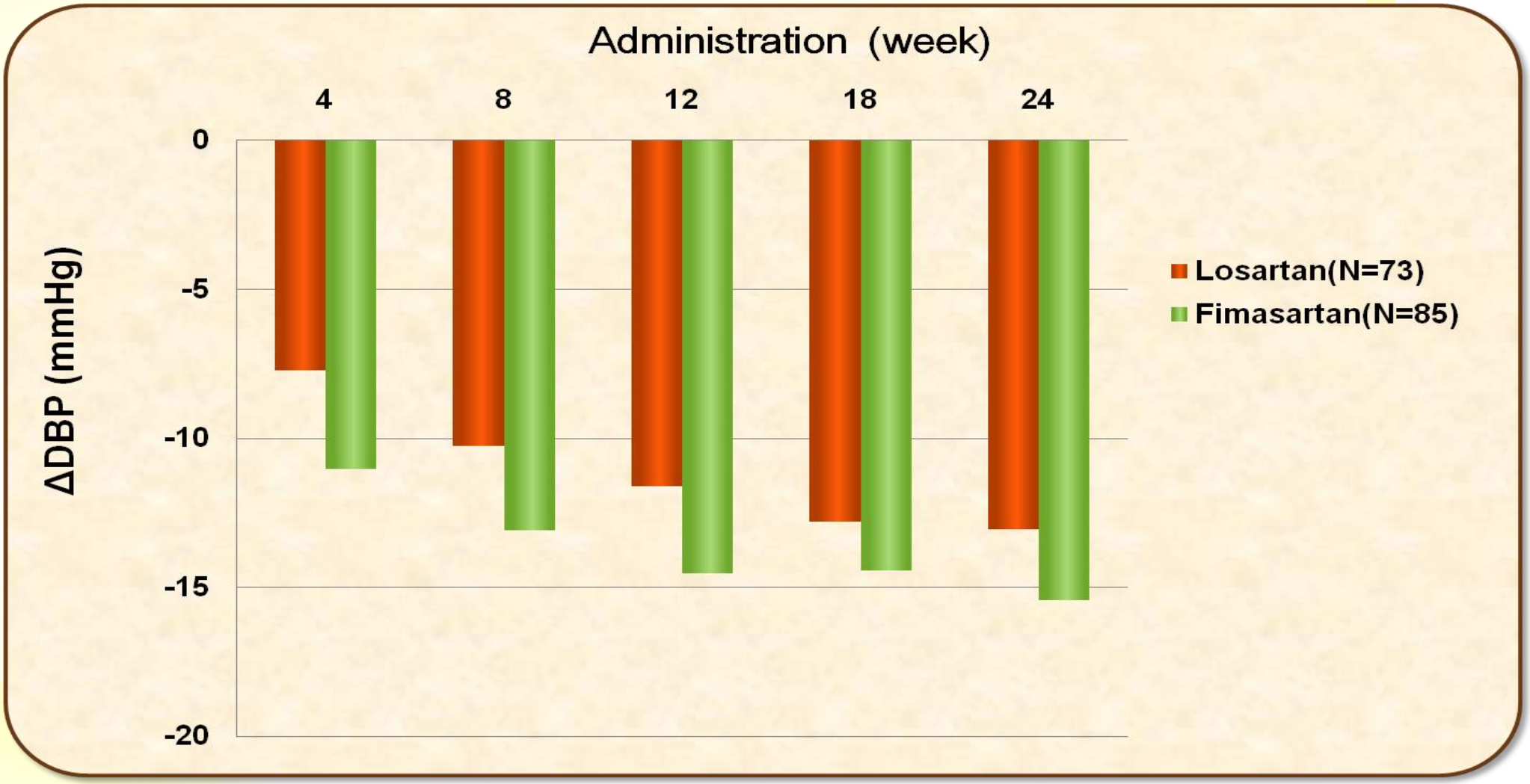
Fimasartan

Extension study for 24 weeks



Phase III efficacy_(2)

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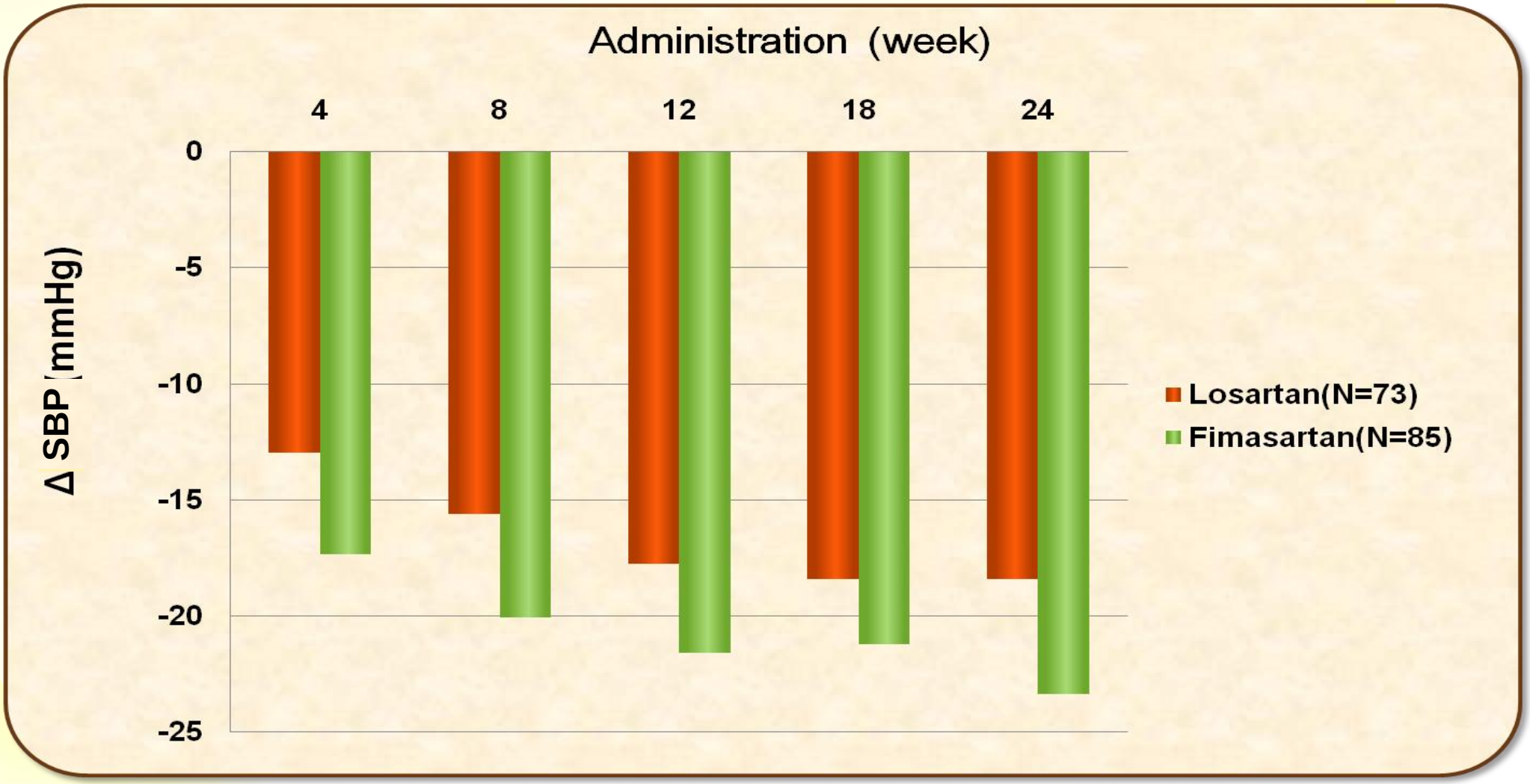
Fimasartan

Extension study for 24 weeks



Phase III – Safety (12weeks)

Kanarb® Fimasartan

Items	TEAEs (subject(%) [event])		Treatment-related TEAEs (subject(%) [event])	
	Fimasartan (N=255)	Losartan (N=250)	Fimasartan (N=255)	Losartan (N=250)
No. of subject with TEAEs	83 (32.5%) [136]	80 (32.0%) [119]	20 (7.8%) [29]	26 (10.4%) [40]
No. of subject with SAEs	3 (1.2%) [3]	5 (2.0%) [5]	0 (0.0%) [0]	0 (0.0%) [0]
TEAEs≥2%				
Headache	16 (6.3%) [17]	17 (6.8%) [18]	6 (2.4%) [7]	11 (4.4%) [12]
Dizziness	11 (4.3%) [11]	9 (3.6%) [10]	7 (2.8%) [7]	7 (2.8%) [7]
Nasopharyngitis	8 (3.1%) [8]	5 (2.0%) [6]		
Dyspepsia		5 (2.0%) [5]		

TEAEs >1%
Fimasartan : upper respiratory tract infection, constipation, pruritus, chest discomfort, ALT increased, AST increased, palpitations, cough
Losartan : upper respiratory tract infection, rhinitis, nausea, gastritis, pruritus, chest discomfort
Treatment-related TEAEs >1%
Losartan : nausea

Subgroup Analysis of Efficacy & Safety in Hypertension Studies

Kanarb® Fimasartan

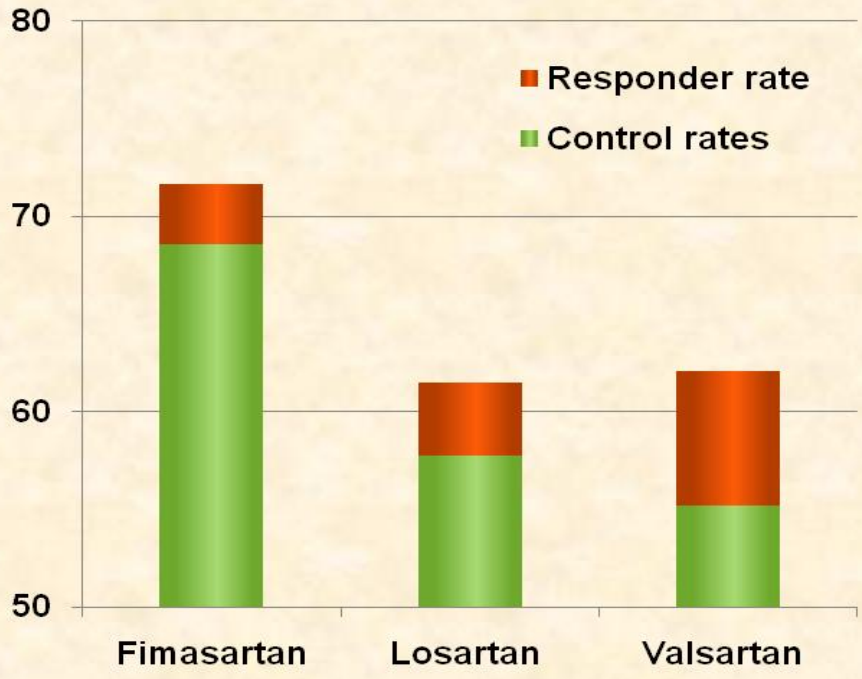
Category		Gender		Age		BMI[3)]			Hyperlipidemia[4)]		Diabetes[5)]		Total
		Male	Female	<65	≥65	18.5<, <23	23≤, <25	25≤, <30	Yes	No	Yes	No	
Efficacy (completed 12-week treatment)	n	156	70	205	21	36	60	112	39	187			226
	ΔDBP (mmHg)	-12.0	-11.6	-11.9	-11.0	-13.2	-13.5	-10.6	-12.3	-11.8			
	p-value[1)]	0.7658		0.5919		0.874*	0.0645**	0.0162***	0.7246				
AEs (all subjects administered FMS 60-120 mg)	n	367	39	280	126	73	115	191	61	345	20	386	406
	Event #	118	10	80	48	27	41	52	10	118	6	122	
	(%)	32.2	25.6	28.6	38.1	37.0	35.7	27.2	16.4	34.2	30.0	31.6	
	p-value[2)]	0.4716		0.0648		0.3714			0.0067		1.0000		

1) p-value from proc mixed model (independent variables: BMI, visit, treatment, interaction)
2) p-value from Fisher exact test
3) The standard guideline of obesity association in Asia
4) Major combination : Statin group (Atorvastatin, Rosuvastatin, Pitavastatin, Simvastatin, Fluvastatin), Fenofibrate
5) Major combination : Metformin, Glimepride, Gliclazide
* 18.5<BMI<23 vs 23≤BMI<25, ** 18.5<BMI<23 vs 25≤BMI<30, *** 23≤BMI<25 vs 25≤BMI<30

Responder rates of ARBs

Kanarb®
Fimasartan

1



2

Responder: DBP<90mmHg or Change from baseline Δ DBP>10mmHg
Control: DBP<90mmH

(1) : Fimasartan Phase III and ABPM study
(2) : Am J. Manged Care 2009;11(13), Sup. :S386-S391

Fimasartan

- Selective and effective in AT1 receptor binding
- Rapid absorption & No accumulation
- Fast and long-acting efficacy :
  - Sustained > 24-hour BP control
  - Early onset of anti-hypertensive effect (from 1-2 weeks of treatment)
- More effective BP lowering effects compared to other ARBs
- Comparable safety profile to other ARBs

Fimasartan Symposium

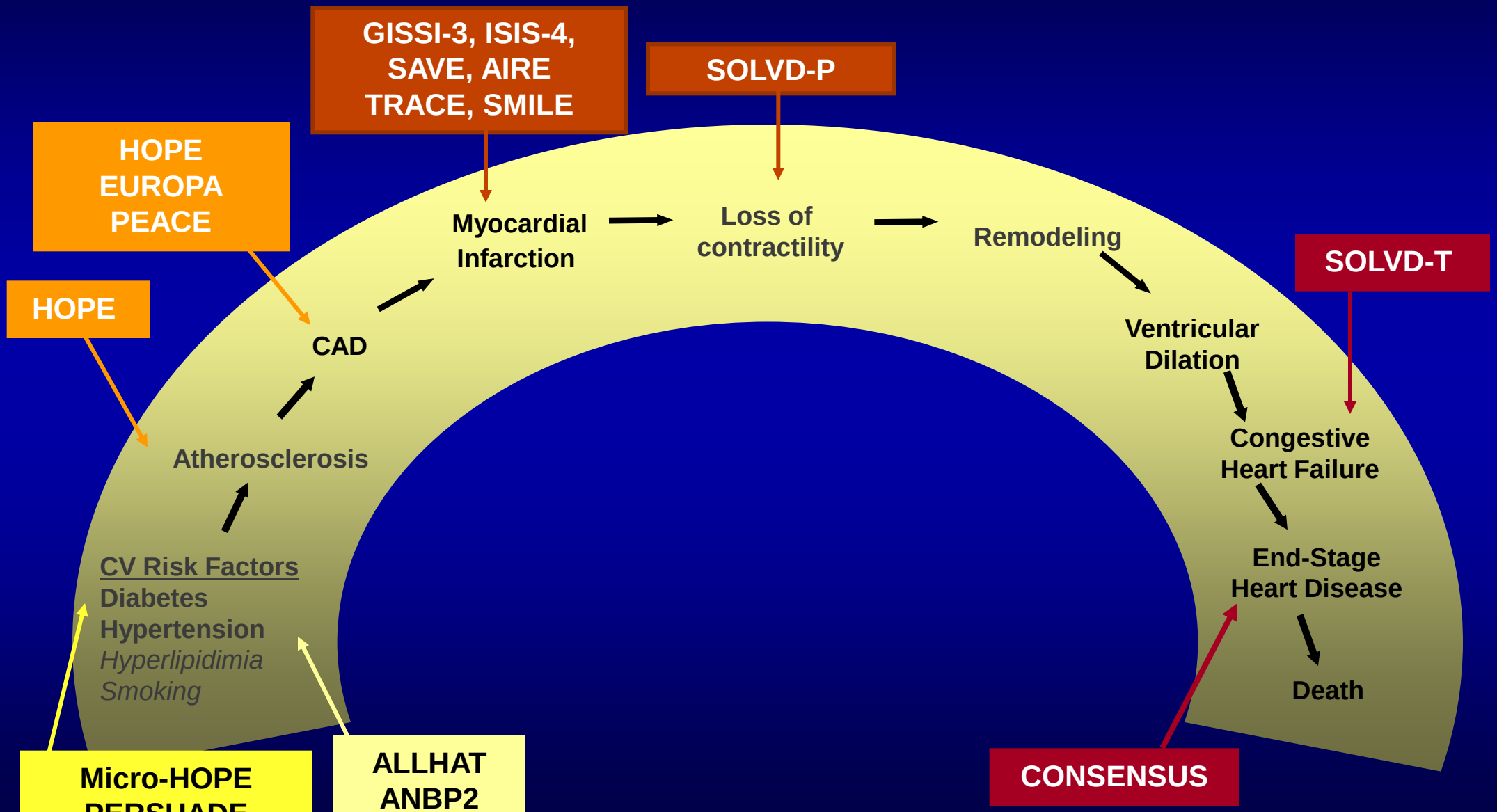
서울 플라자 호텔 Dec 1, 2010

Fimasartan Clinical Trial: Direction for Acute Myocardial Infarction

Myung Ho Jeong, MD, PhD, FACC, FAHA, FESC, FSCAI, FAPSIC

Professor, Principal Investigator of Korea Acute Myocardial Infarction Registry,
Director of Heart Research Center Designated by Korea Ministry of Health and Welfare,
Director of Korea Cardiovascular Stent Research Institute,
Chonnam National University Hospital,
Gwangju, Korea

Role of ACEI Along the Cardiovascular Continuum

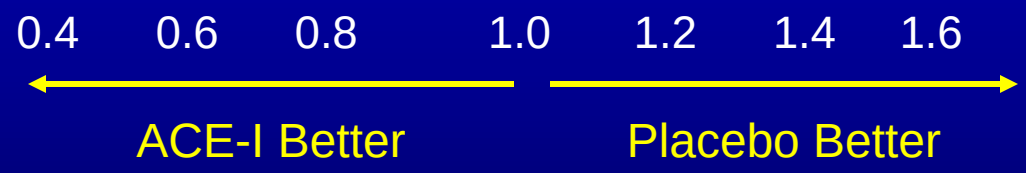


Adapted from Dzau V, Braunwald E. Am Heart J. 1991

ACE Inhibitor Evidence: Secondary Prevention

Meta-Analysis of the HOPE, EUROPA, and PEACE Trials*

Clinical Trial	N	Deaths	RR of Mortality
HOPE	9,297	1051	HR=0.84 P=0.005
EUROPA	12,218	795	HR=0.89 P=0.10
PEACE	8,290	633	HR=0.89 P=0.13
All Trials	33,960	>3000	HR=0.86 P<0.001

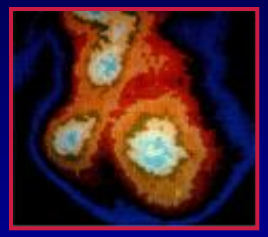


*7 RCTs, 33,960 randomized patients, and 4.4 years of mean follow-up.
Other findings include a CVD HR=0.81, MI HR=0.82, and stroke HR=0.77

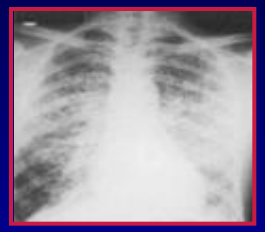
ACE-I=Angiotensin converting enzyme inhihbitors,
CVD=Cardiovascular disease, MI=Myocardial infarction

Danchin N et al. *Arch Intern Med* 2006;166:787-796

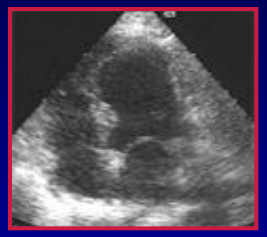
ACE Inhibitor Evidence: Secondary Prevention



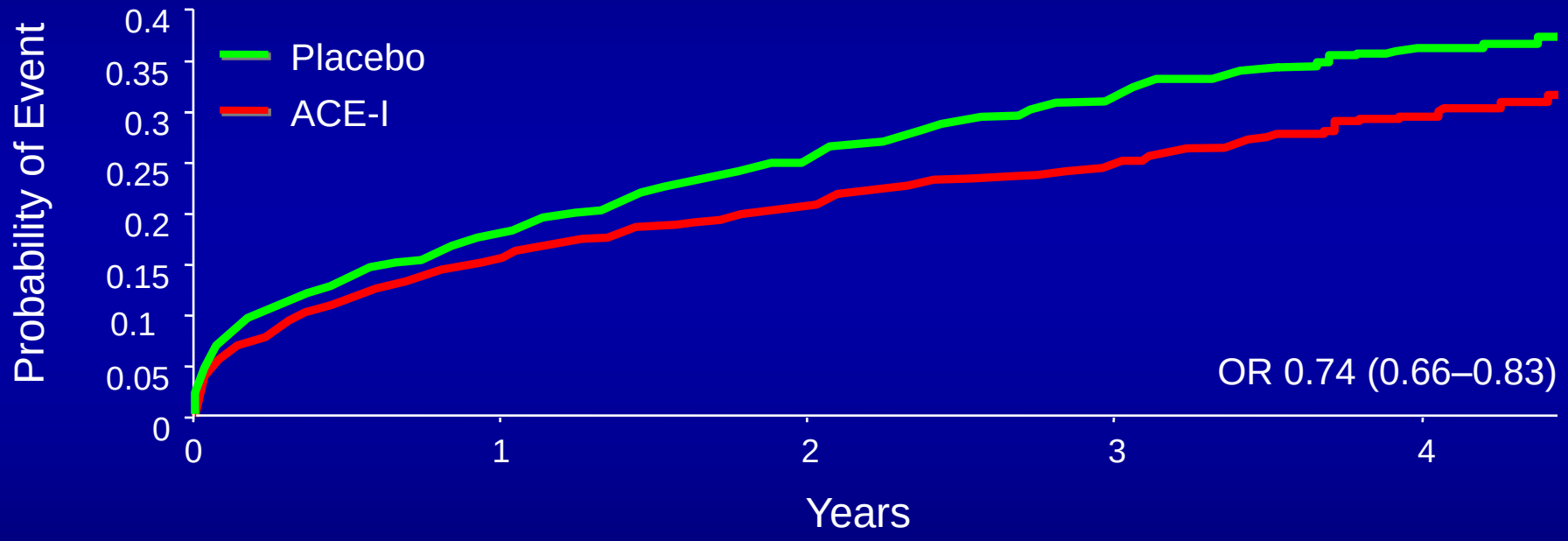
SAVE
Radionuclide
EF ≤40%



AIRE
Clinical and/or
radiographic signs
of HF



TRACE
Echocardiogram
EF ≤35%

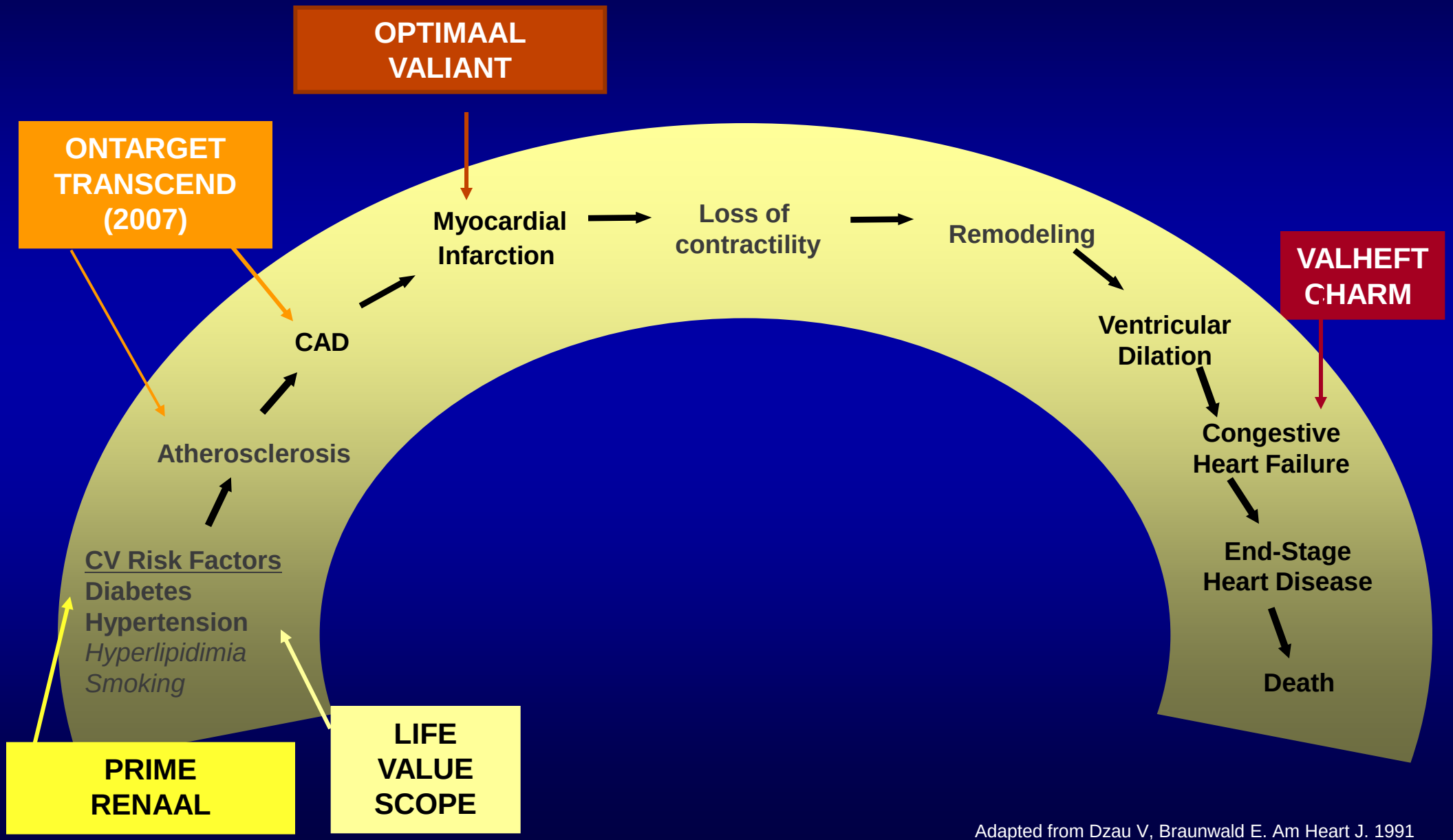


ACE-I provide substantial benefit in post-MI LVSD

ACE-I=Angiotensin converting enzyme inhibitors, EF=Ejection fraction, LVSD=Left ventricular systolic dysfunction, MI=Myocardial infarction, OR=Odds ratio

Flather MD et al. *Lancet* 2000;355:1575–1581

Role of ARBs Along the Cardiovascular Continuum



Adapted from Dzau V, Braunwald E. Am Heart J. 1991

Difference in Target Dosing Among ARB Trials

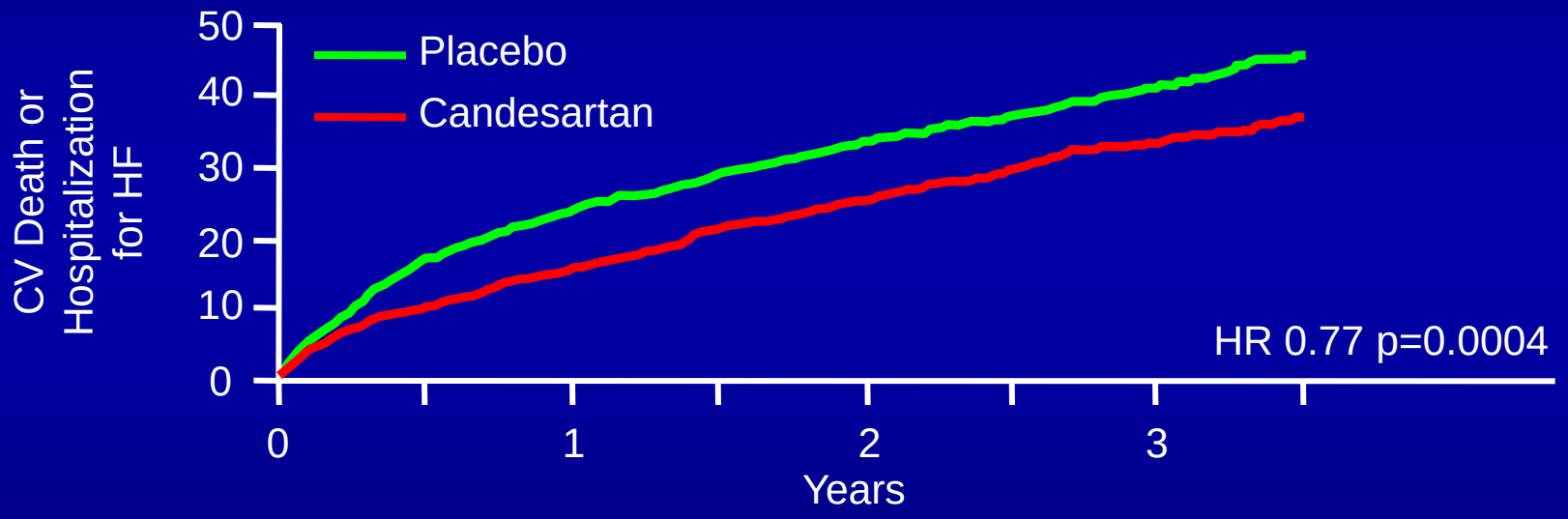
Trial	Patients	Study drug	Outcome
CHARM Overall	HF LVEF ≤40% LVEF >40%	Candesartan 32 mg qd vs Placebo	10% ↓ mortality 13% ↓ CV death 23% ↓ HF hosp
ELITE II	HF LVEF ≤40% ≥ 60 years	Losartan 50 mg qd vs Captopril 50 mg tid	Similar ↓ morbidity/mortality
OPTIMAAL	Post-MI + HF	Losartan 50 mg qd vs Captopril 50 mg tid	Mortality trend favors captopril No difference in morbidity
Val-HeFT	HF	Valsartan 160 mg bid vs Placebo + conventional HF Rx	No ↓ mortality 13.2% ↓ morbidity/mortality 28% ↓ HF hosp
VALIANT	Acute MI + HF/LV dysfunction	Valsartan 160 mg bid or Captopril 50 mg tid or Valsartan 80 mg bid + captopril 50 mg tid	Similar ↓ mortality/morbidity No added benefit with ACEI+ARB

Pfeffer MA et al. *Lancet*. 2003;362:759-66.
Pitt B et al. *Lancet*. 2000;355:1582-7.
Dickstein K et al. *Lancet*. 2002;360:752-60.
Cohn JN et al. *N Engl J Med*. 2001;345:1667-75.
Pfeffer MA et al. *N Engl J Med*. 2003;349:1893-906.

ARB Evidence: Secondary Prevention

Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) Alternative Trial

2,028 patients with symptomatic HF, LVSD (EF ≤40%), and intolerance to ACE-I randomized to candesartan (32 mg) or placebo for 34 months



ARB reduce CV events in those intolerant of ACE-I

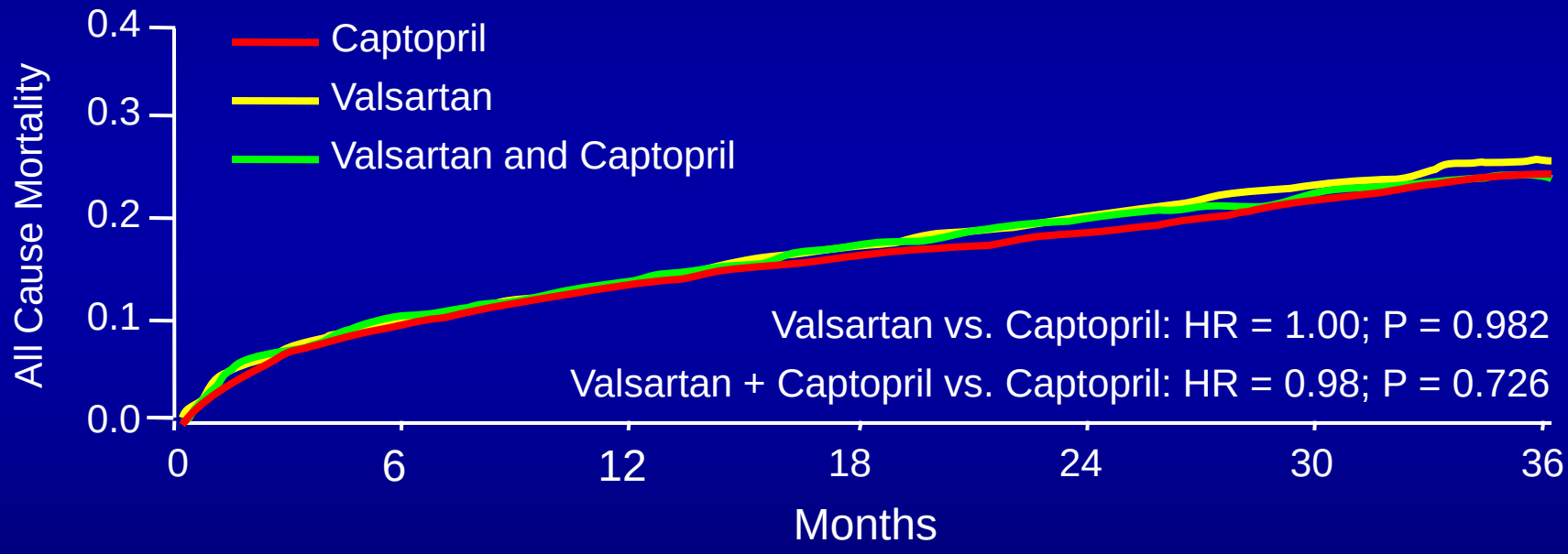
ACE-I=Angiotensin converting enzyme inhibitors,
ARB=Angiotensin receptor blockers, EF=Ejection fraction,
HF=Heart failure, LVSD=Left ventricular systolic dysfunction

Granger CB et al. *Lancet* 2003;362:772-777

ARB Evidence: Secondary Prevention

Valsartan in Acute Myocardial Infarction Trial (VALIANT)

14,703 patients with post-MI HF or LVSD (EF <0.40) randomized to captopril (50 mg tid), valsartan (160 mg bid), or captopril (50 mg tid) plus valsartan (80 mg bid) for 2 years

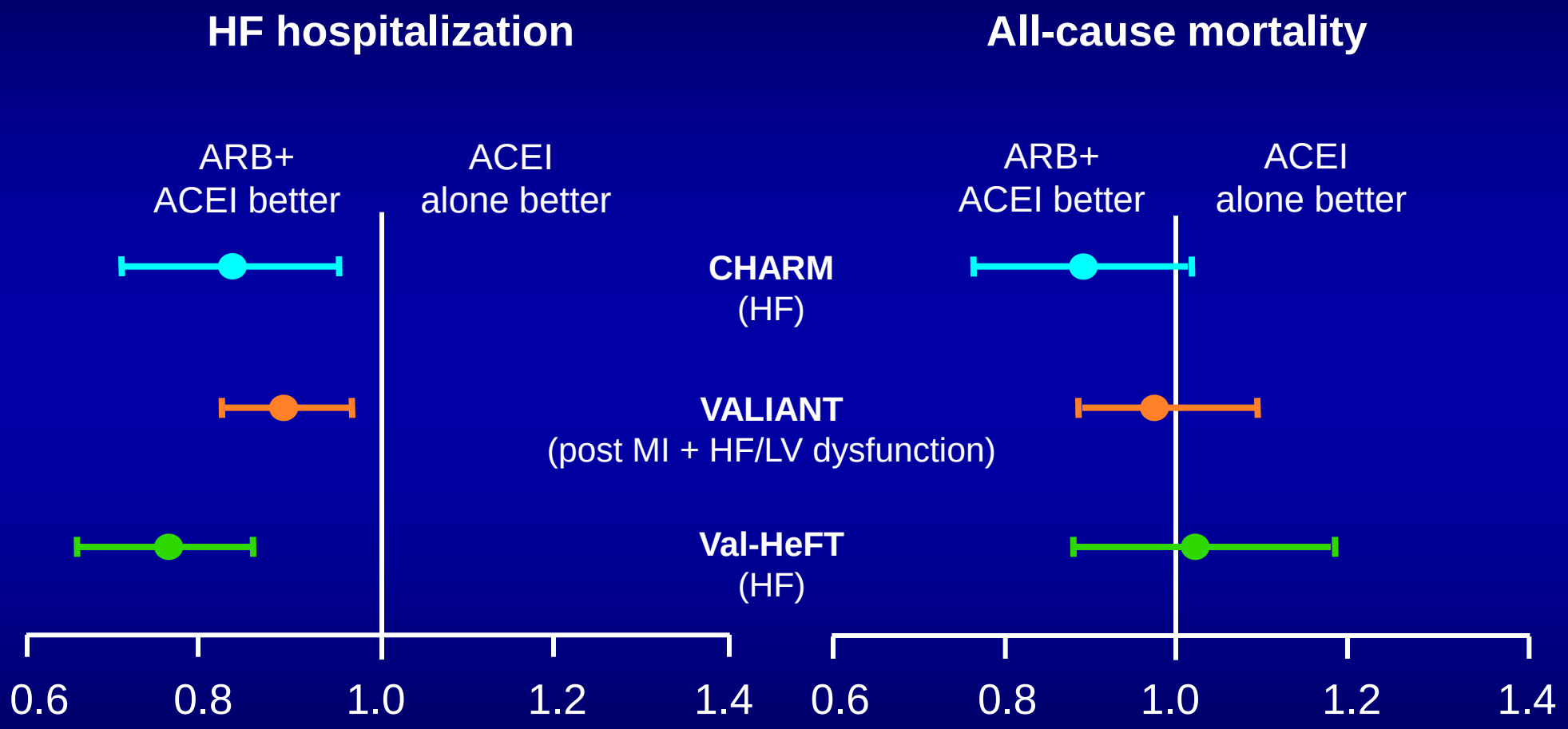


ARB provide similar efficacy to ACE-I in Post-MI LVSD

ACE-I=Angiotensin converting enzyme inhibitors,
ARB=Angiotensin receptor blockers, EF=Ejection fraction,
LVSD=Left ventricular systolic dysfunction

Pfeffer M et al. *NEJM* 2003;349:1893-1906

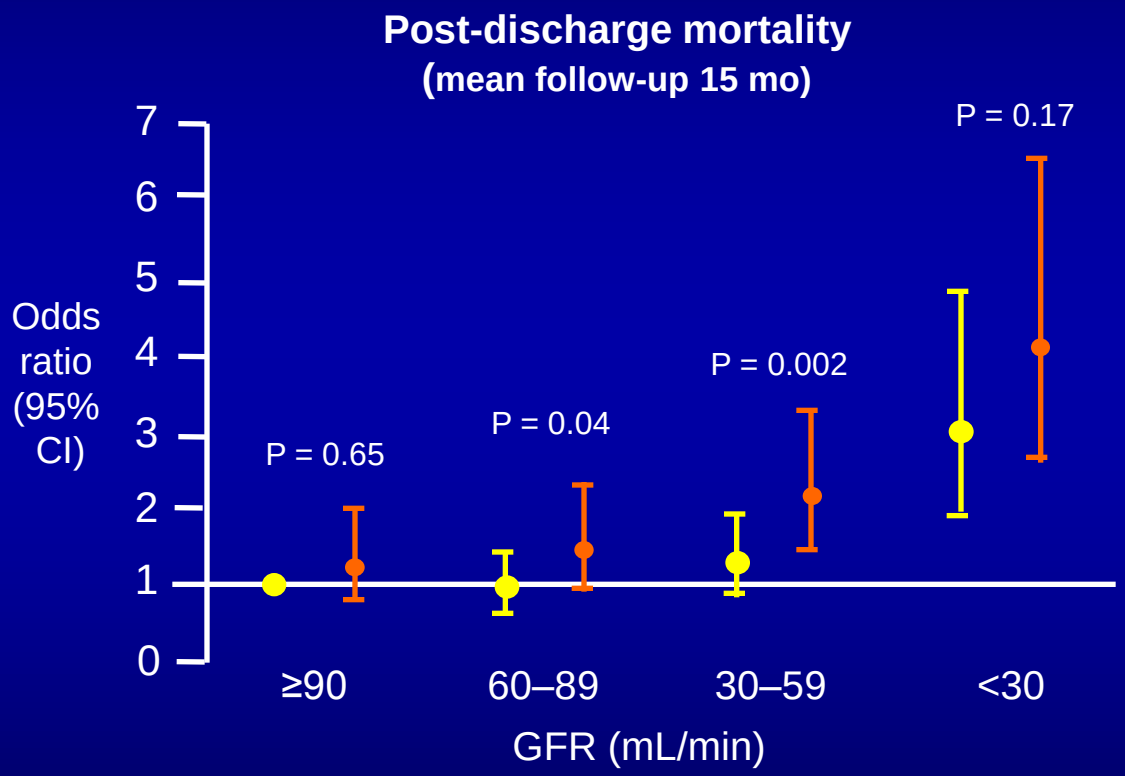
Benefit of ARB + ACE inhibitor in HF

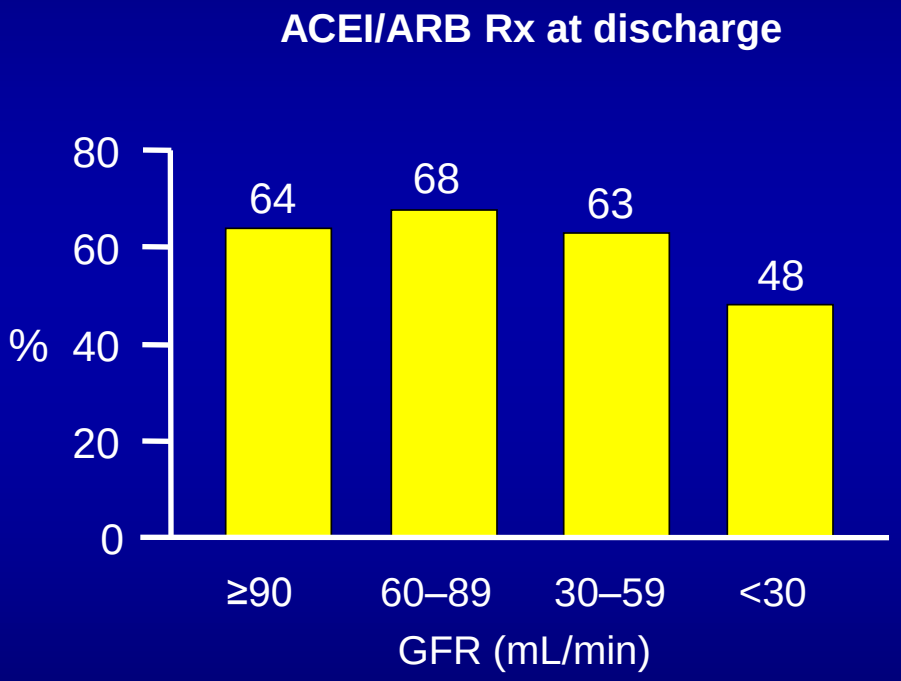


Voors AA, van Veldhuisen DJ. *Int J Cardiol*. 2004;97:345-8.

Impact of RAAS Modulation on Mortality in HF Patients with Renal Insufficiency

Minnesota Heart Survey





No ACEI/ARB at discharge

ACEI and/or ARB at discharge

4926 patients hospitalized with HF

Berger AK et al. *Circulation*. 2004;110 (suppl III):III-749.

ACC/AHA Recommendations on Role of ACEI in Post-MI Patients

UA/NSTEMI (2007)

Class I

ACEIs for patients with HF, LV dysfunction (EF<40%), hypertension, or DM (LOE: A)

STEMI (2007)

Class I

ACEI for all patients with EF≤40% and for those with hypertension, DM, or CKD (LOE: A)

ACEI for patients who are not lower risk (lower risk: normal EF in whom CV risk factors are well controlled & revascularization has been performed (LOE: B)

2007 ACC/AHA STEMI Guidelines Focused Update
2007 ACC/AHA UA/NSTEMI Guidelines

ACC/AHA Recommendations on Role of ARB in Post-MI Patients

UA/NSTEMI (2007)

Class I

ARB in patients who are intolerant of ACEI & have either clinical or radiological signs of HF & EF<40%

STEMI (2007)

Class I

ARB in all patients who are intolerant of ACEI & have HF or EF≤40% (LOE: A)

ARB in other patients who are ACEI intolerant & have hypertension (LOE: B)

2007 ACC/AHA STEMI Guidelines Focused Update
2007 ACC/AHA UA/NSTEMI Guidelines

ACEI/ARB in KAMIR

- 5627 AMI patients (63.8 ± 12.7 years, 3825 males)
- between Nov. 2005 and Dec. 2006 in KAMIR
- Followed-up during one year after discharge
- Primary endpoint: composite MACE (cardiac death, re-MI, CABG, TLR)

ARB alone group	• n=481, 63.4±13.1 years, 318 males
ACE inhibitor alone group	• n=3657, 63.1±12.6 years, 2570 males
Combination group	• n=270, 66.2±11.9 years, 179 males
Control group	• n=1219, 65.7±12.6 years, 758 males

CNUH Data, presented at 2008 Korean Society of Cardiology

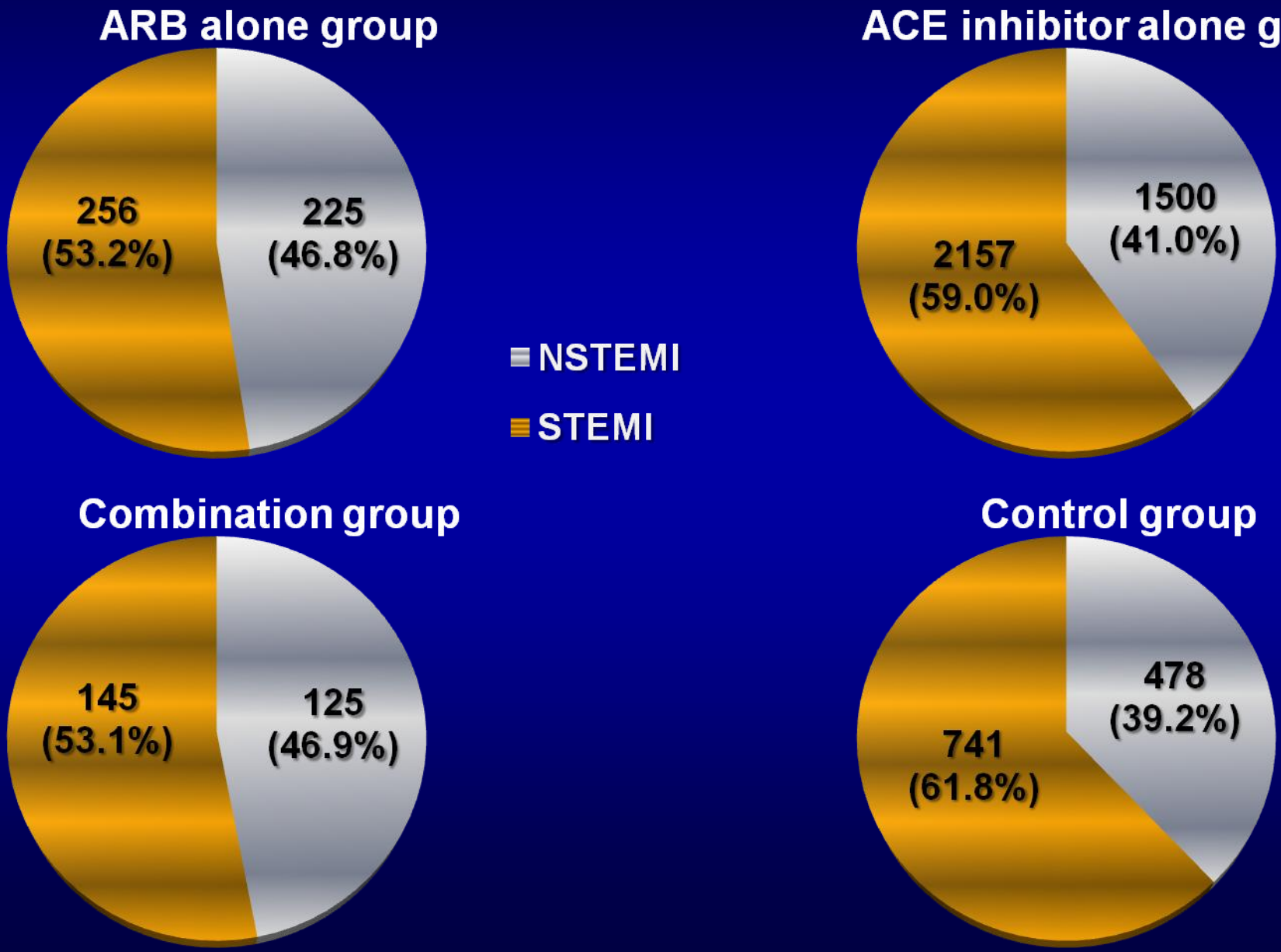
Result (I) - Comparison of baseline clinical characteristics

Variable	ARB alone group (N=481)	ACE inhibitor alone group (N=3657)	Combination group (N=270)	Control group (N=1219)	*p*
Age (years)	63.4±13.1	63.1±12.6	66.2±11.9	65.7±12.6	0.082
Male (%)	318(66.1)	2570(70.5)	179(66.3)	758(62.7)	0.062
Hypertension (%)	289(60.1)	1685(46.1)	172(63.7)	594(48.7)	<0.001
Diabetes mellitus (%)	161(33.5)	967(26.4)	100(37.0)	330(27.1)	<0.001
Smoking (%)	248(51.6)	2187 (59.8)	147(54.4)	580(47.6)	<0.001
Hyperlipidemia (%)	58(12.1)	336(9.2)	18(6.7)	88(7.2)	<0.001
Family history (%)	36(7.5)	274(7.5)	19(7.0)	51(4.2)	0.072
Summation of risk factors (N)	1.65±0.9	1.69±0.9	1.69±0.9	1.65±0.8	0.414

Result (II) - Symptoms and hemodynamics on admission

Variable	ARB alone group (N=481)	ACE inhibitor alone group (N=3657)	Combination group (N=270)	Control group (N=1219)	*P*
Chest pain (%)	374(77.8)	2978(81.8)	214(79.2)	931(77.5)	0.084
Dyspnea (%)	133(27.8)	1009(27.2)	78(29.0)	350(29.5)	0.107
Systolic blood pressure (mmHg)	131.3±29.5	130.4±28.3	137.0±35.2	135.4±34.0	0.118
Heart rate (n/min)	78.9±21.2	78.0±22.5	81.9±24.7	27.2±41.6	0.120
Shock (%)	26(5.4)	164(4.5)	14(5.1)	61(5.0)	0.562
Killip class (%)					
I or II	409(85.0)	3115(85.2)	230(85.1)	1025(84.1)	0.812
III or IV	72(15.0)	542(14.8)	40(14.9)	194(15.9)	0.627

Result (III) – Final Diagnosis



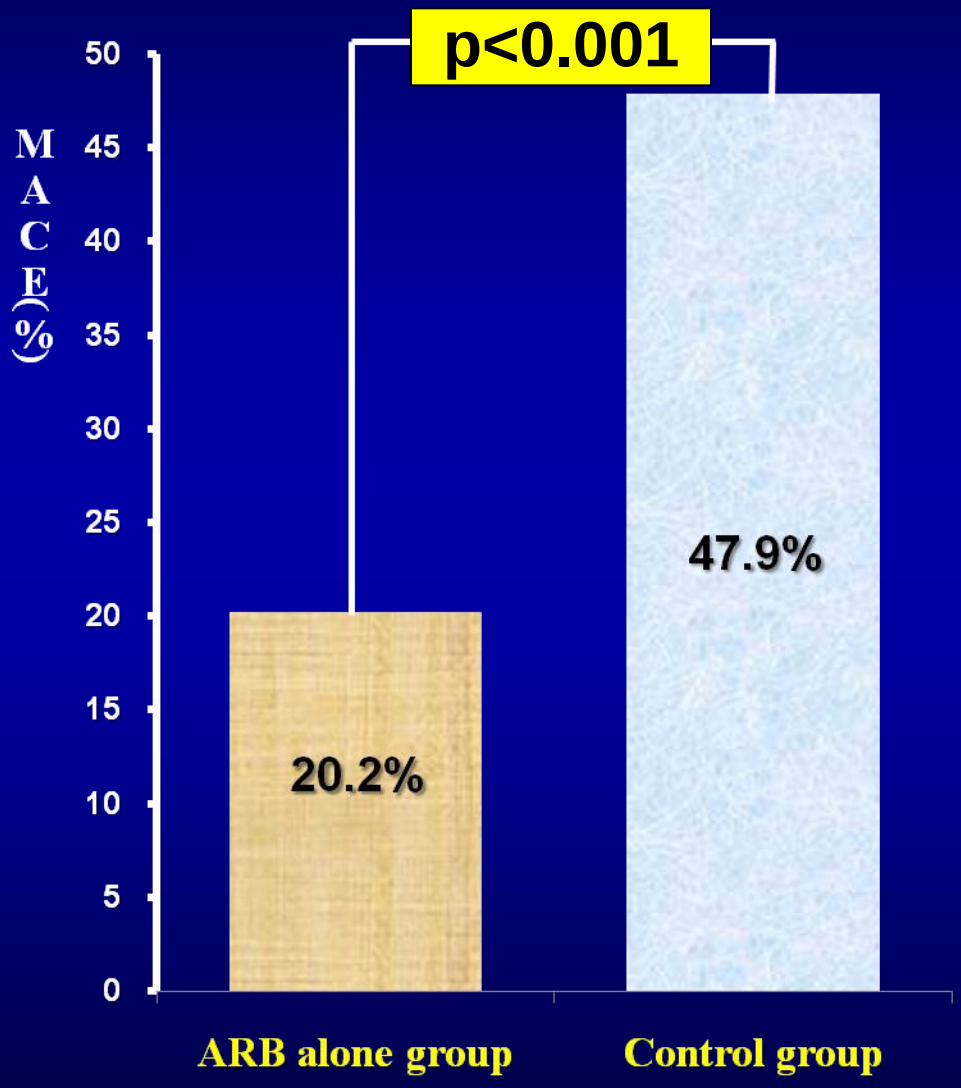
Result (IV) - ECG and echocardiogram findings

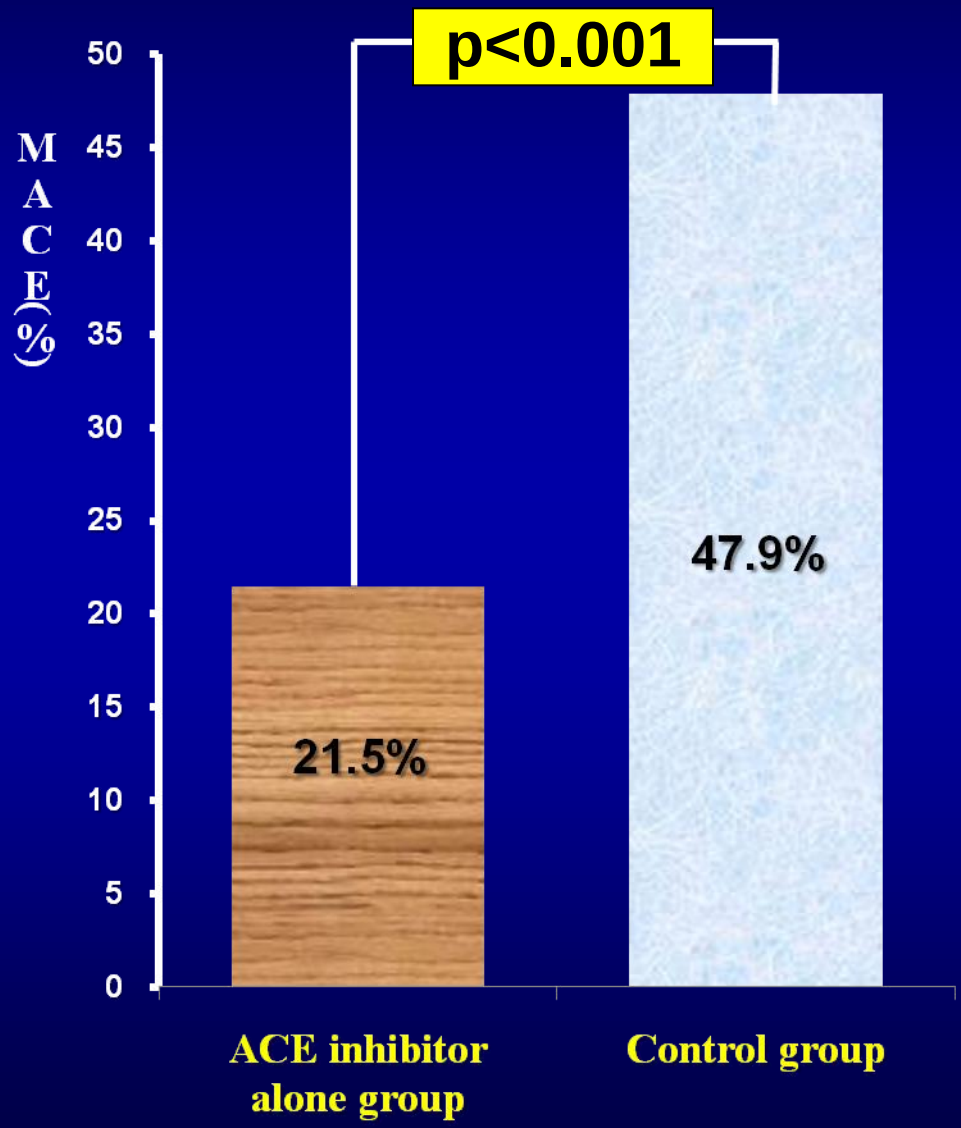
Variable	ARB alone group (N=481)	ACE inhibitor alone group (N=3657)	Combination group (N=270)	Control group (N=1219)	*P*
ECG finding					
LBBB	9(2.0)	66(1.8)	6(2.1)	195(1.6)	0.146
AV block	7(1.5)	47(1.3)	3(1.2)	18(1.5)	0.819
Atrial fibrillation	32(6.6)	227(6.2)	16(6.0)	85(6.9)	0.717
Ventricular tachycardia and fibrillation	10(2.1)	66(1.8)	46(1.7)	27(2.2)	0.454
Echocardiogram findings					
Left ventricular ejection fraction (%)	53.4±31.6	51.6±12.4	51.3±13.0	51.8±37.4	0.298
Total wall motion score	18.86±11.4	19.6±10.6	19.5±10.0	18.2±10.7	0.637

Result (V) – Laboratory finding

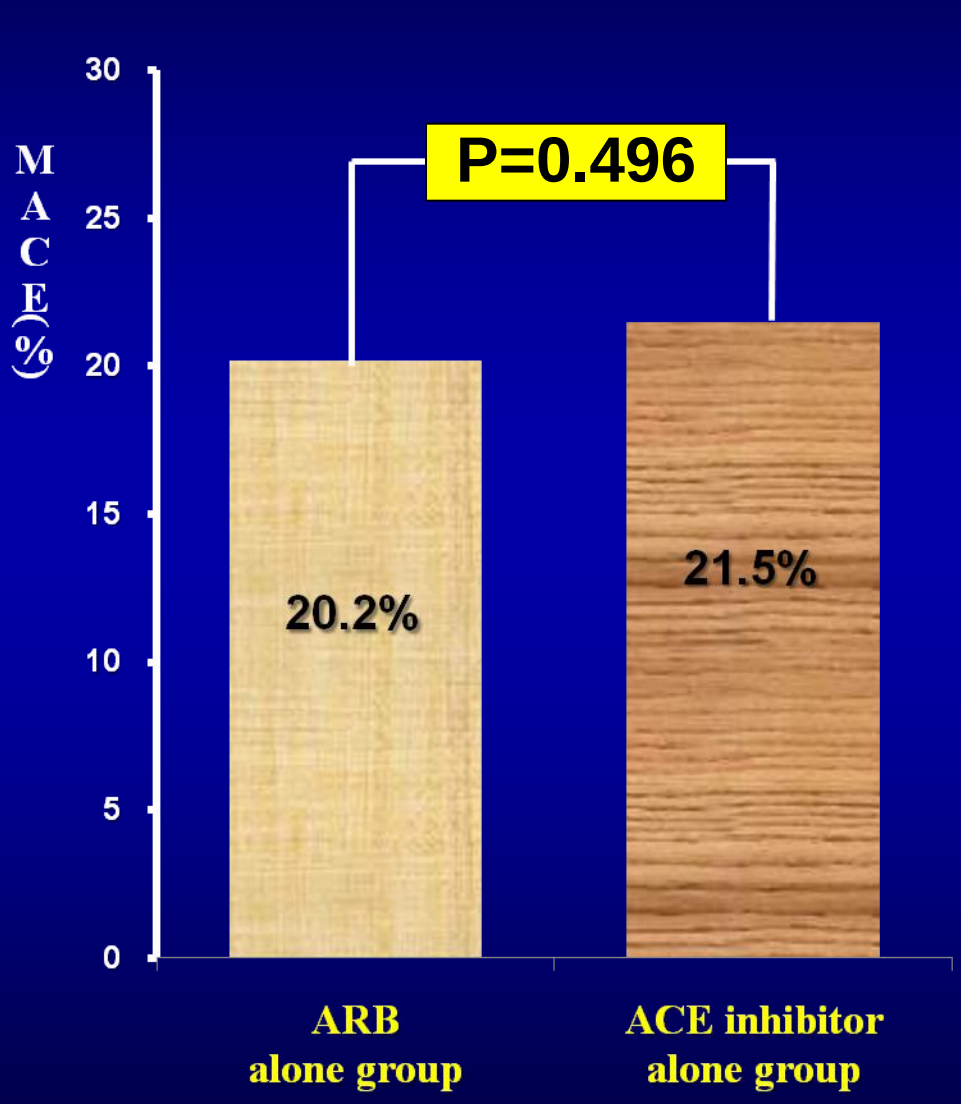
Variable	ARB alone group (N=481)	ACE inhibitor alone group (N=3657)	Combination group (N=270)	Control group (N=1219)	*P*
Creatine kinase-MB (U/L)	124.4±20.4	135.8±20.8	126.8±12.6	151.4±29.3	0.797
Troponin I (ng/ml)	35.4±6.1	53.0±18.7	48.1±8.2	56.7±19.2	0.372
Troponin T (ng/ml)	8.9±7.0	16.9±10.3	11.1±7.8	20.9±12.4	0.837
Triglyceride (mg/dl)	132.4±86.3	130.4±108.2	118.1±68.7	120.6±94.6	0.428
HDL-cholesterol (mg/dl)	45.4±27.2	46.3±28.1	44.6±12.2	47.6±63.7	0.967
LDL-cholesterol (mg/dl)	116.9±46.4	119.6±46.1	116.2±35.4	114.4±77.5	0.498
High sensitivity-CRP (mg/dl)	3.8±1.2	3.4±1.2	3.3±6.7	3.0±1.3	0.445
N-terminal pro-BNP (pg/ml)	4501.1±898.3	4526.3±603.6	5492.9±927.0	4246.1±882.0	0.009

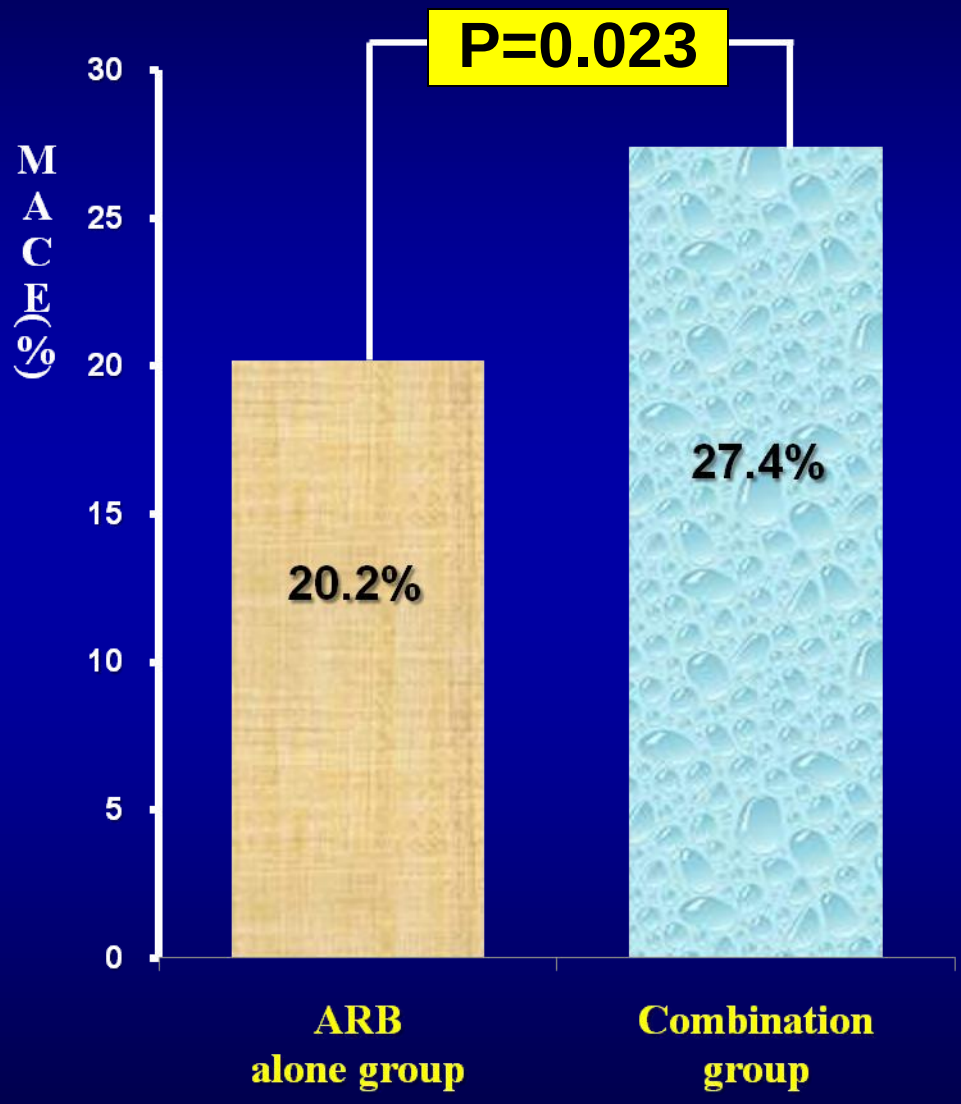
Result (VI) – Primary end points





Result (VI) – Primary end points





Result (VII) – Composite of primary end points

Variable	ARB alone group (N=481)	ACE inhibitor alone group (N=3657)	Combination group (N=270)	Control group (N=1219)	*P*
Composite of MACE (%)	97(20.2)	787(21.5)	74(27.4)	584(47.9)	<0.001
In hospital death (%)	28(5.8)	239(6.5)	10(3.7)	434(35.8)	<0.001
Cardiac death (%)	41(9.0)	351(10.0)	29(11.5)	468(40.2)	<0.001
Re-infarction (%)	7(1.7)	67(2.0)	8(3.5)	22(3.0)	0.203
CABG (%)	4(1.0)	22(0.7)	1(0.4)	10(1.4)	0.243
TLR (%)	16(3.8)	122(3.7)	14(6.1)	20(2.7)	0.135

Result (VIII) – Multivariate analysis of primary end points

	Odd ratio	95% confidence interval		p
		Lower	Upper	
Angiotensin receptor blocker treatment	0.971	0.964	0.978	<0.001
Old age	1.019	1.012	1.027	<0.001
Statin treatment	0.634	0.524	0.767	<0.001
Angiotensin converting enzyme inhibitor treatment	0.779	0.628	0.966	0.023
ST segment elevation myocardial infarction	1.141	0.953	1.366	0.152
Beta blocker treatment	0.864	0.704	1.061	0.164
Left ventricular ejection fraction	1.093	0.845	1.415	0.498

ACEI/ARB in KAMIR: Conclusion

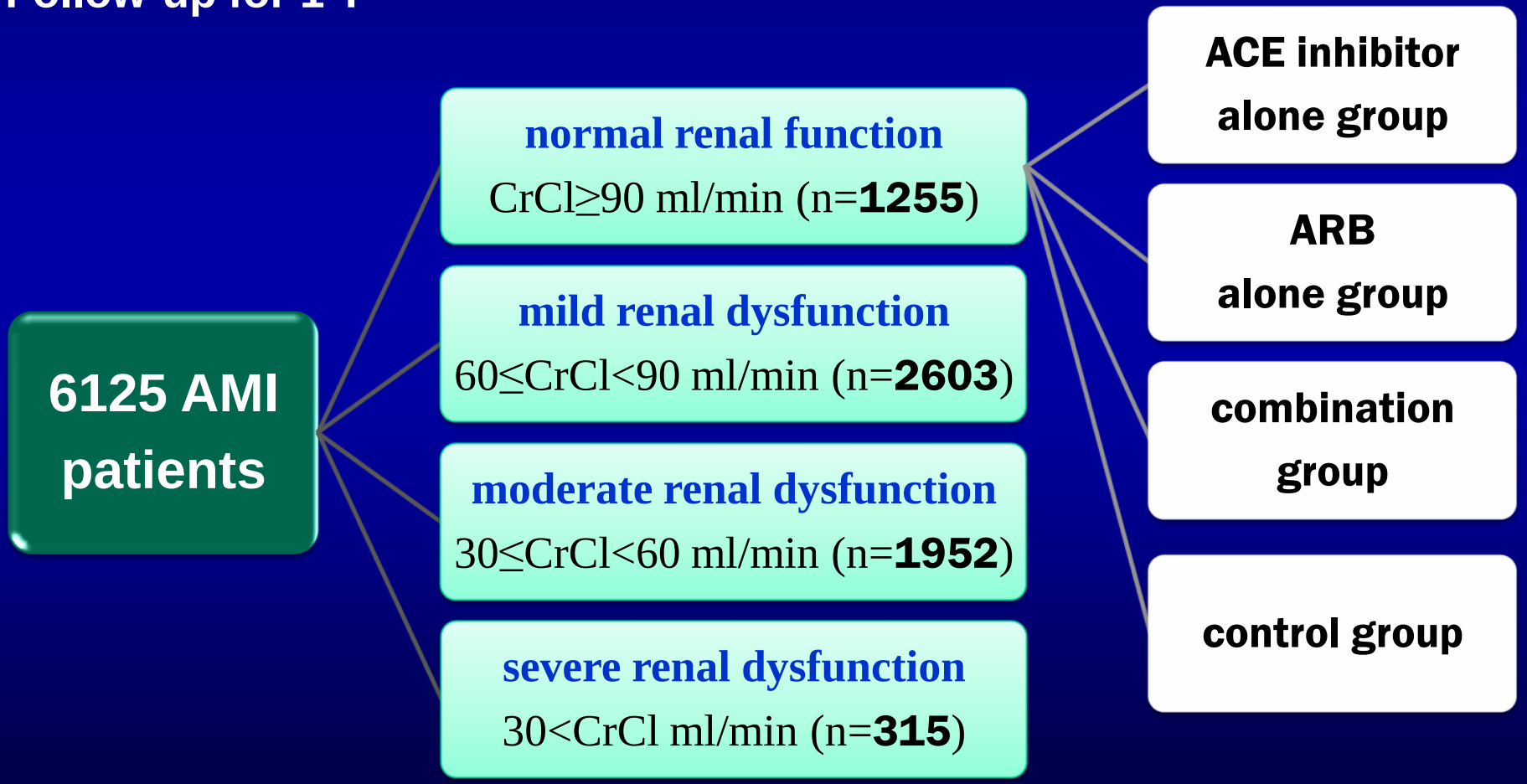
- The beneficial effects of ARB were **equivalent** to those of ACE inhibitor in Korean patients with AMI
- The combination of the two drugs was associated with more adverse events without an increase in benefit in KAMIR data
- **ARB may be recommended** in Korean patients with AMI as an **initial treatment**

CNUH Data, presented at 2008 Korean Society of Cardiology

ACEI/ARB in Renal Dysfunction in KAMIR

Nov. 2005 and Dec. 2007 in KAMIR who underwent successful PCI

Follow-up for 1 Y



CNUH Data, presented at 2009 Korean Society of Cardiology

Prescribed ACEI and ARB in KAMIR

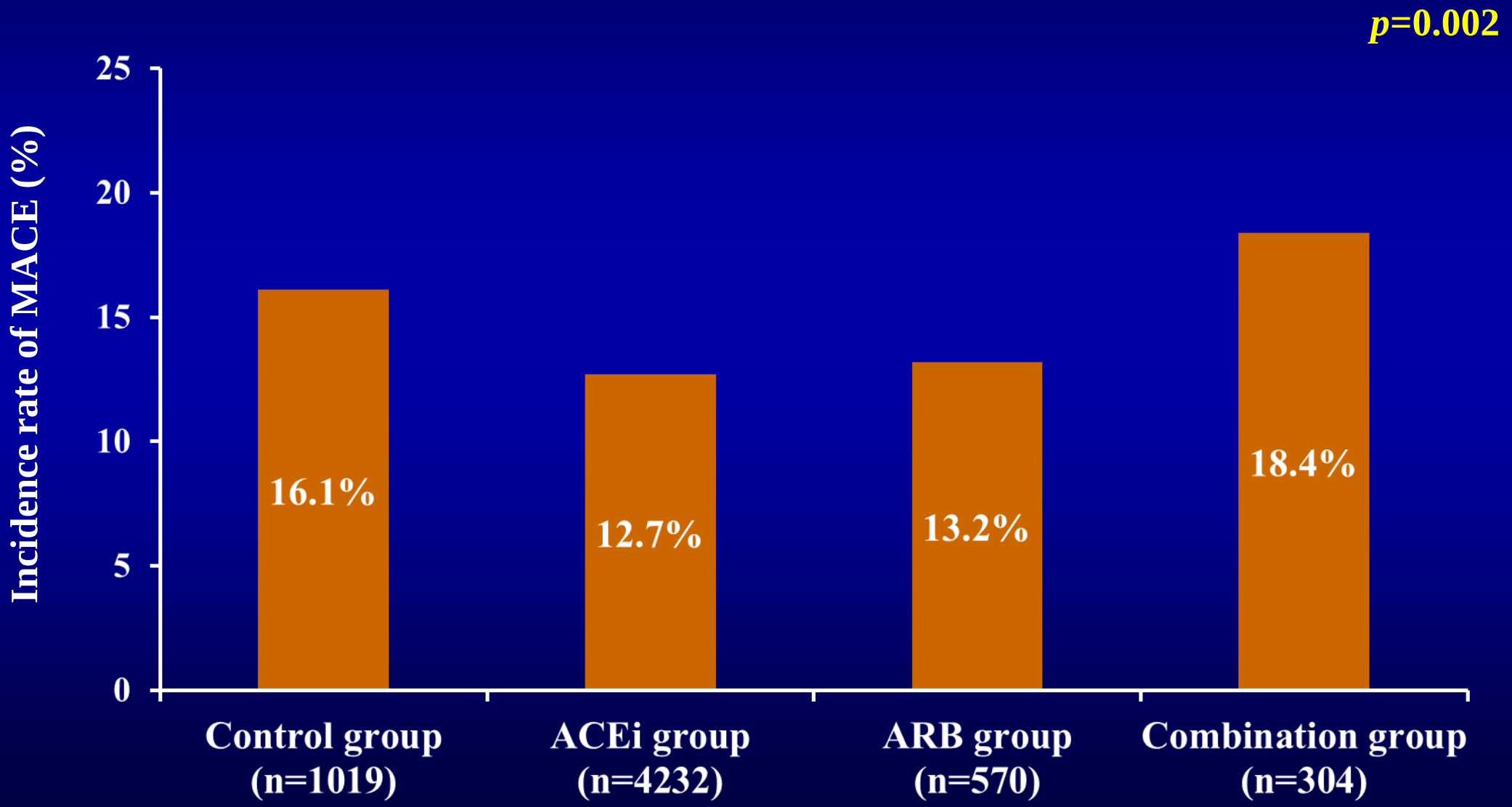
ACEi

- Ramipril (Tritace®)
- Imidapril (Tanatril®)
- Captopril (Capril®)
- Cilazapril (Inhibace®)
- Lisinopril (Zestril®)
- Perindopril (Acertil®)
- Enalapril (Renipril®)
- Fosinopril(Monopril®)
- Moexipril (Univasc®)

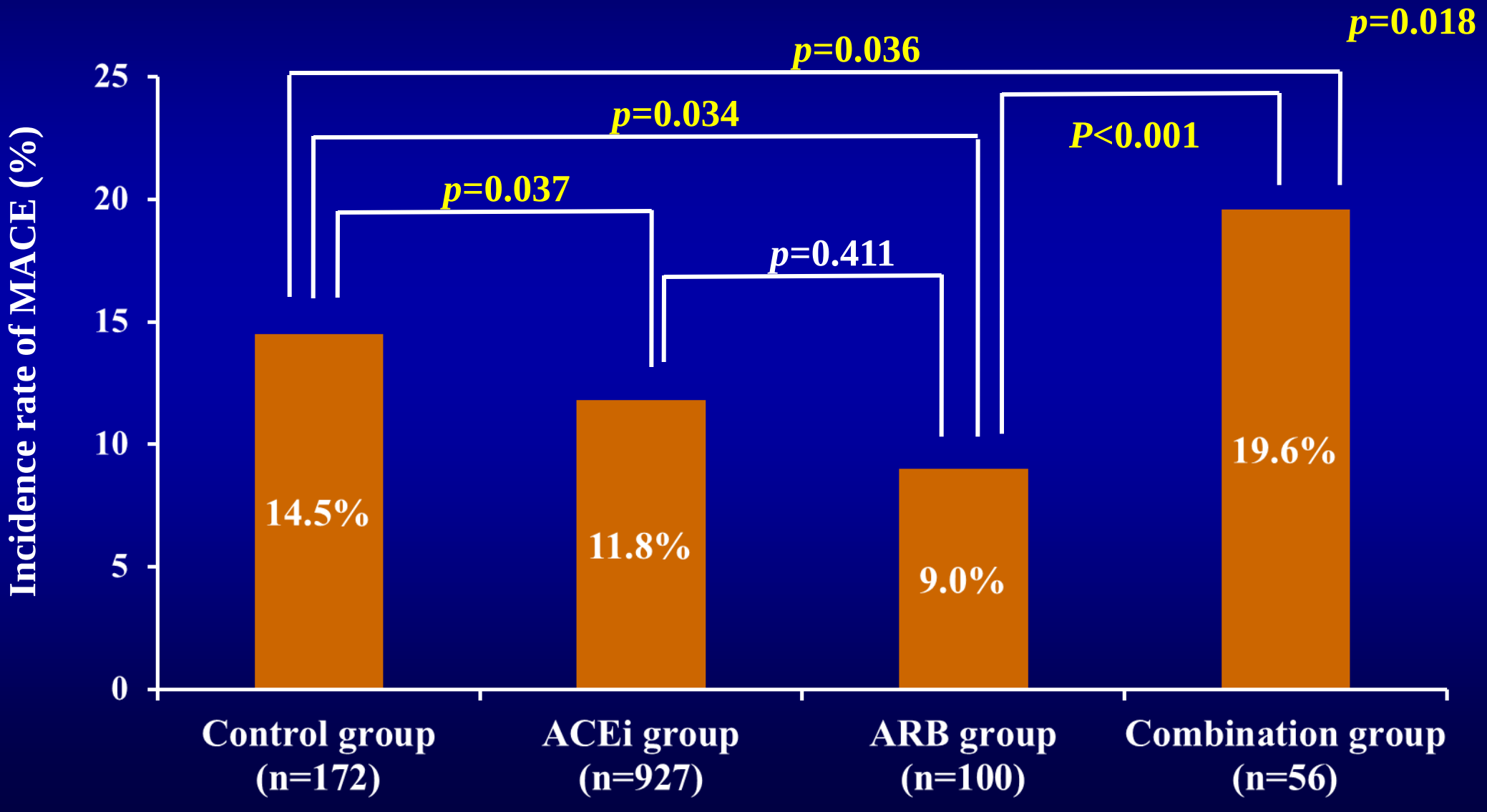
ARB

- Telmisartan (Pritor®, Micardis®)
- Candesartan (Atacand®)
- Ibesartan (Aprovel®)
- Olmesartan (Olmetec®)
- Valsartan (Diovan®)
- Losartan (Cozaar®)
- Eprosartan (Teveten®)

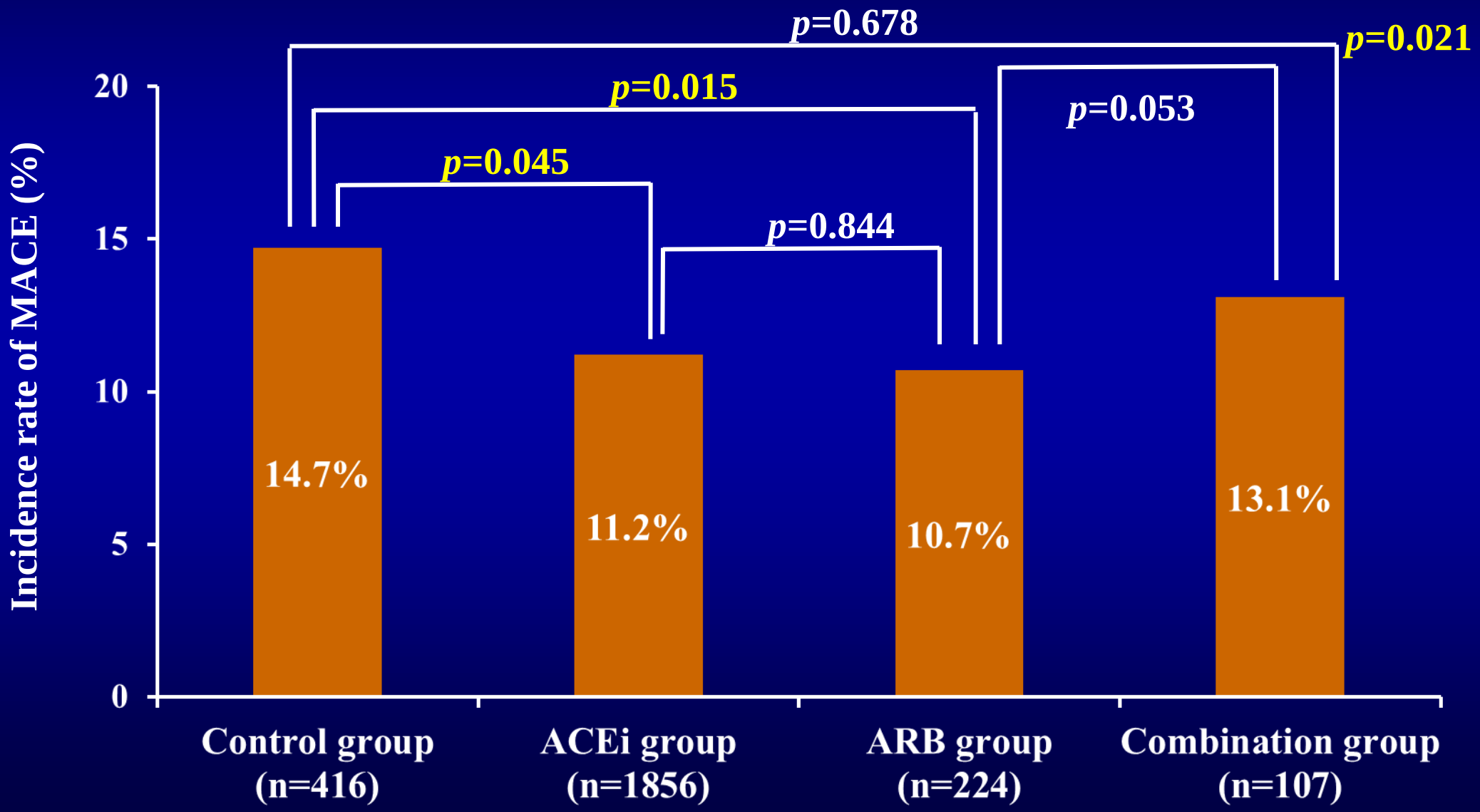
MACE: Overall Patients (n=6,125)



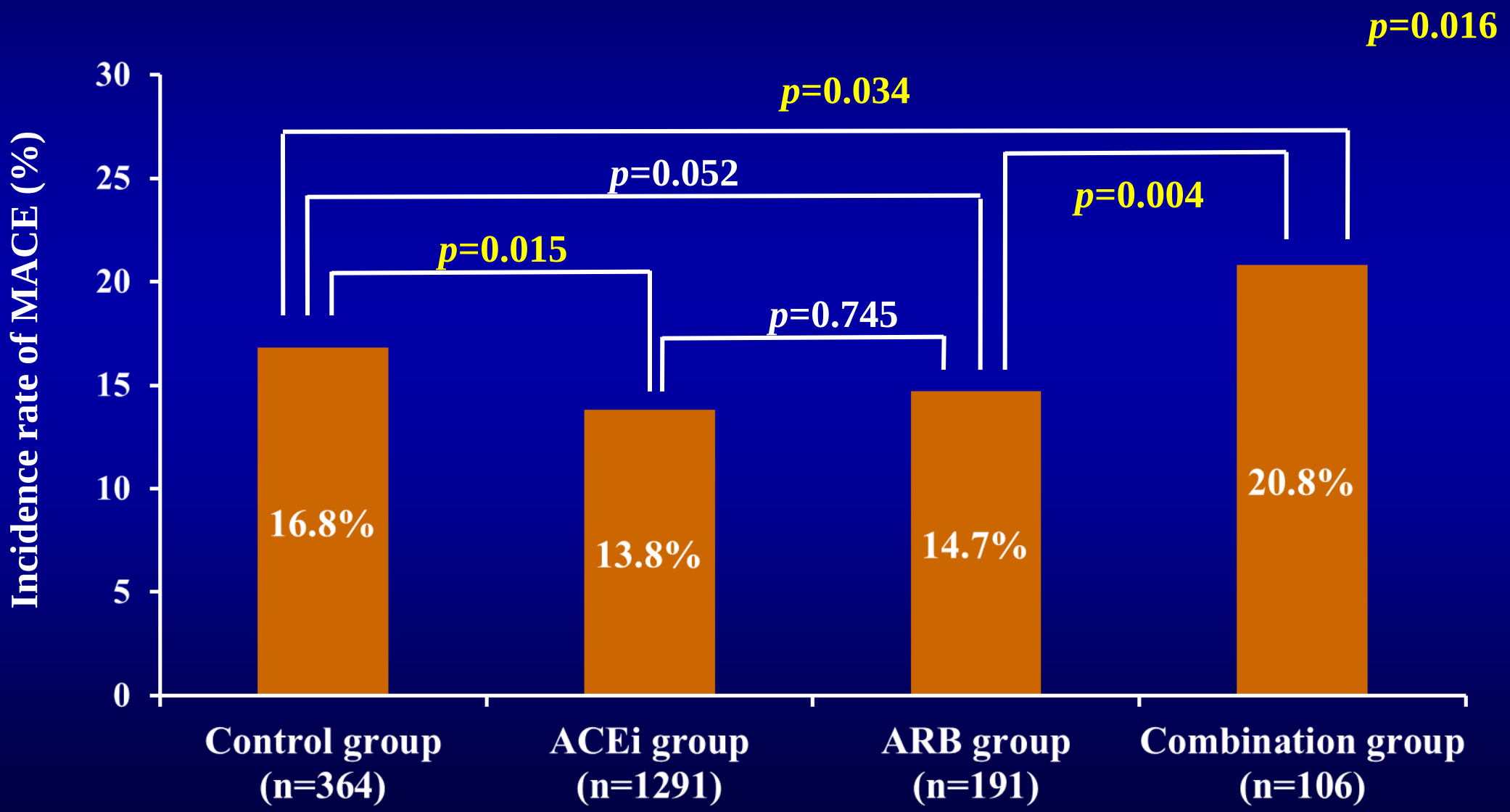
MACE: Normal Renal Function (n=1,255)



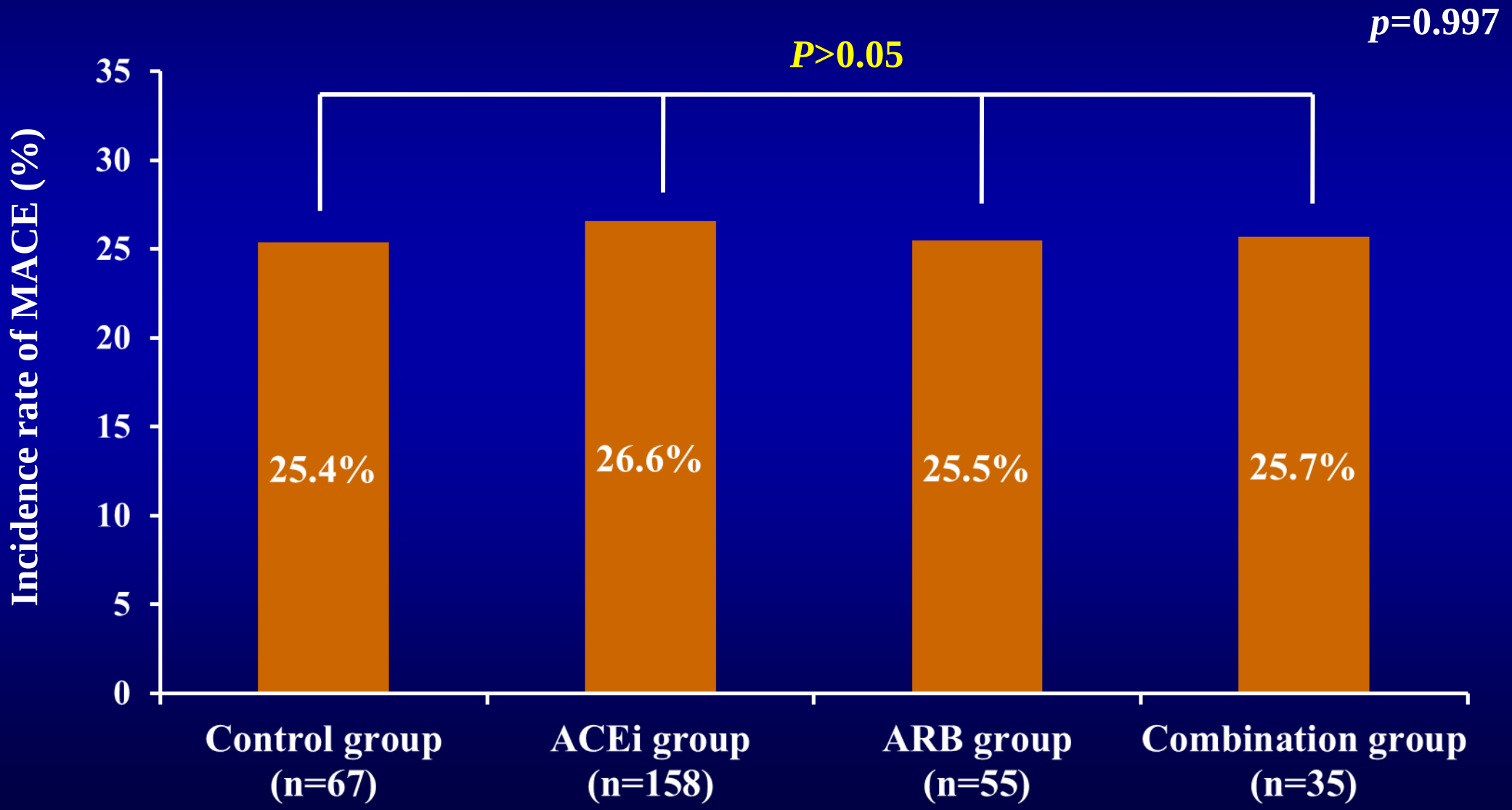
MACE: Mild Renal Dysfunction (n=2,603)



MACE: Moderate Renal Dysfunction (n=1,952)



MACE: Severe Renal Dysfunction (n=315)



ACEI/ARB in Renal Dysfunction in KAMIR: Conclusion

- ✓ ARB was equivalent to ACEI
- ✓ ACEI + ARB was associated with more adverse events than ACEI or ARB alone in patients with normal and mild to moderate renal dysfunction
- ✓ Neither monotherapy with ACEI or ARB nor combination therapy with ACEI + ARB showed clinical benefit in patients with severe renal dysfunction

CNUH Data, presented at 2009 Korean Society of Cardiology

Sildenafil + ACEI on Infarct Size in Swine

AMI induction by m-LAD occlusion with balloon for 40 min

24 swine (20-25kg) randomized to 4 groups:

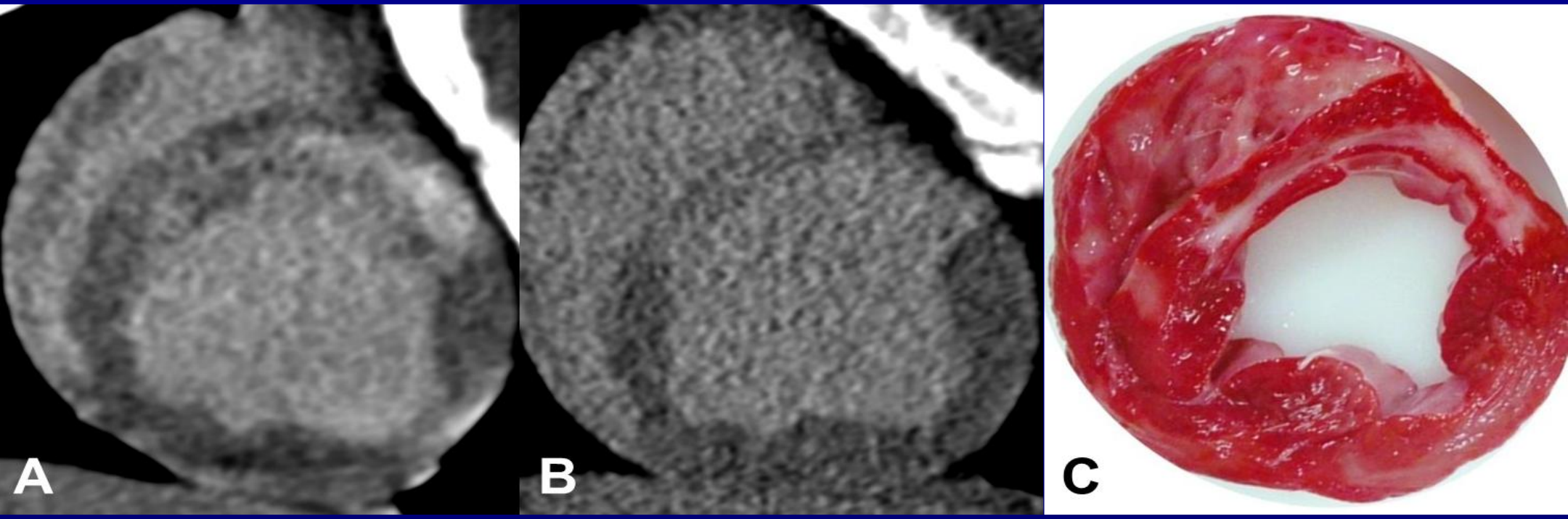
- **Group 1 (n=6):** control
- **Group 2 (n=6):** perindopril 2 mg daily
- **Group 3 (n=6):** sildenafil 50 mg daily
- **Group 4 (n=6):** perindopril 2 mg + sildenafil 50 mg daily

DE MDCT at 3-5 days and 30 days after AMI induction

Infarct size, LV function, Infarct thinning ratio were assessed

CNUH Data, Int J Cardiol 2011;46:459-60

DE MDCT & TTC Stain



Day 3 Day 30 TTC stain

CNUH Data, Int J Cardiol 2011;46:459-60

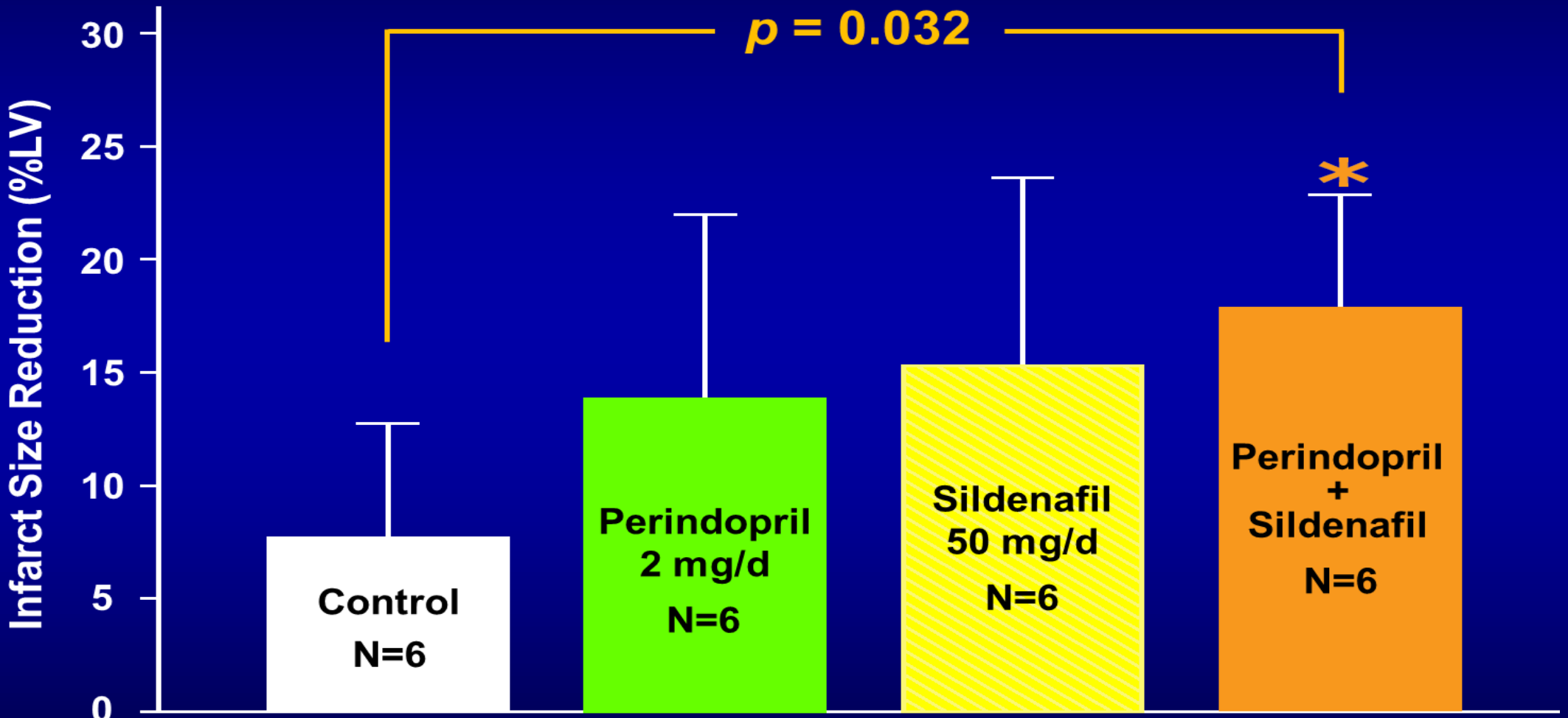
Results

Change between MDCT at day 30 & day 3-5:

Change between day 30 & day 3-5	Control (n=6)	Perindopril (n=6)	Sildenafil (n=6)	Perindopril + Sildenafil (n=6)	*p*
LVEF (%)	0.4±13.8	1.2±5.4	3.9±6.5	2.1±3.9	0.912
Infarct wall (mm)	-0.9±1.8	-1.7±1.3	-1.7±1.5	-2.6±1.9	0.693
Non-infarct wall (mm)	-1.3±0.8	-1.1±0.5	-1.6±0.6	-1.1±0.3	0.458
Infarct thinning ratio	-0.28±0.27	-0.29±0.21	-0.44±0.21	-0.51±0.22	0.414
Infarct size (% LV)	-7.7±5.1	-13.8±8.2	-15.3±8.3	-17.8±5.0	0.086

CNUH Data, Int J Cardiol 2011;46:459-60

Infarct Size Reduction



IS change between day 3-5 & 30. Columns are shown as mean ± SD.

CNUH Data, Int J Cardiol 2011;46:459-60

Animal Experiment Study at CNUH

Effects of Fimasartan in A Porcine Model of Ischemic Heart Failure

Heart Research Center Designated by Korea Ministry of Health and Welfare,
Chonnam National University Hospital,
Gwangju, Korea

Objective

To investigate whether fimasartan, a new ARB, could limit LV remodeling after MI by reducing infarct size and improving LV function in a porcine model of ischemic heart failure.

Methods

Creation of Acute Myocardial Infarction:

- Aspirin 300 mg, clopidogrel 300 mg loading
- After 10,000 U of heparin, 7F coronary artery guiding catheter at opening of coronary artery under fluoroscopic guidance
- Placement of balloon (3.0*20 mm) just distal to first diagonal branch or septal branch and complete occlusion by balloon dilatation (up to 8 atm) for 40-min

Methods

Study groups and medications:

Animal Cath Lab of CNUH

50 swine (20-25kg) were randomized into 5 groups

Group 1 (n=10): sham operation

Group 2 (n=10): AMI only

Group 3 (n=10): perindopril 2 mg daily post-MI

Group 4 (n=10): valsartan 160 mg daily post-MI

Group 5 (n=10): fimasartan 30 mg daily post-MI

Methods

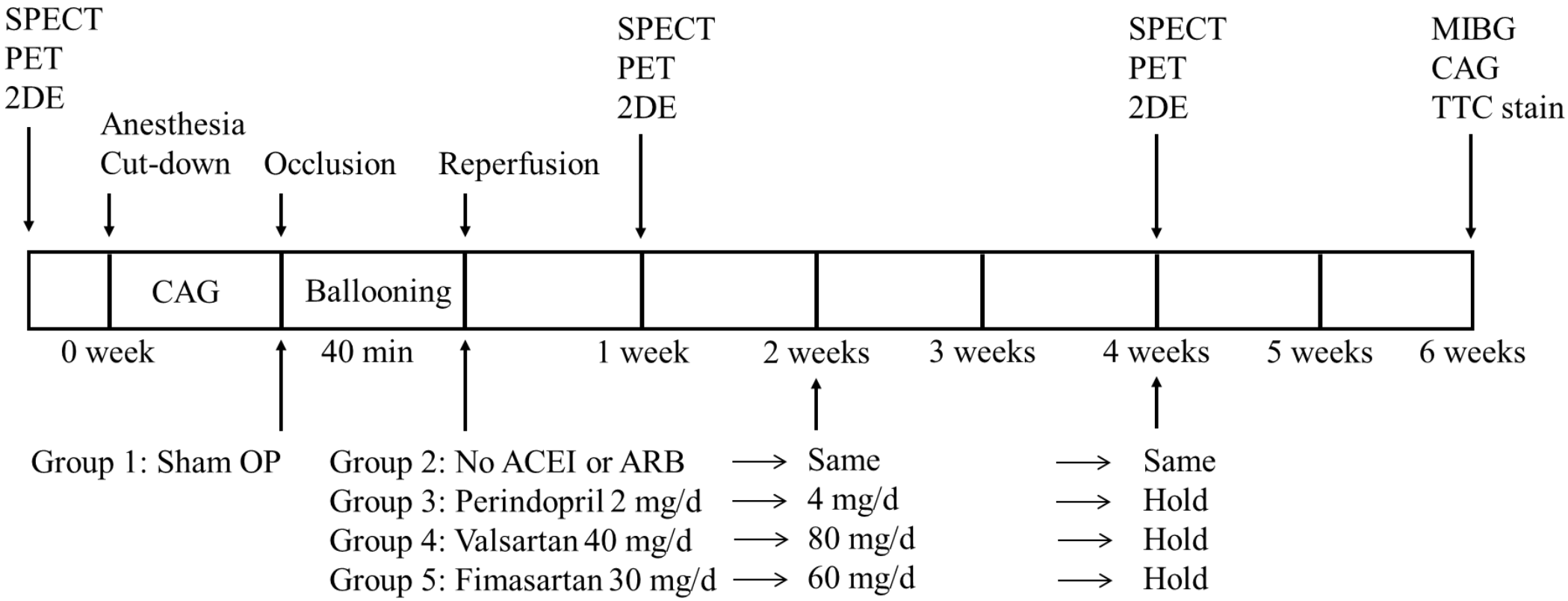
Study groups and medications:

Drug dosage was arbitrarily selected as half the initial oral dose in adult humans:

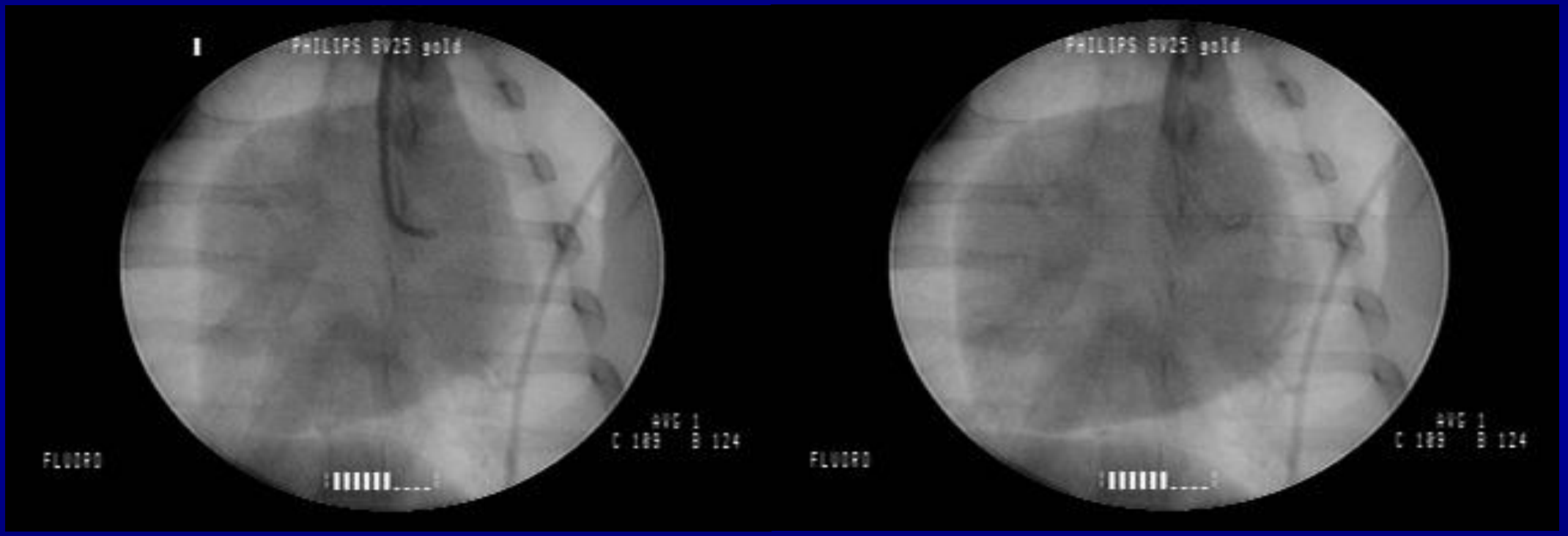
- Perindopril 2 mg daily
- Valsartan 40 mg daily
- Fimasartan 30 mg daily

Study medications will be started within 6~12 hours after the experiment and maintained for four weeks afterwards

Study Design



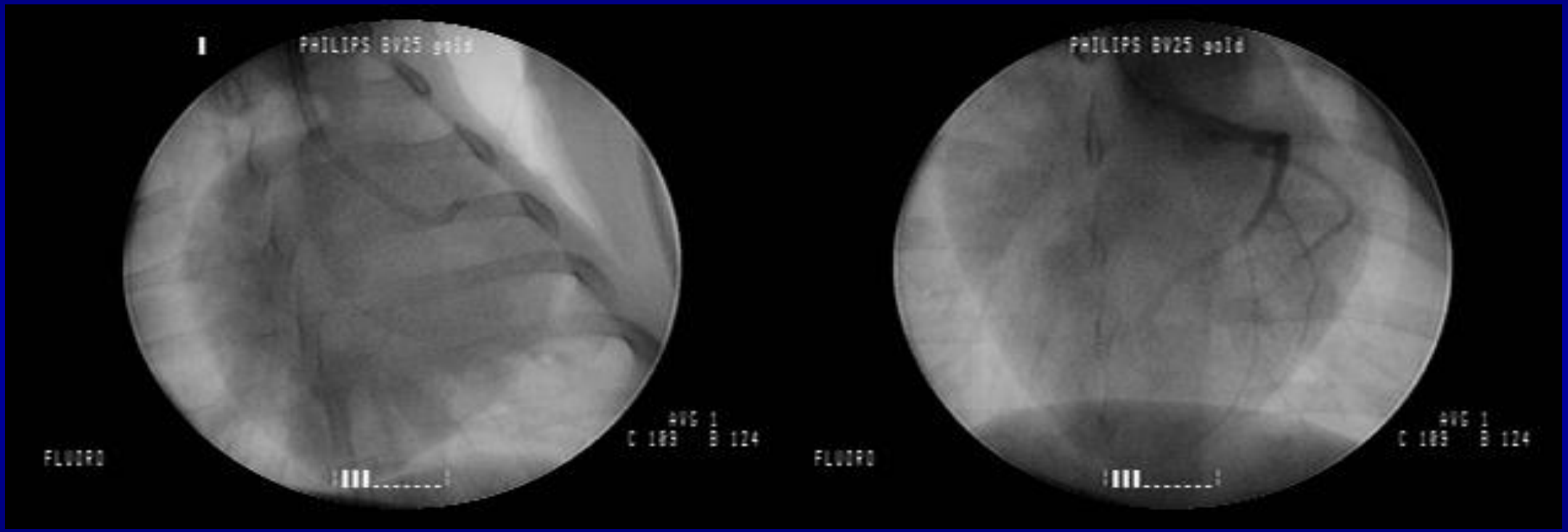
Induction of Acute MI



Baseline

3.0 mm balloon in m-LAD
6-8 atm for 40 min

Induction of Acute MI



Immediately after MI induction

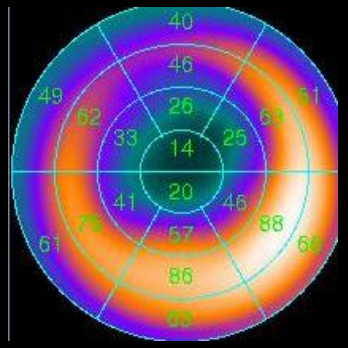
FU 30 days later

Methods: Parameters
Tc-99m sestaMIBI perfusion SPECT and cardiac F-18 FDG PET

SPECT&PET

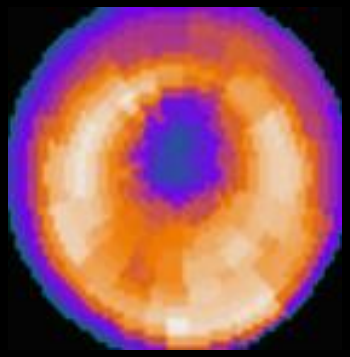
Volume	11ml
EDV	17ml
ESV	4ml
EF	79%

Baseline



SPECT

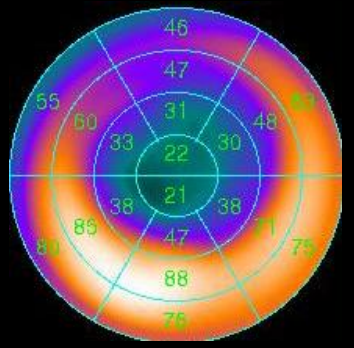
Volume	48ml
EDV	54ml
ESV	32ml
EF	40%



FDG PET

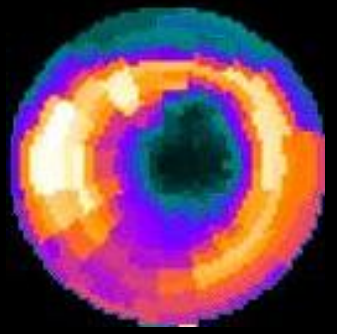
Matched defect
Mismatched defect

After MI (1week)



SPECT

Volume	72ml
EDV	101ml
ESV	53ml
EF	47%



FDG PET

Matched defect
Mismatched defect

After MI (4week)

Methods

Infarct size and viability assessment

At day 3-5 and day 30
99m-Tc Tetrofosmin SPECT
Stress-rest protocol (adenosine)
Infarct size measured as a percent of the LV

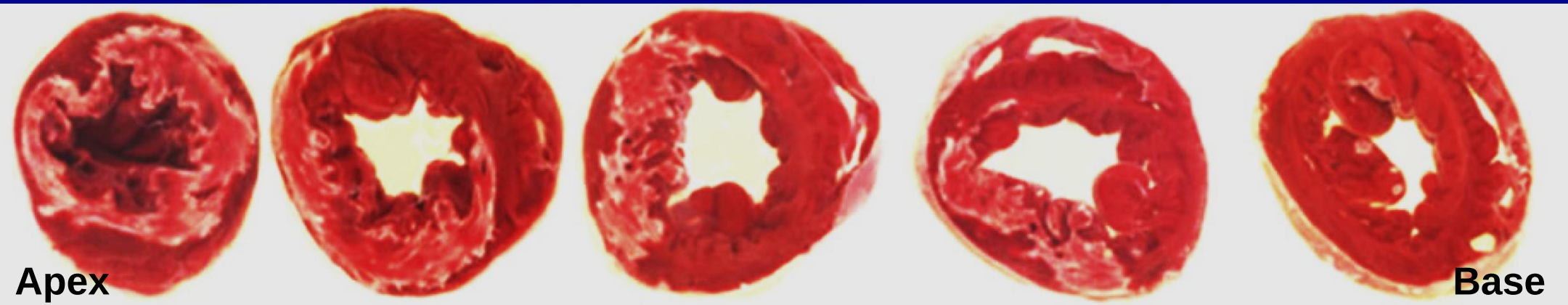
Echocardiographic analysis

At day 3-5 and day 30
Wall motion score index
LVEF, LVESV, LVEDV, DT, E/E’

Methods

Histomorphometric Infarct Size by TTC Stain

- ✓ Infarct volume (mL) and LV volume (LVV, mL)
  = ∑ (summed area of each slice [mm^2] x slice thickness [3 mm])
- ✓ Mean infarct volume and LVV were then converted to mass unit (g) assuming a specific gravity of the myocardium of 1.05 g/mL. Infarct size was then expressed as % LVA



Results (MIBG and Pathology)

	Sham (n=3)	AMI only (n=3)	Perindopril (n=3)	Valsartan (n=3)	Fimasartan (n=3)	*P*
MIGB scan (6 weeks)						
H/M ratio (15 min)	22.7±3.5	16.7±3.5	20.7±5.1	19.4±1.1	20.4±3.7	0.445
H/M ratio (3hr 50 min)	20.4±3.6	14.8±3.2	18.9±4.4	17.3±1.4	18.1±3.4	0.455
Washout (%)	10.7±3.2	11.0±1.2	8.7±2.0	11.3±3.6	11.0±0.3	0.736
Infarct size (% LV)	0	8.5±1.4	5.8±4.4	10.9±1.8	4.5±2.4	0.366

Preliminary Results and Clinical Implications

Fimasartan used post-MI

- ✓ Is comparable to ACEI or other ARB in reducing LV remodeling in porcine model of AMI
- ✓ may confer additional cardioprotective benefit comparable to that of other ACEI or ARB by restoring cardiac sympathetic nerve activity
- ✓ May improve clinical outcome in patients with AMI and ischemic heart failure

Conclusions

Kanarb®
Fimasartan

1. Fimasartan is a new **safe** type1 angiotensin II receptor antagonist

2. Fimasartan has **excellent BP lowering and Cardiovascular protective** effect

Fimasartan Will Be a King of ARB!