Comparison of Candesartan vs Amlodipine and vs. ACEI in High-Risk Hypertension

CASE-J Study and HIJ-CREATE Studies

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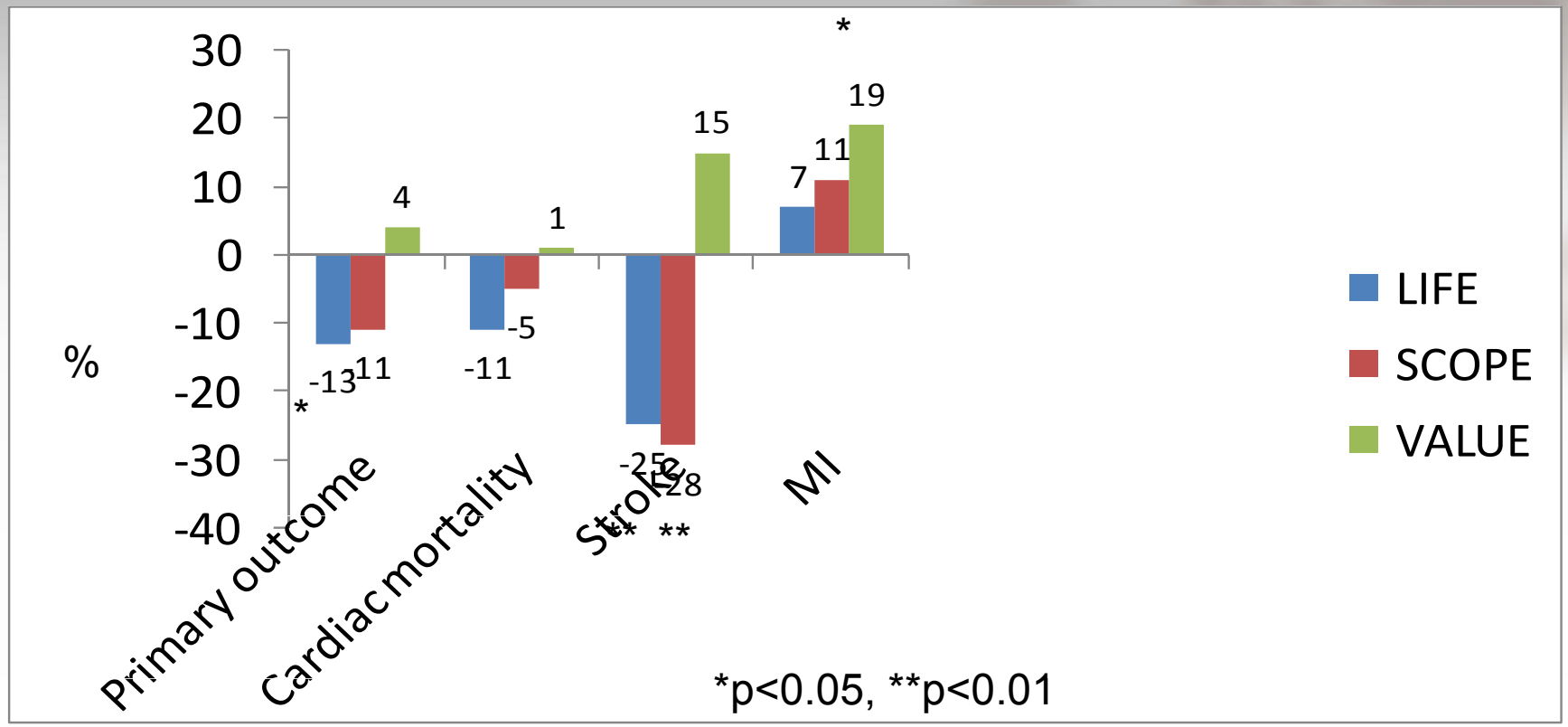
박 창 규

Key clinical trials of ARBs per clinical condition

High-risk Hypertension	Coronary artery Ds/ Myocardial infarction	DM &/or Renal Ds	Congestive Heart failure
LIFE	VALIANT	RENAL	ELITE I and II
SCOPE	OPTIMAAL	IDNT	Val-HeFT
VALUE		IRMA 2	CHARM

High-risk Hypertension trials ; Cardiovascular and Outcome Results



BP difference; LIFE 0.9/0.2 mmHg, SCOPE 3.1/1.6 mmHg, VALUE -2.1/-1.7mmHg

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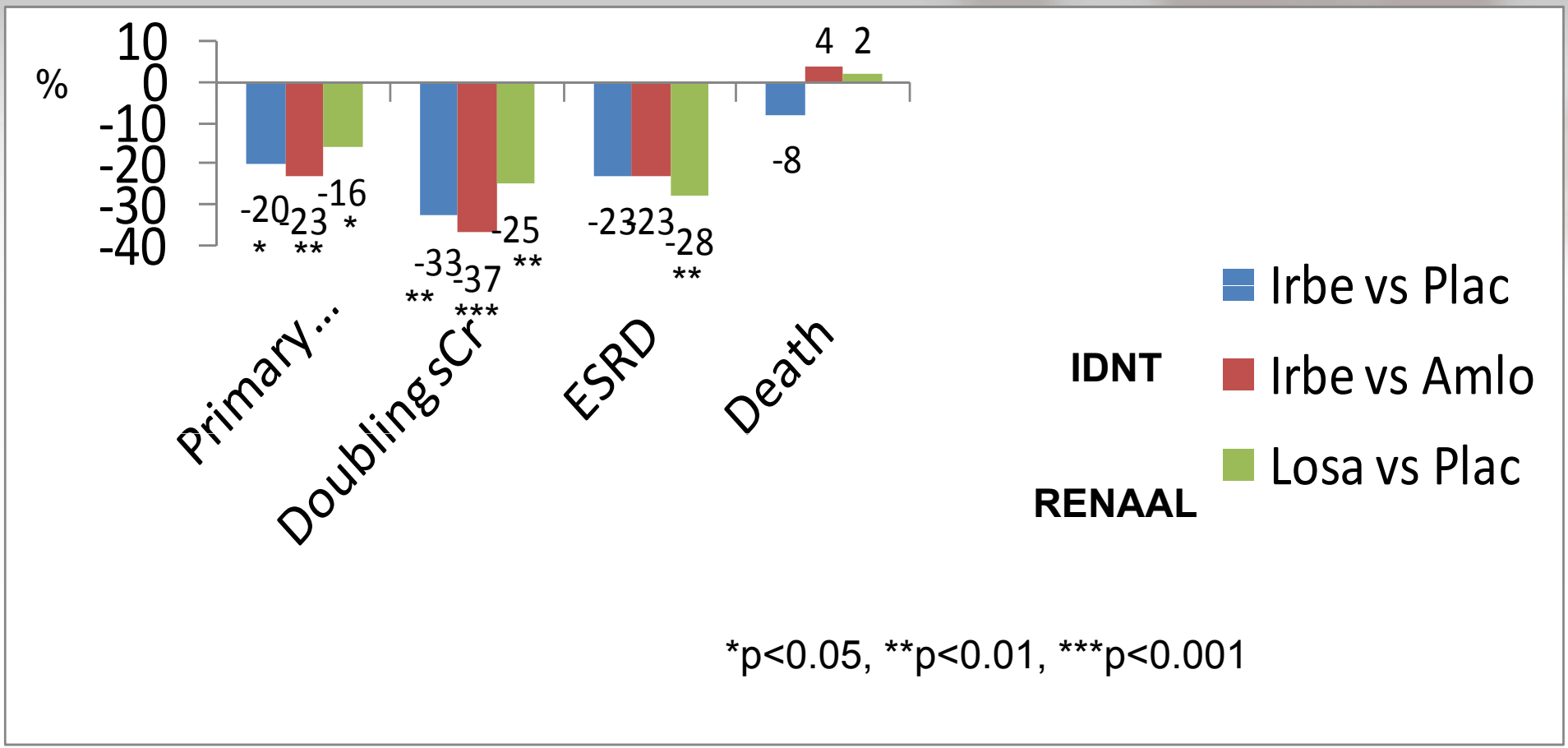
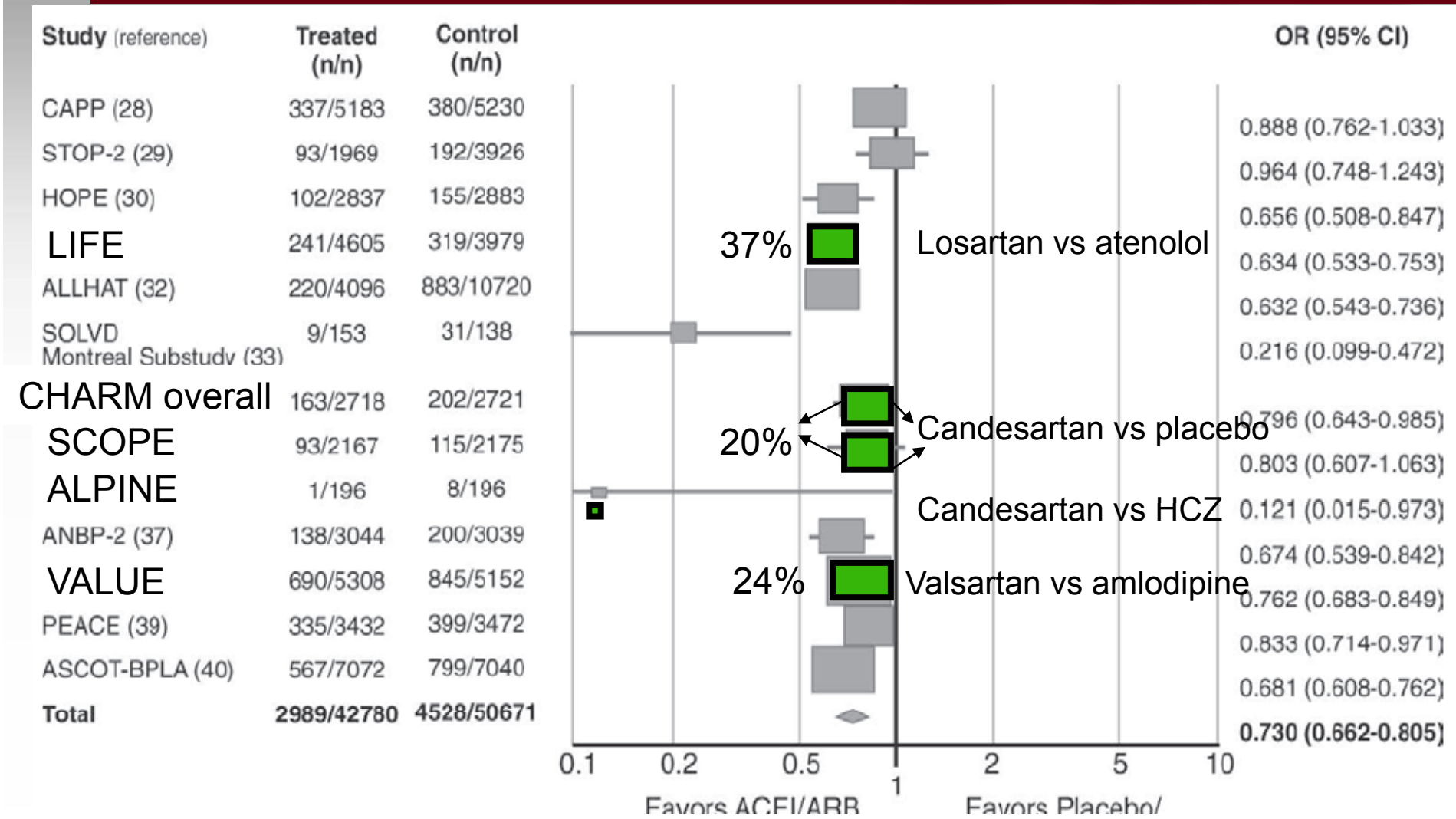
Reduction of Endpoints in NIDDM with ARB Losartan (RENAAL) & Irbesartan (IDNT)

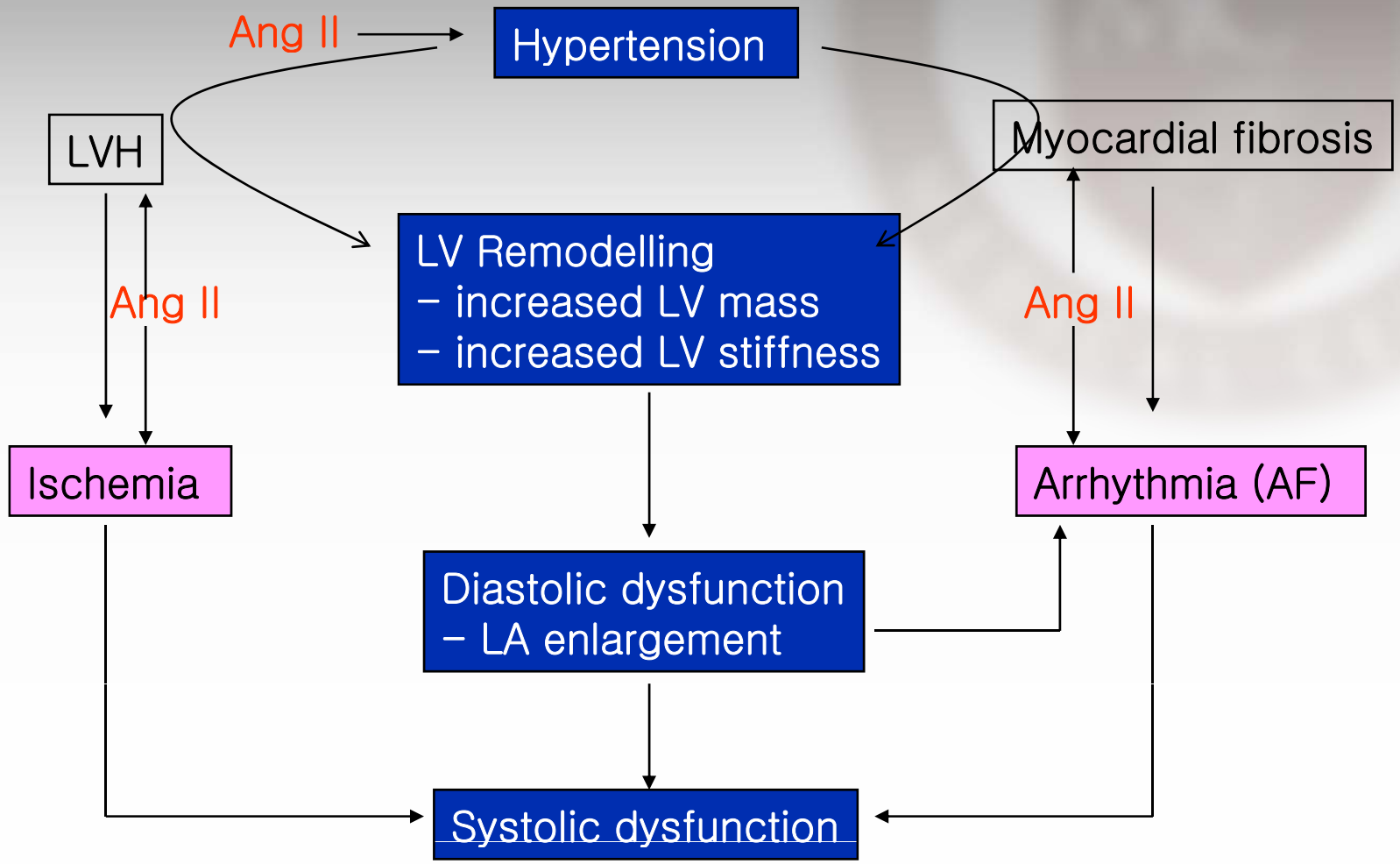


Incidence of Diabetes Mellitus – All Trials

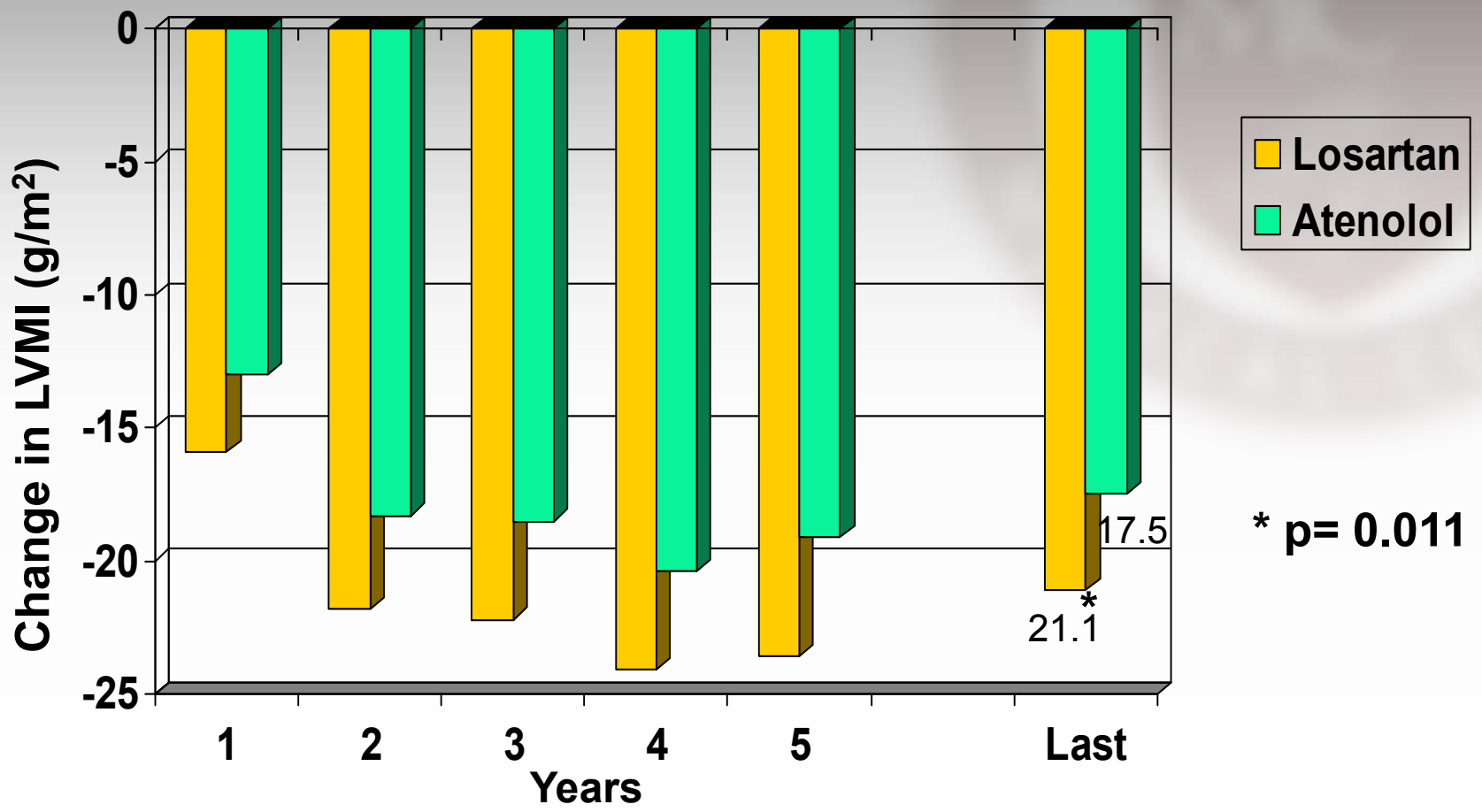


- DM developed in 8.2% with ARBs, compared with 10.5% with placebo or other agents (OR 0.73, 95% CI 0.64 to 0.84, p< 0.001)

Angiotensin II & LVH Pathophysiology



LIFE Echo Substudy—Losartan vs. Atenolol: Losartan Had a Greater Reduction in LVMI



Adapted from Devereux et al *Circulation* 2004;110:1456–1462.

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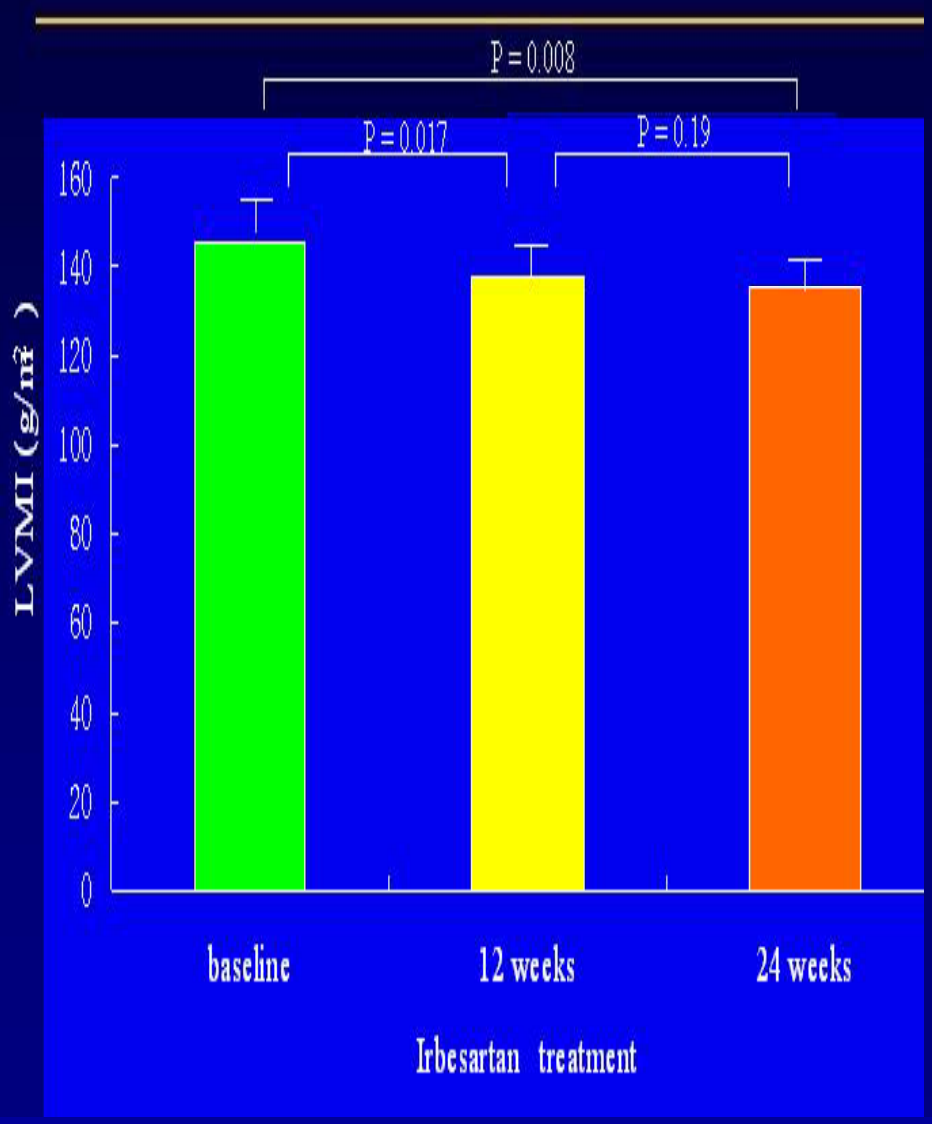
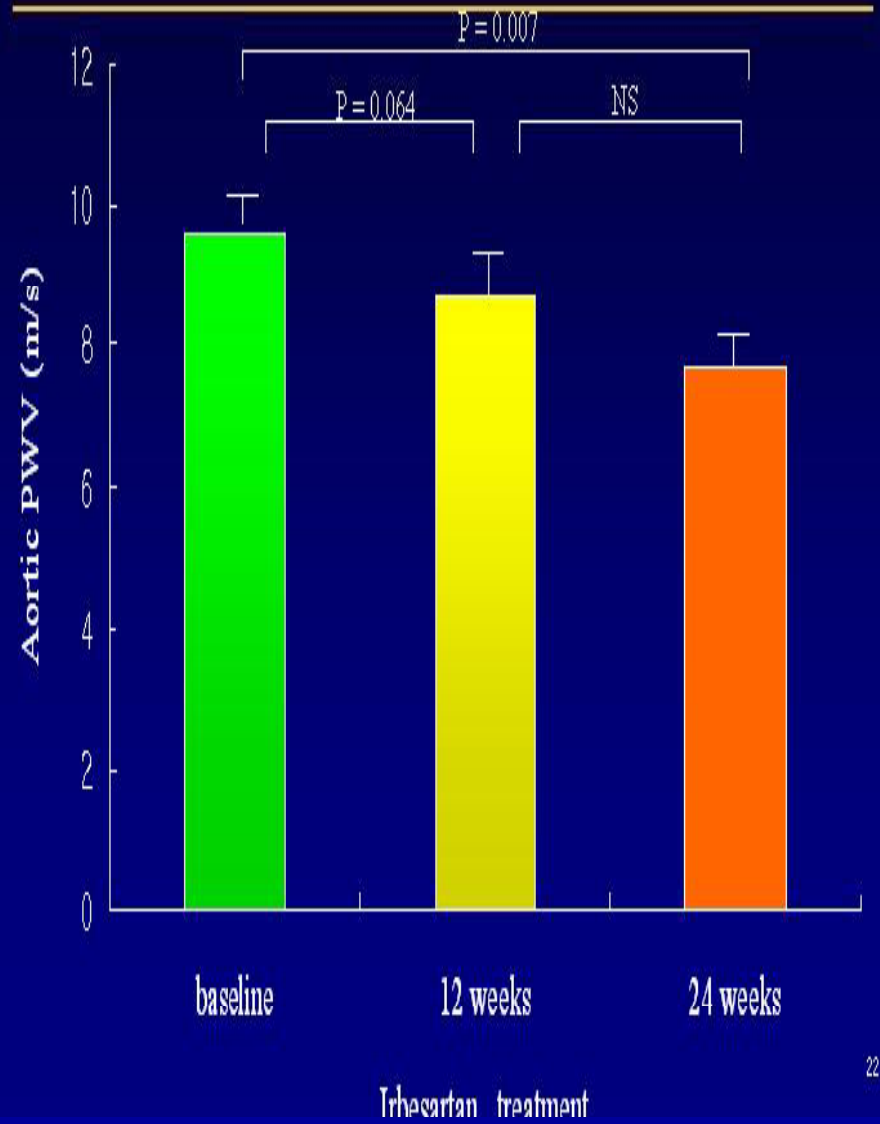
ECHO-LVH and afPWV after Irbesartan Treatment





Park CG. et al. J Hypertension 2003. Korean J Intern Med. 2006;21:103-8

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ARBs for New-onset Atrial Fibrillation

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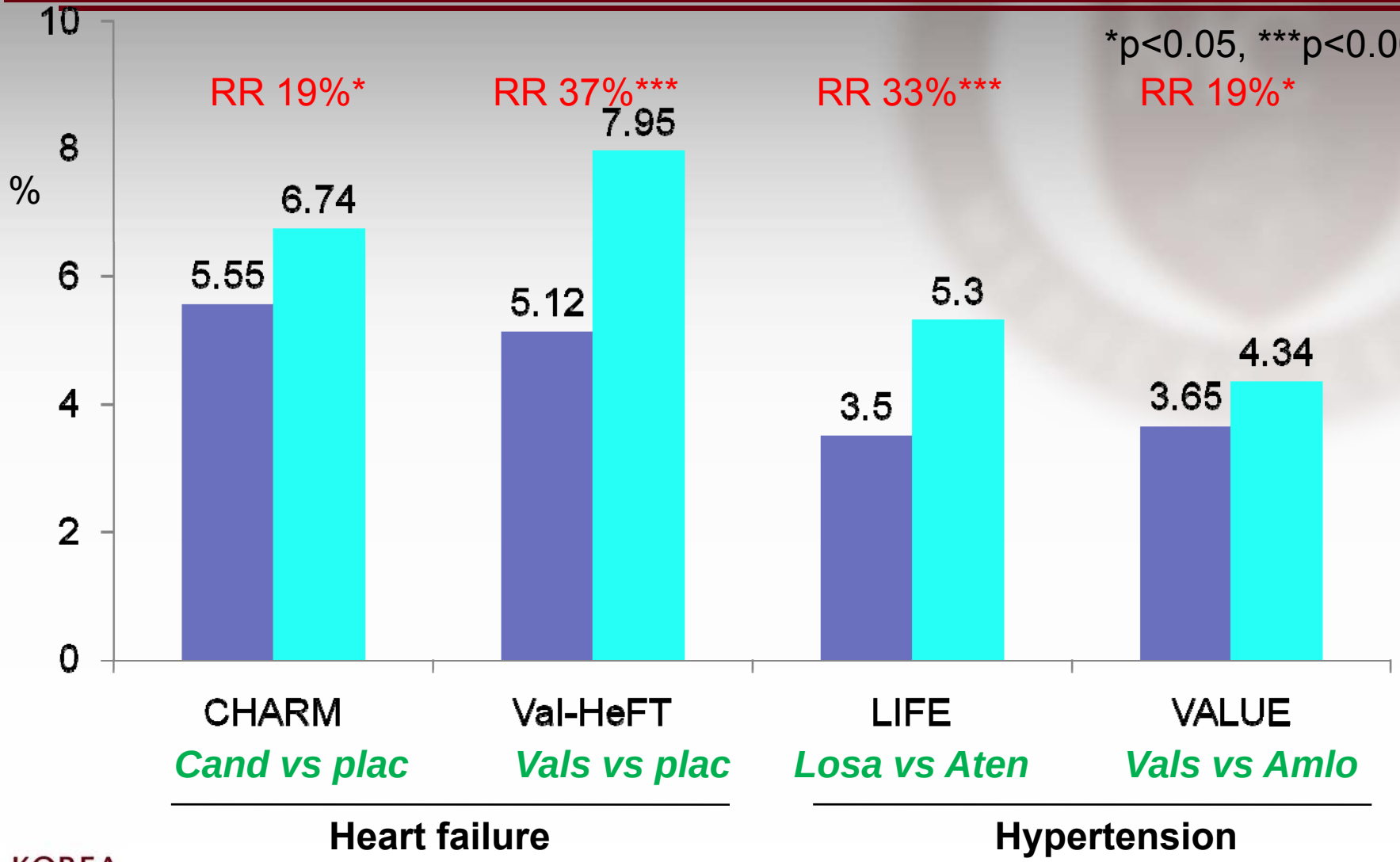
Relative Risk of developing AF

- Hypertension 1.4–2.1
- Heart failure 6.1–17.5
- Valvular disease 2.2–8.3

→ However, because of the high prevalence of hypertension, it accounts for more cases of atrial fibrillation than the other risk factors

Healey JS, Connolly SJ. Am J Cardiol 2003; 91:9G–14G.

New-onset AF with ARB
→ Preventive effects of AF



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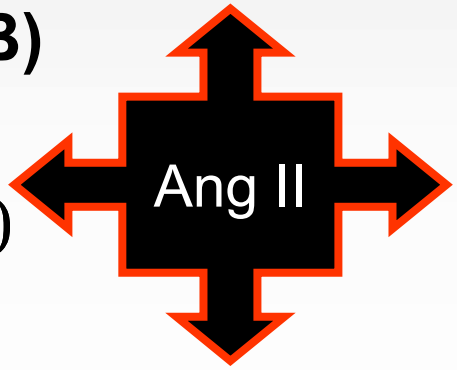
Clinical Trials with AT_1 Receptor Blockers

Post MI **(Stage B)**

OPTIMAL (losartan)

VALIANT (valsartan)



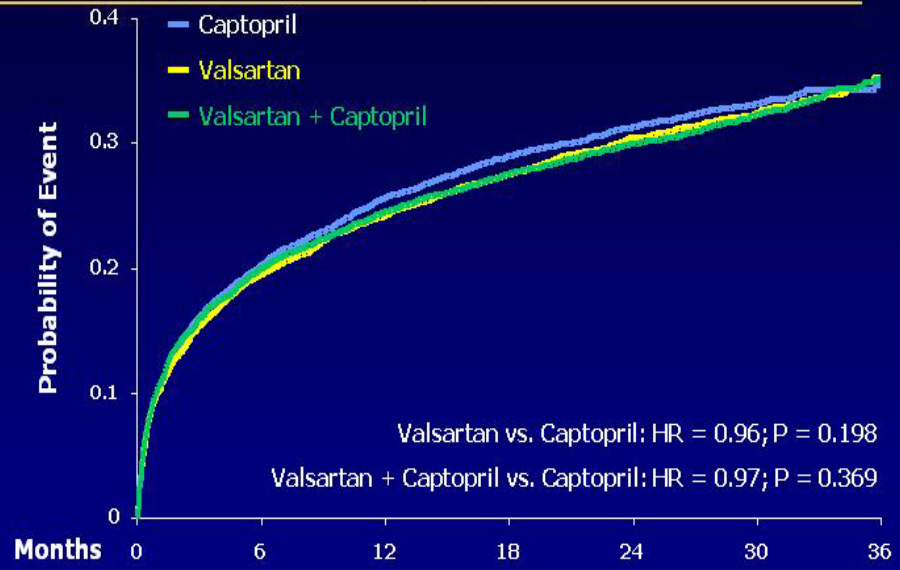
CHF **(Stage C,D)**

ELITE 2 (losartan)

Val-HeFT (valsartan)

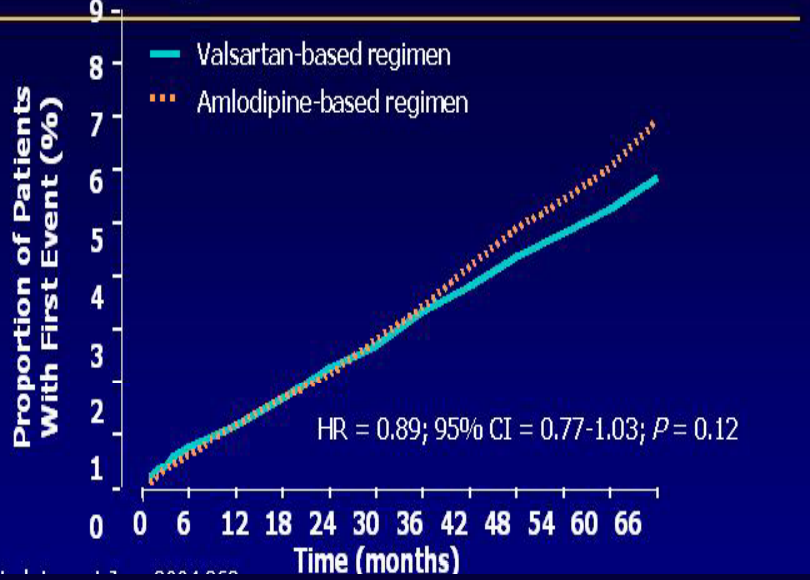
CHARM (candesartan)

VALIANT: CV Death, MI, or HF in Post-MI

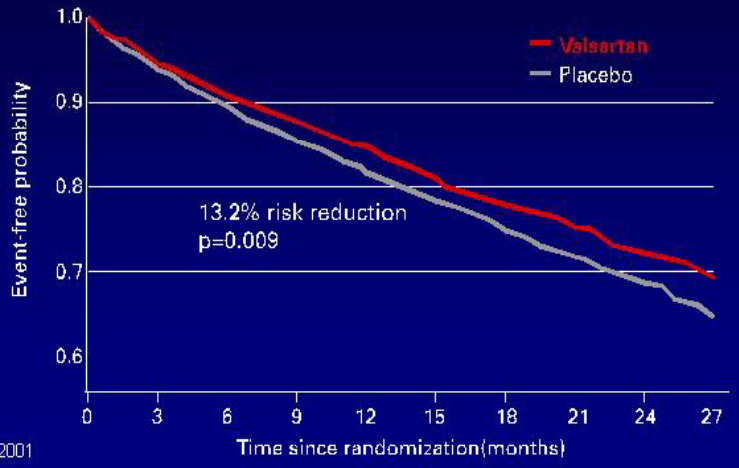


VALUE: Heart Failure

Hospitalisation for HF or death from HF



Val-Heft: Significant benefits on combined mortality /morbidity endpoint



Cohn et al. NEJM 2001 345:1667

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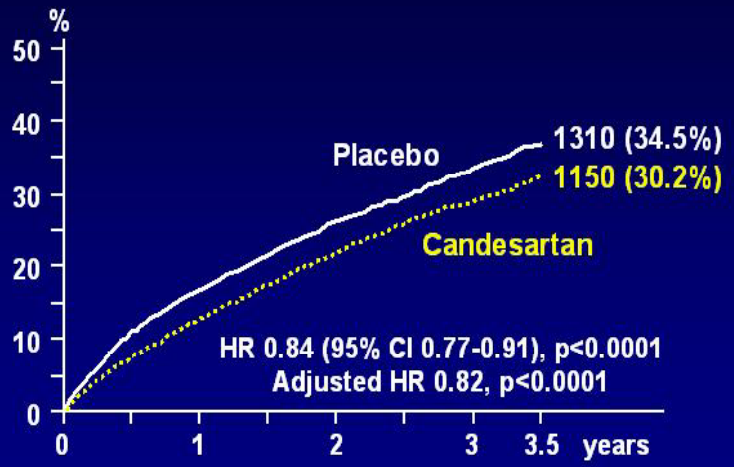
CHARM-Overall

CV death or CHF hospitalisation



Pfeffer et al, Lancet 2003

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Beyond BP effect of ARBs

- High-risk Hypertension
- Diabetes & Renal disease
- New onset AF
- Post-MI
- CHF
- LVH regression

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Recent Update on Candesartan Outcome Study

CASE-J and CREATE

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CASE-J

Candesartan Antihypertensive Survival Evaluation in Japan Trial

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Ogihara T et al. Hypertension. 2008;51:1-6

Rationale of the Study

- ARBs and CCBs are the most widely used antihypertensive drugs in the world.

- The incidences of stroke and coronary artery diseases, however, are significantly different in Japan compared to Europe and the USA.

- The CASE-J Study was designed as a large-scale clinical trial to evaluate the efficacy of Candesartan and Amlodipine for reducing the incidences of cardiovascular morbidity and mortality in Japanese patients.

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Outline of the study

Objectives : A comparison of the efficacies of ARB and CCB for reducing cardiovascular mortality and morbidity

Subjects : High-risk hypertensive patients

Test drugs : Candesartan and Amlodipine

Follow-up period: 3.0 years or more

Study period : September 2001 to December 2005

Study design : Open Label Randomized Controlled Trial

Evaluation : The PROBE method

Inclusion Criteria
High-risk hypertensive patients

Age 20 – 85 years old

BP ≧140 and/or 90mmHg (<70y.o) ≧160/90mmHg (≧70y.o)

+

At least one of the following risk factors

Risk Factors	
Severe HBP	≧180 and/or 110mmHg
Type 2 Diabetes	
Cerebrovascular Risk	History of Stroke or TIA
Cardiac Risk	LVH, History of MI, AP
Renal Risk	s-Cr ≧1.3mg/dL, Positive proteinuria
Vascular Risk	ASO (Fontaine Category ≧2)

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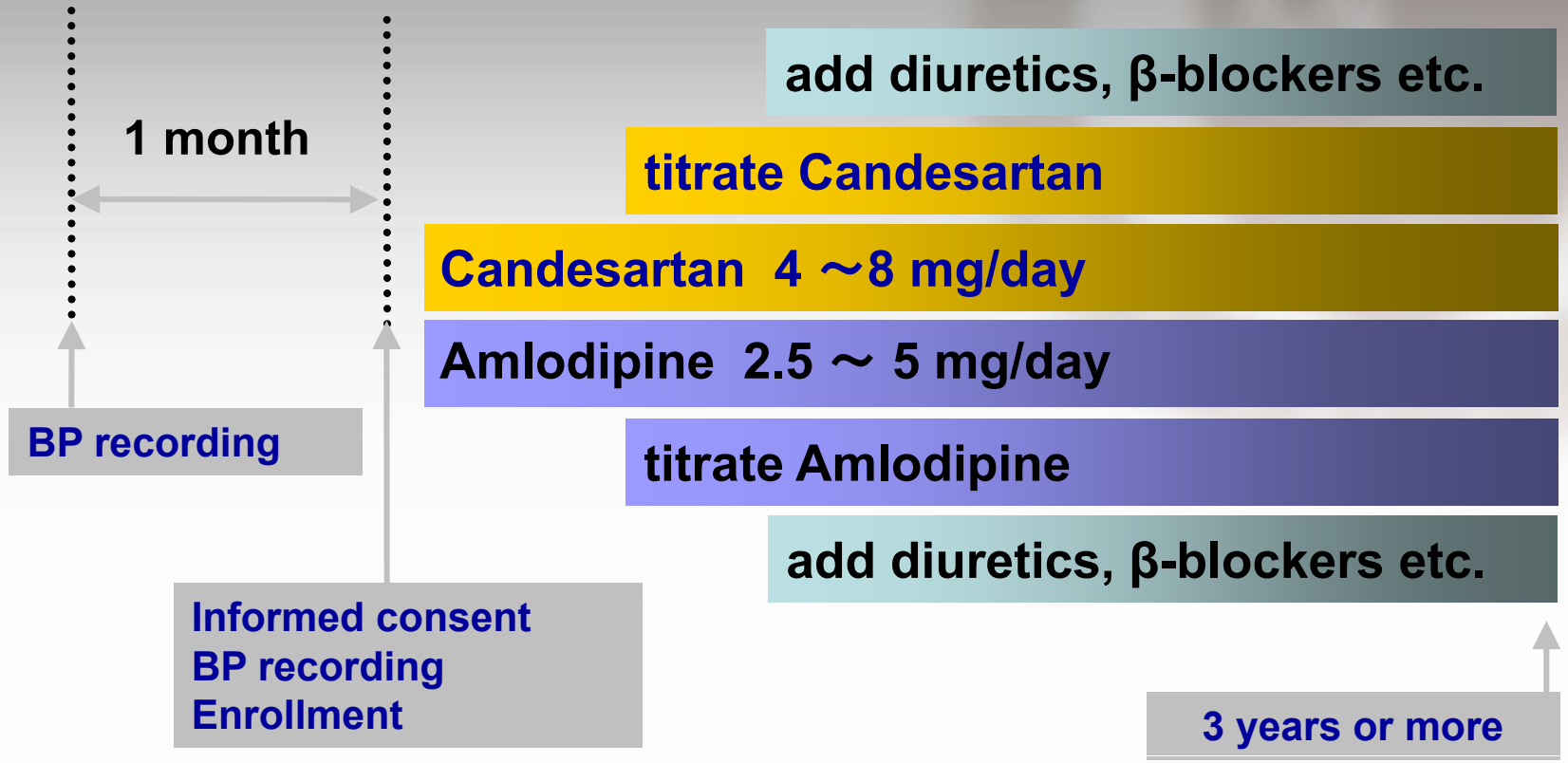
Dosage Schedule



Candesartan cilexeti : 4 to 8 mg/day. If necessary, the dose was increased up to 12 mg/day.
Amlodipine besilate : 2.5 to 5 mg/day. If necessary, the dose was increased up to 10 mg/day.

If the response was insufficient, diuretics or β-blockers etc were added to the regimen in both groups.

Therapeutic Targets of Blood Pressure

Age of patient (years)	BP (mmHg)
<60	< 130 / 85
60s	< 140 / 90
70s	< 150 / 90
80s	< 160 / 90

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Endpoints

- **Primary Endpoints**

  A composite of cardiovascular mortality and morbidity

  Sudden death, Cerebrovascular events,

  Cardiac events, Renal events,Vascular events

- **Secondary Endpoints**

  All-cause deaths, LVMI values, Withdrawal ratio

- **Pre-specified Analysis**

  New-onset Diabetes

[Evaluation]

the PROBE method performed by the Event Evaluation Committee

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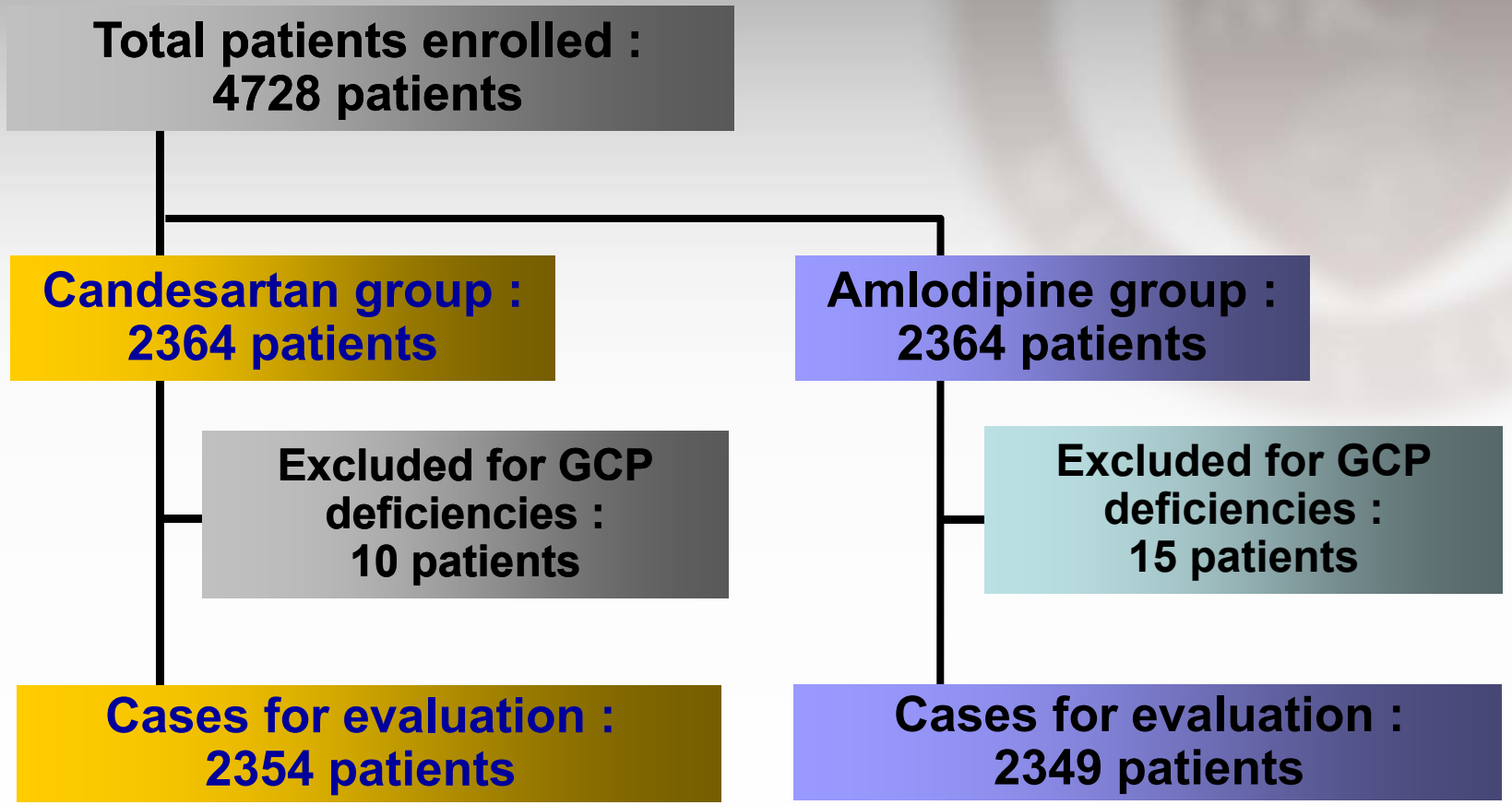
Study Flow Chart



- **Mean follow-up period :** 3.2 years
- **Follow-up rate :** 97.1%

Patient Characteristics

	Candesartan	Amlodipine
Total number	2354	2349
Males (%)	1262 (53.6%)	1335 (56.8%)
Age (years)	63.8 ± 10.5	63.9 ± 10.6
BMI (kg/㎡)	24.6 ± 3.7	24.5 ± 3.6
SBP (mmHg)	162 ± 14	163 ± 14
DBP (mmHg)	92 ± 11	92 ± 11

mean ± SD

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Patient Characteristics (2)

Cardiovascular risk factors（including duplications）

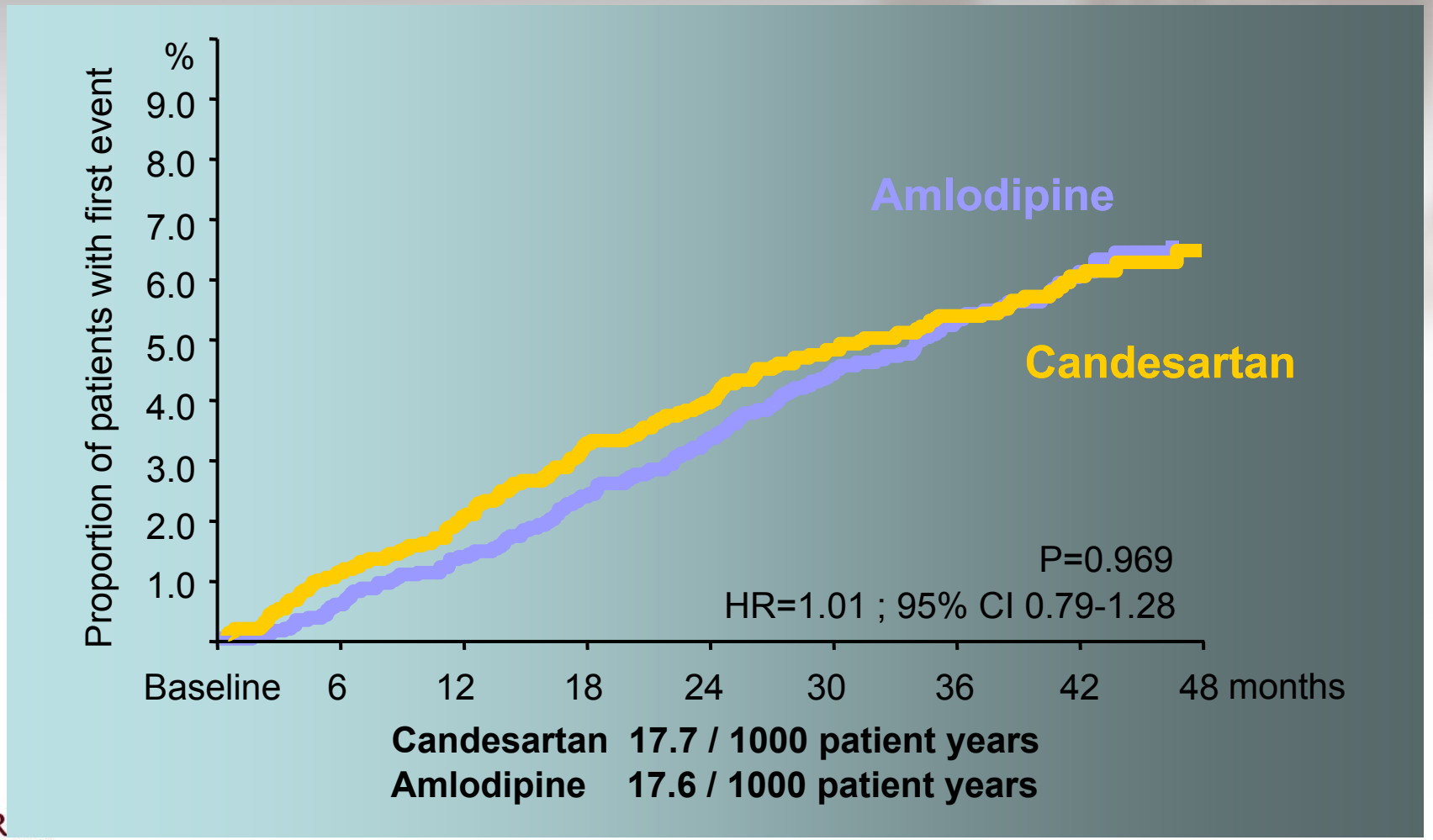
		Candesartan (n=2354)	Amlodipine (n=2349)
Severe HBP ≧180 and/or 110 mmHg		454 (19.3%)	493 (21.0%)
Type 2 diabetes		1011 (42.9%)	1007 (42.9%)
Cerebro-vascular disease	Cerebral hemorrhage	42 (1.8%)	44 (1.9%)
	Cerebral infarction	165 (7.0%)	159 (6.8%)
	TIA	48 (2.0%)	26 (1.1%)
Cardiac disease	LVH	799 (33.9%)	813 (34.6%)
	Angina pectoris	192 (8.2%)	177 (7.5%)
	MI	127 (5.4%)	140 (6.0%)
Renal dysfunction	Proteinuria	460 (19.5%)	445 (18.9%)
	s-Cr ≧1.3mg/dL	193 (8.2%)	174 (7.4%)
Vascular disease	ASO	29 (1.2%)	24 (1.0%)

Antihypertensive Drugs at Entry

	Candesartan (n=2354)	Amlodipine (n=2349)
Antihypertensive drugs at entry	1610 (68.4%)	1552 (66.1%)
CCB	941 (40.0%)	946 (40.3%)
ARB	480 (20.4%)	421 (17.9%)
ACE-Inhibitor	345 (14.7%)	339 (14.4%)
β-blocker	315 (13.4%)	262 (11.2%)
α-blocker	159 (6.8%)	131 (5.6%)
Diuretics	74 (3.1%)	78 (3.3%)
Others	14 (0.6%)	15 (0.6%)

Primary Composite Endpoints

Comparison of Cardiovascular Events



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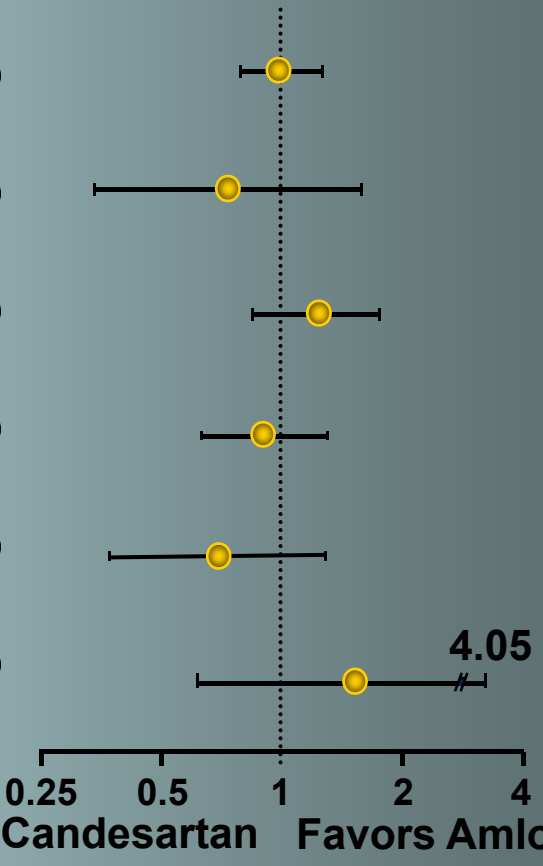
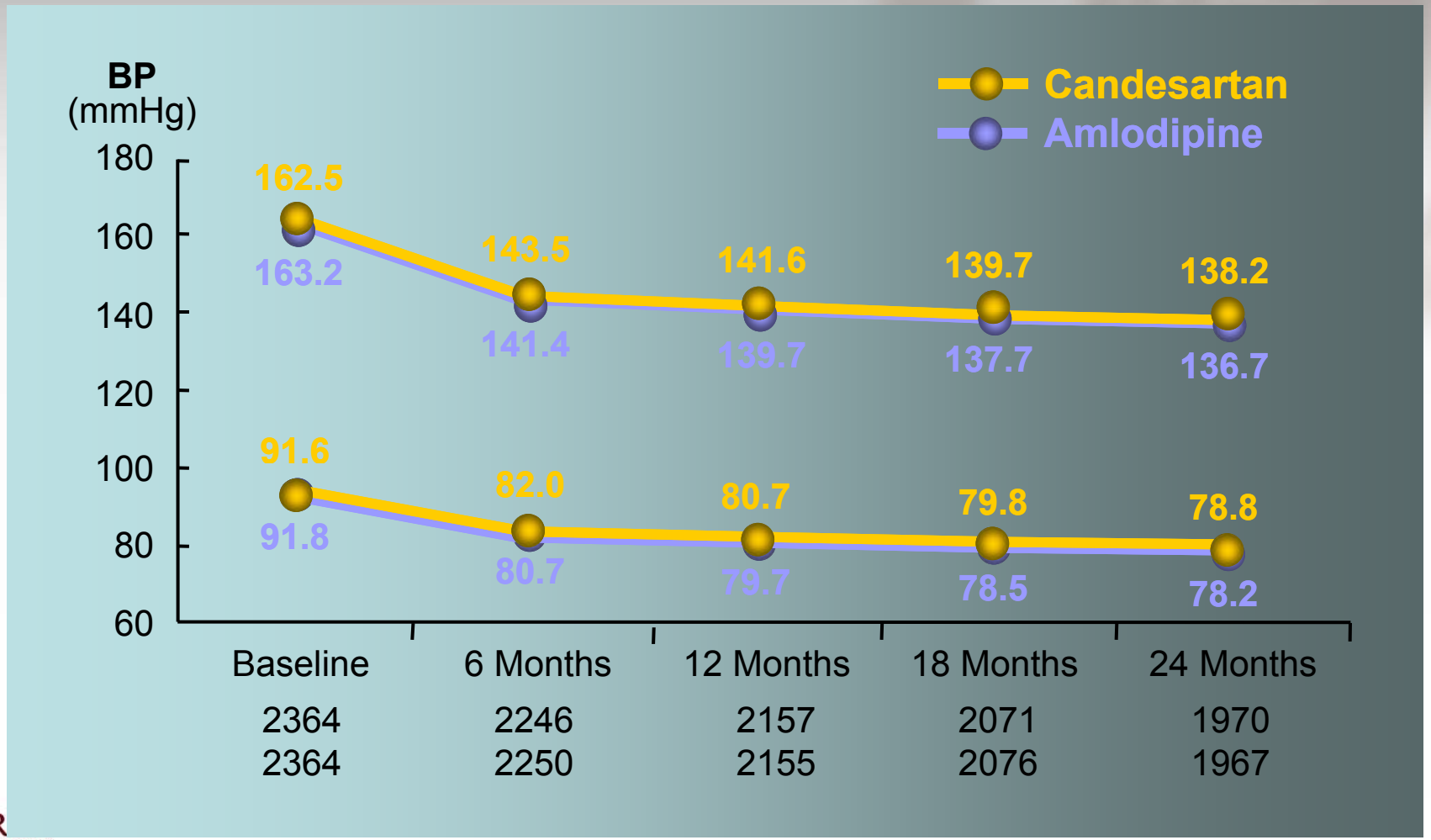
Comparison of Cardiovascular Events

Event	Candesartan (n=2354)	Amlodipine (n=2349)	*P* Value
Cardiovascular events	134 (5.7%)	134 (5.7%)	0.969
Sudden deaths	11 (0.5%)	15 (0.6%)	0.434
Cerebrovascular events	61 (2.6%)	50 (2.1%)	0.282
Cardiac events	43 (1.8%)	47 (2.0%)	0.680
Renal events	19 (0.8%)	27 (1.1%)	0.230
Vascular events	11 (0.5%)	7 (0.3%)	0.348

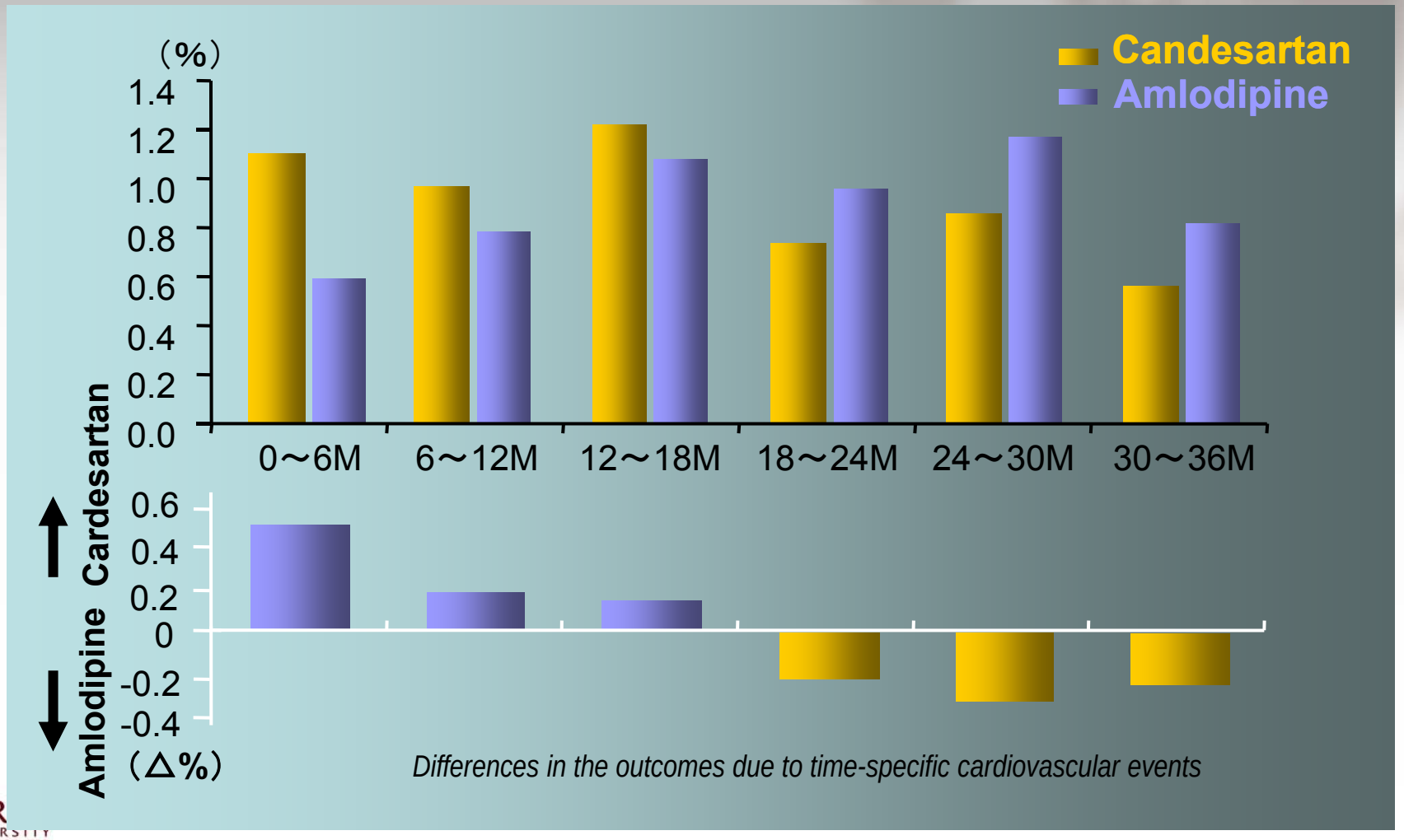


CASE-J: Candesartan Antihypertensive Survival Evaluation in Japan



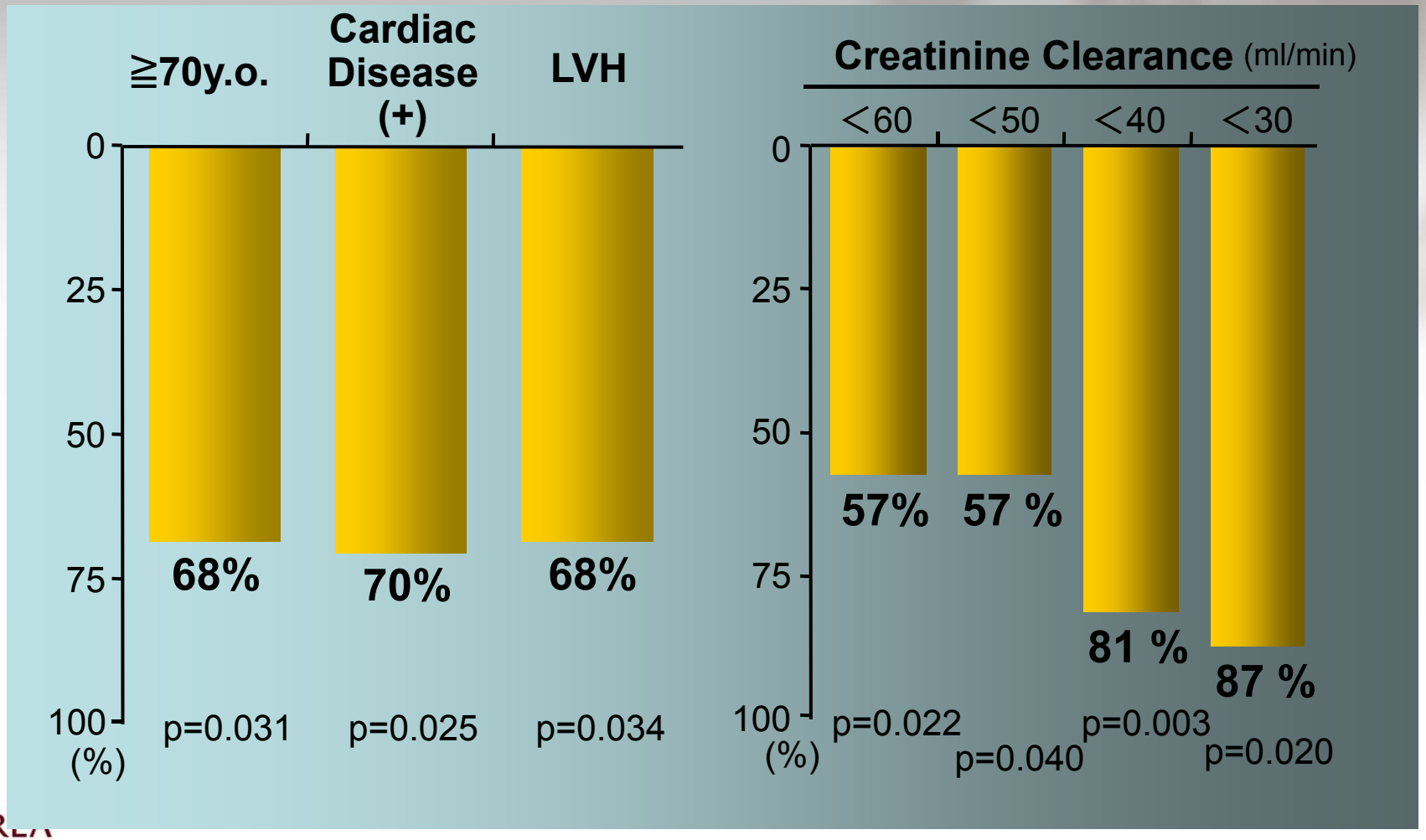
Time-specific Events Rates

Cardiovascular Events

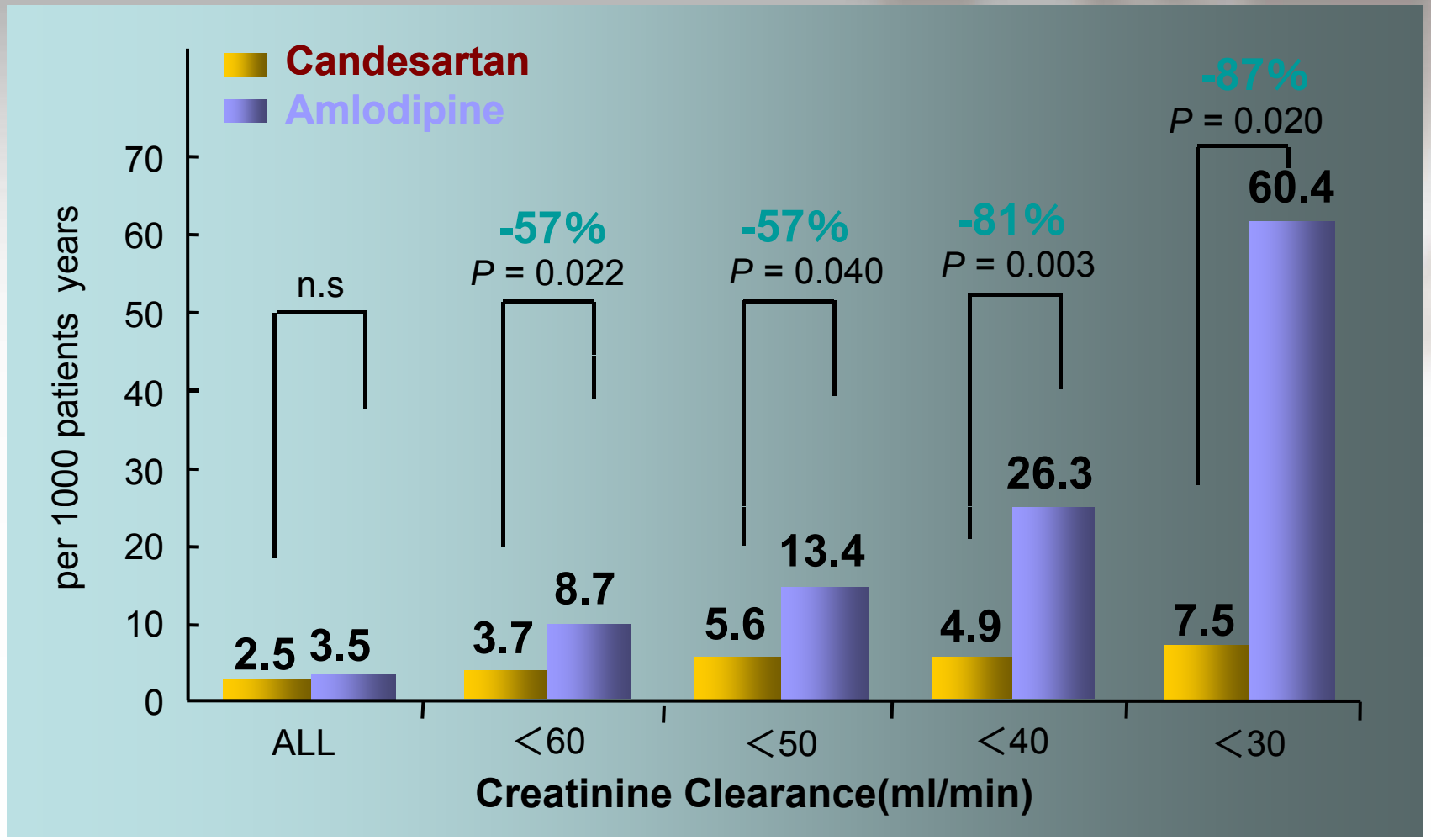


Differences in the outcomes due to time-specific cardiovascular events

Risk Reduction of Renal Events with Candesartan by Baseline Risk Factors



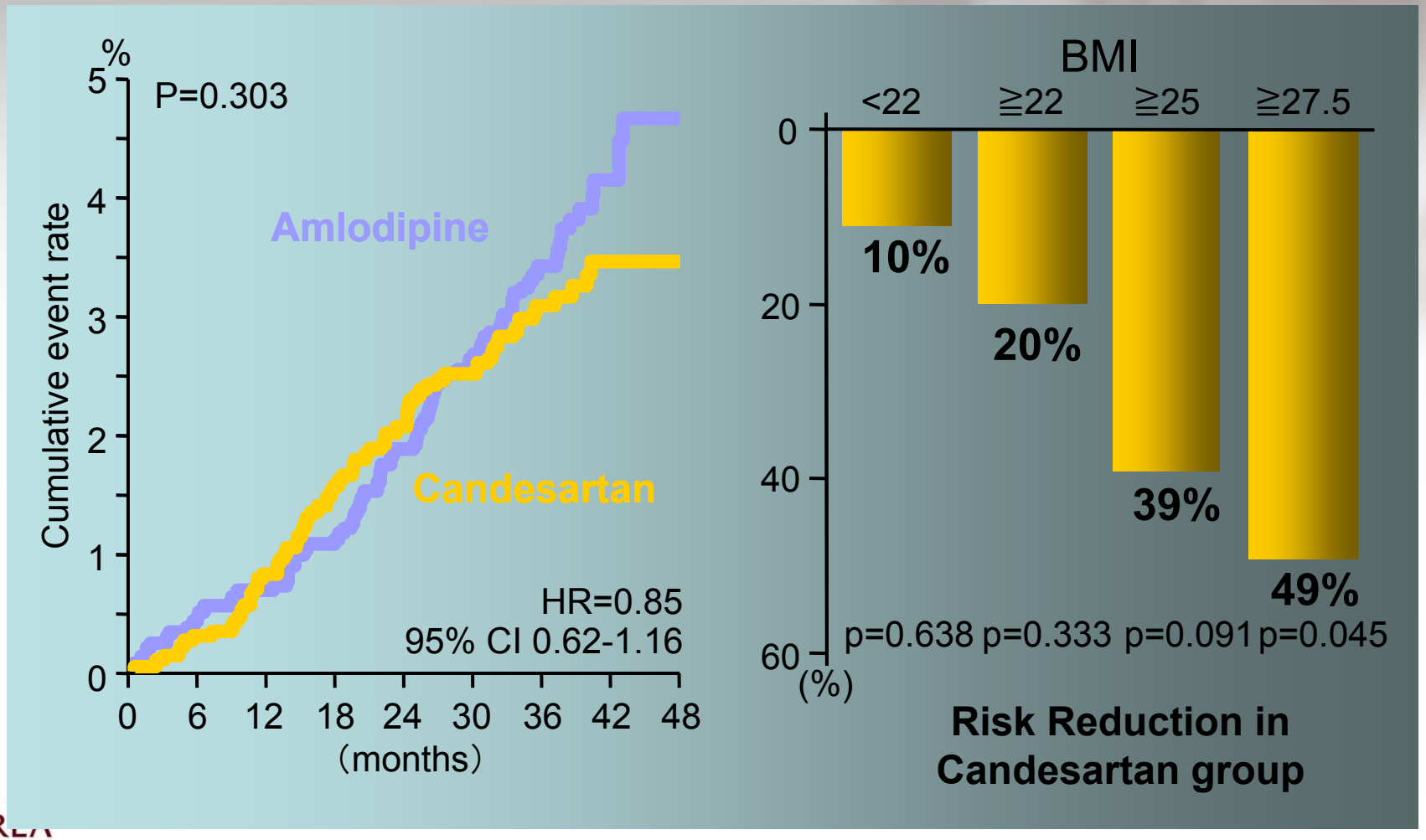
Renal Events



Calculation : Cockcroft-Gault formula

Secondary Endpoint

All-Cause Mortality



CASE-J vs. VALUE

Dose titration

	VALUE (Valsartan)		CASE-J (Candesartan)	
	valsartan	amlodipine	Atacand®	amlodipine
Titration-step				
1	80	5	4-8	2.5-5
2	160	10	**12**	**10**
3	160+12.5	10+12.5	diuretic/β-block	diuretic/β-block
4	160+25	10+25		
5	**160+25+** ”free add-on”	**10+25+** ”free add-on”		

Primary endpoint

VALUE (Valsartan)

Time to first cardiac event

- Cardiac death
- heart failure requiring hospitalisation
- Non-fatal AMI
- any other interventional procedure performed to prevent full blown MI

CASE-J (Candesartan)

Composite of CV mortality and morbidity

- Sudden death
- Cerebrovascular events
- Cardiac events
- Renal events
- Vascular events

Baseline characteristics

	VALUE (Valsartan)		CASE-J (Candesartan)	
	val n= 7649	amlo n= 7596	Atacand® n=2354	amlo n=2349
Mean age (years)	67	67	64	64
Men (%)	58	57	54	57
SBP mmHg	155	155	162	163
DBP mmHg	87	88	92	92
BMI Kg/m^2	29	29	25	25
Medical history (%)				
coronary disease	46	46		
myocardial infarction			5	6
diabetes			43	43
stroke/TIA	20	20	11	10
proteinuria			20	19

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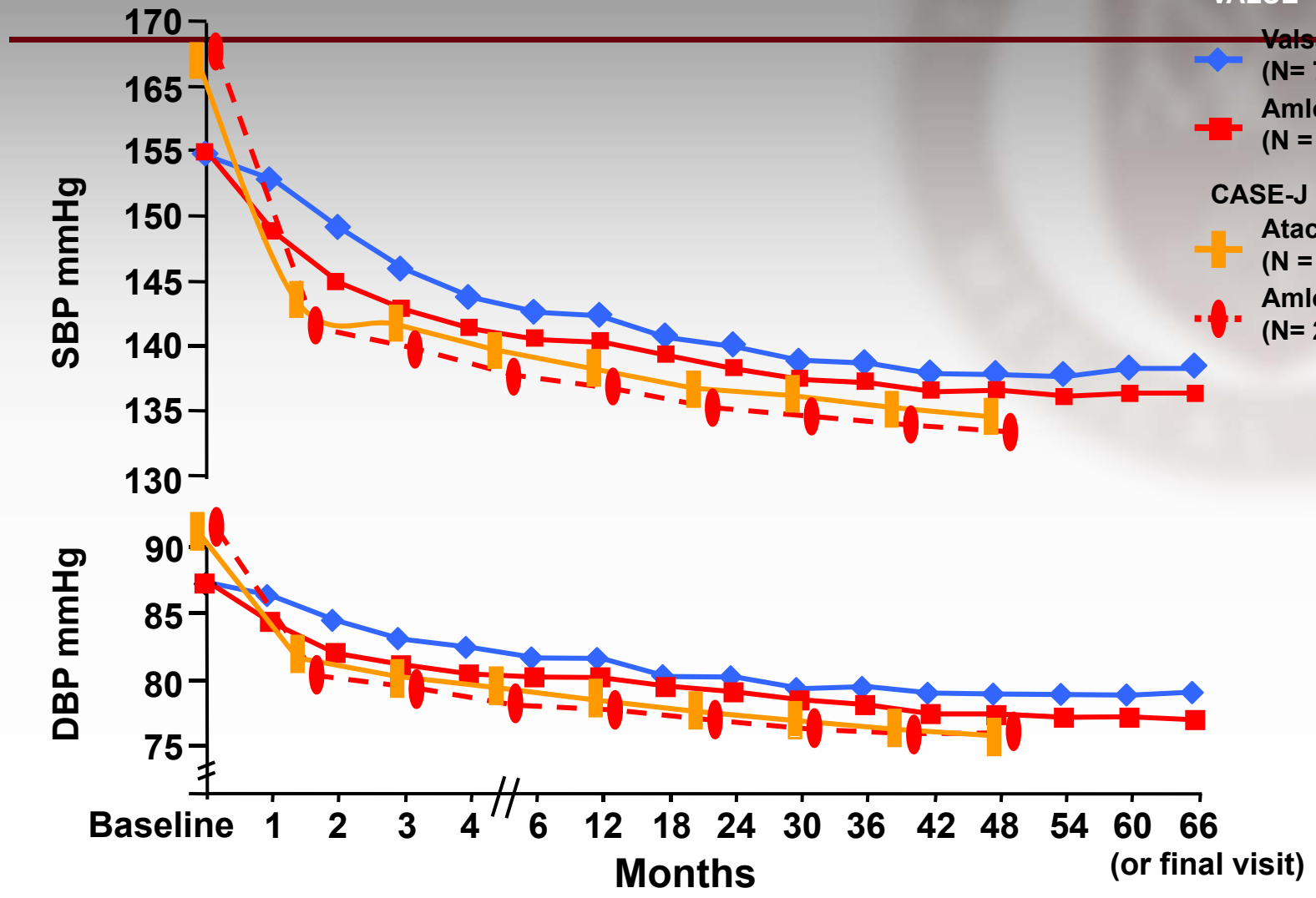
BP reduction during studies



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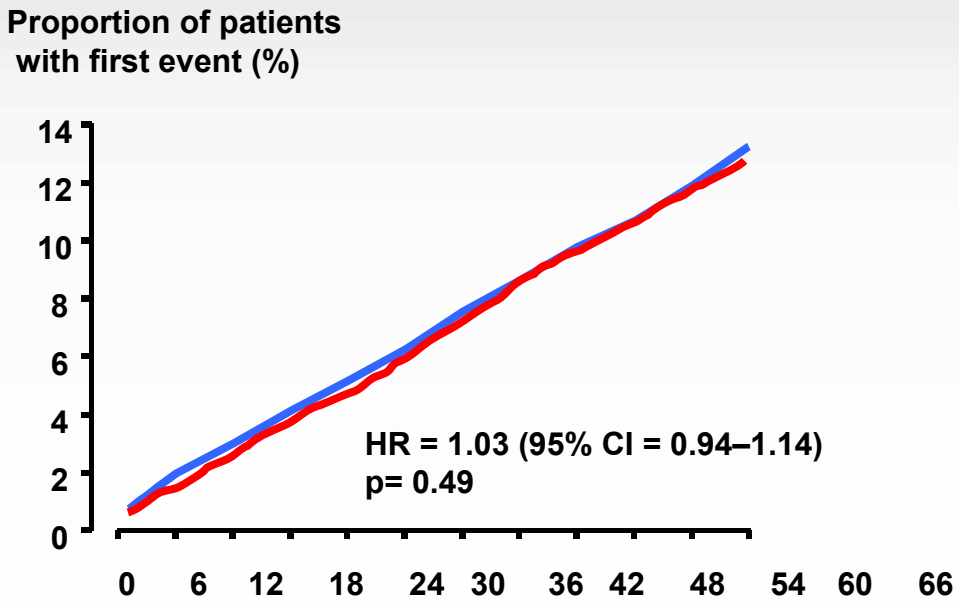
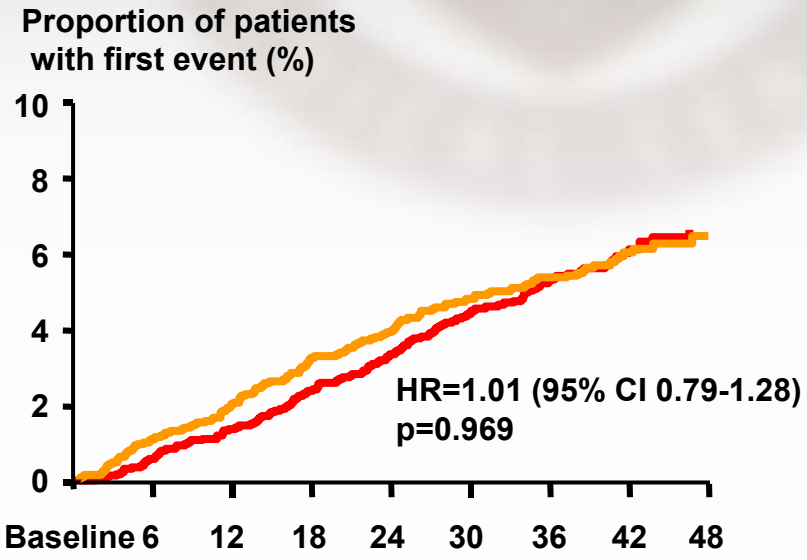
Cardiac event
(VALUE Primary endpoint)

VALUE (Valsartan)



CASE-J (Candesartan)



Time (months)

- Valsartan-based regimen
- Amlodipine-based regimen
- Atacand®-based regimen

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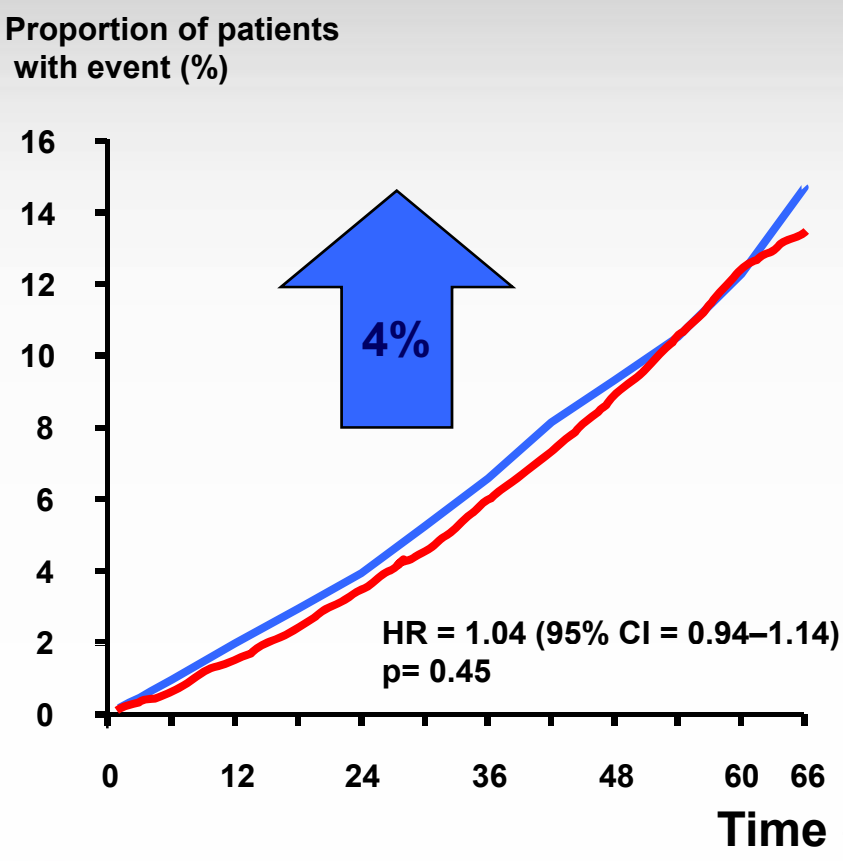
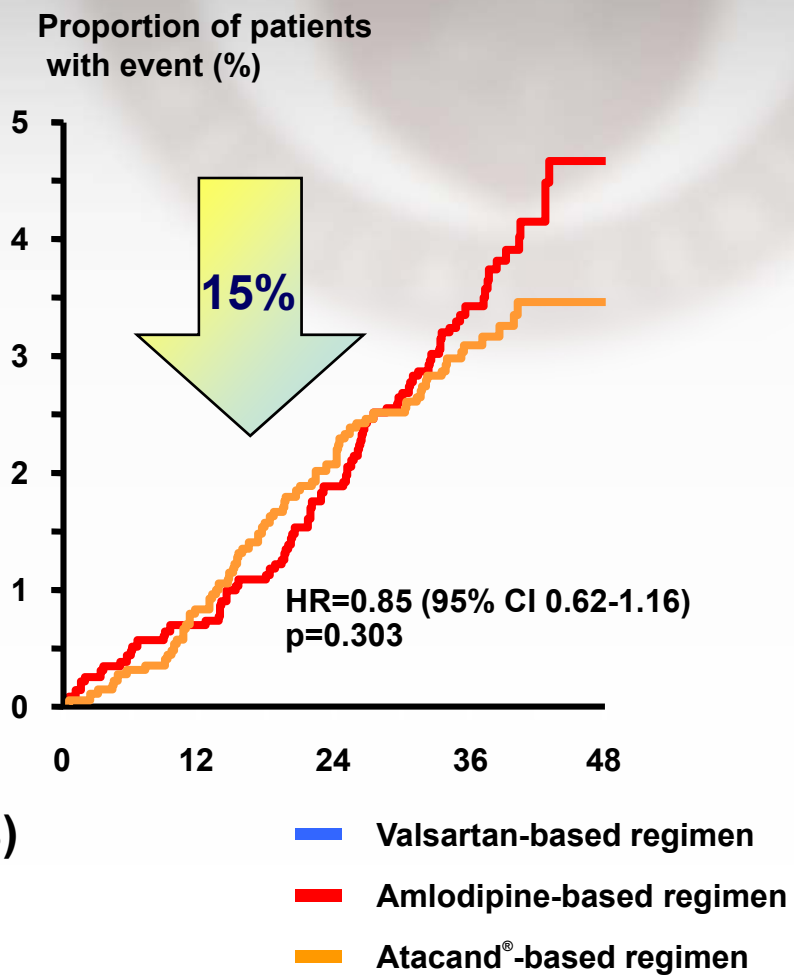
All-cause mortality
(CASE-J Primary endpoint)

VALUE (Valsartan)



CASE-J (Candesartan)



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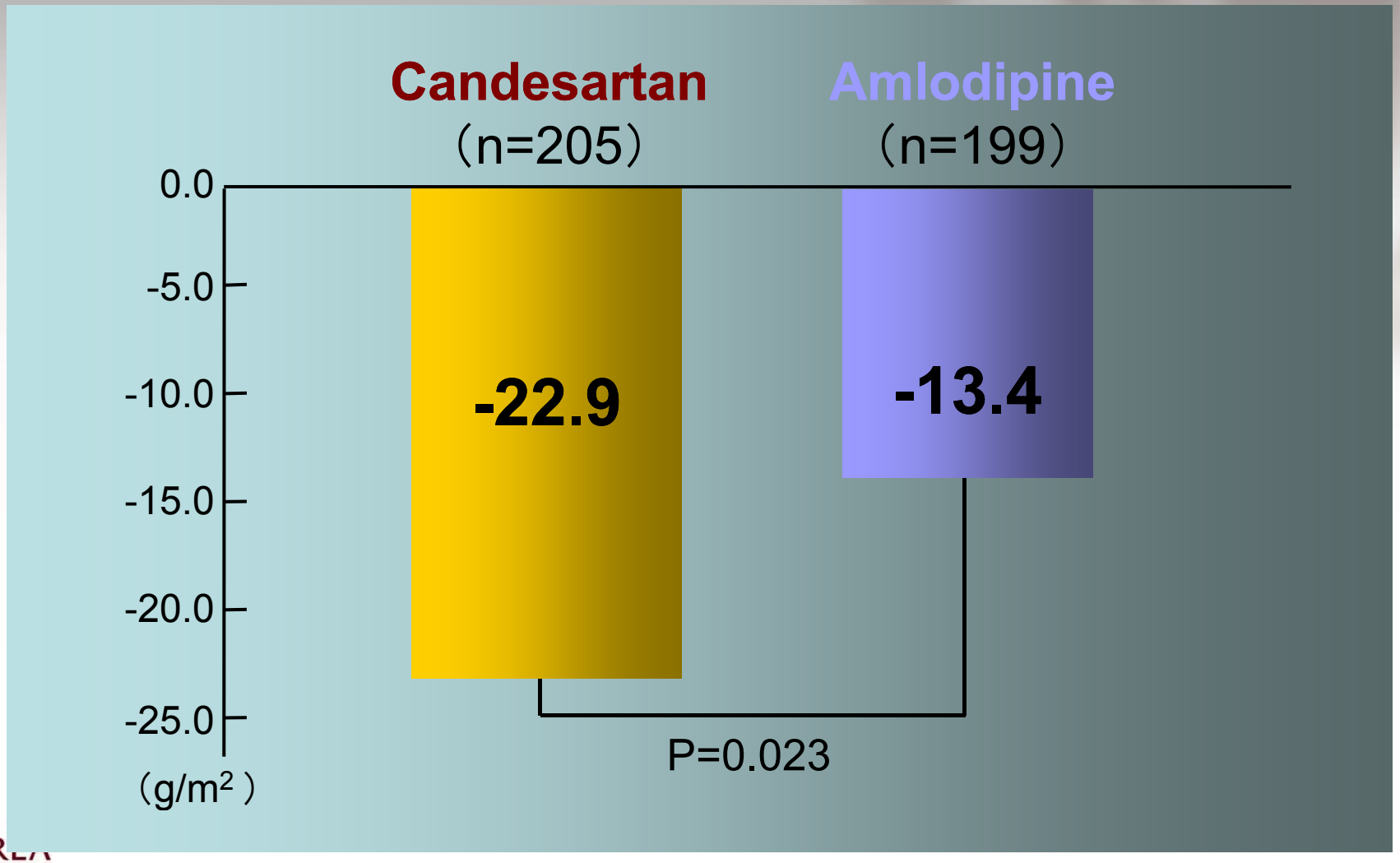
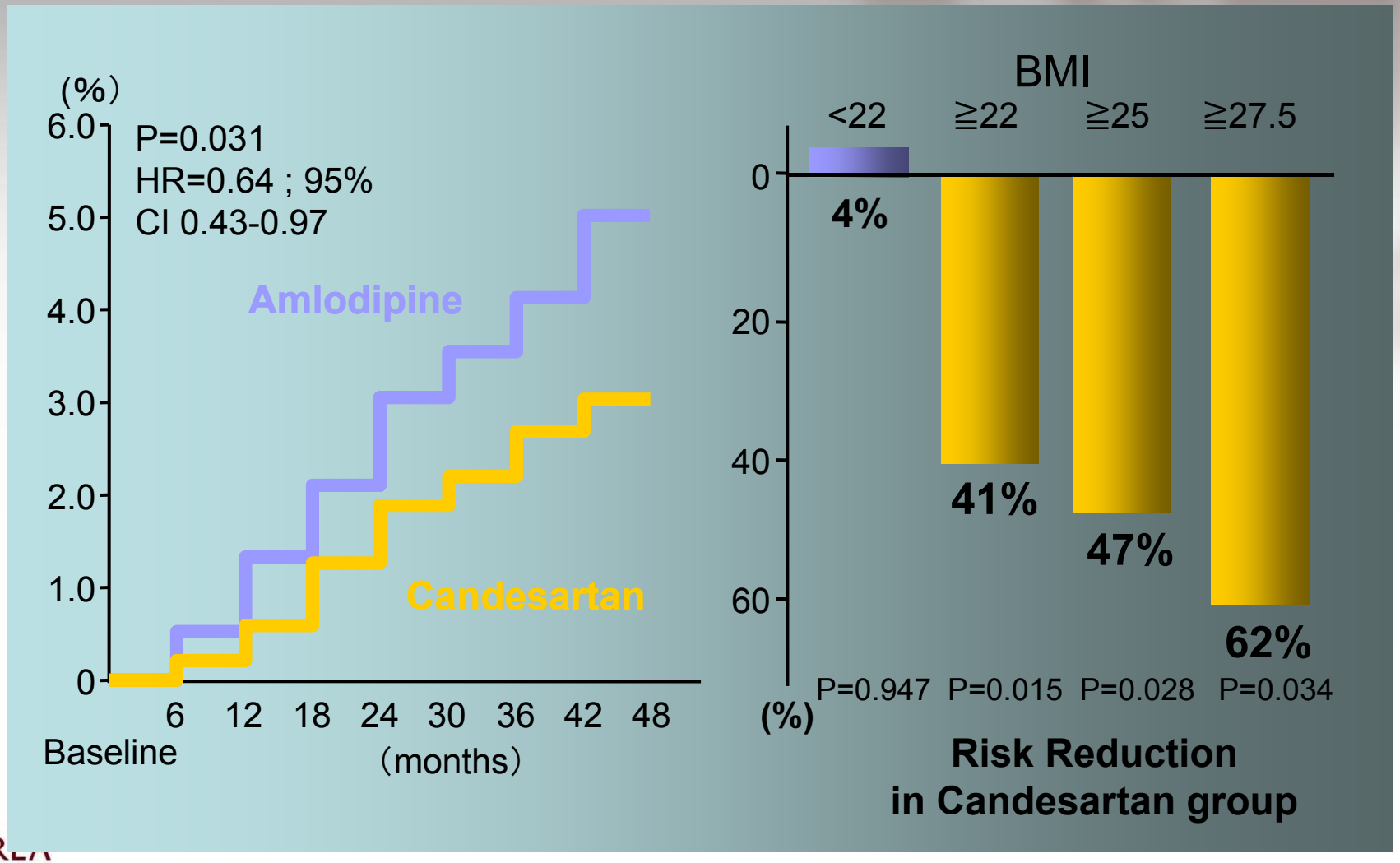
Changes in LVMI in Patients with LVH



New-onset Diabetes



Summary

- Candesartan and Amlodipine equally reduced the number of CV events in high-risk hypertensive patients under strict BP control (< 140/80 mmHg).
- Candesartan suppressed the progression of renal dysfunction in patients with renal impairments.
- Candesartan decreased total mortality in obese patients.
- A significantly larger decrease in the left ventricular mass index values was observed in the Candesartan group than in the Amlodipine group.
- Candesartan prevented new-onset diabetes.

Conclusions

- Candesartan and Amlodipine equally reduce the number of CV events in high-risk hypertensive patients under strict BP control.
- Candesartan is more beneficial than Amlodipine for hypertensive patients with chronic kidney disease or obesity, and may be preferable for patients with metabolic syndrome.

Randomized Trial of ARB based versus NonARB Standard Therapy in Patients with CAD and Hypertension

The Heart Institute of Japan Candesartan Randomized trial for Evaluation in Coronary Artery Disease (HIJCREATE)

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Presented at 2007 AHA

Background

ACE-inhibitors improve clinical outcome in patients with coronary artery disease (CAD).

However, it still remains uncertain whether Angiotensin II receptor blockers (ARB) reduce the risk of cardiovascular events.

Hypothesis

Candesartan-based pharmacotherapy reduces the cardiovascular events compared to non-ARB-based standard pharmacotherapy
in angiographically documented CAD patients with hypertension.

Eligibility

- **Inclusion criteria :**

  Angiographically documented

  coronary artery disease patients with hypertension, aged 20-80 yrs

  Coronary Artery Disease :

  ACS, Stable Coronary Artery Disease

  Hypertension :

  SBP≥140mmHg, DBP≥90mmHg or current use of antihypertensive medication

- **Major exclusion criteria :**

  AMI within week

  Cerebrovascular disease within months sCr ≥2.0mg/dL

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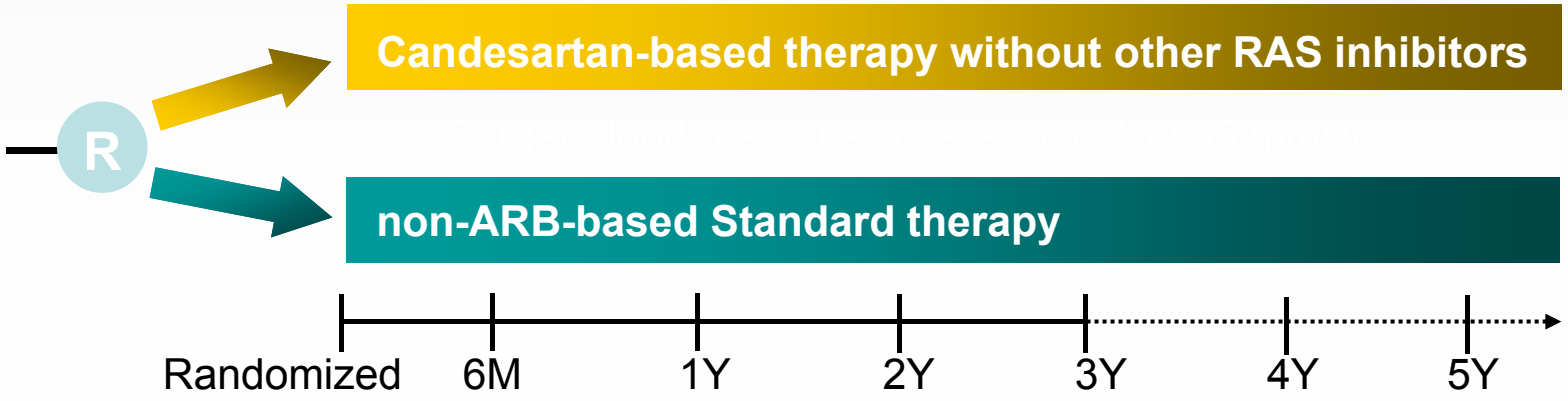
Design and Treatment

- **Study Design :**
  Prospective randomized open-label blinded-endpoint (PROBE) design.
  Conducted at 14 medical centers in Japan.

- **Treatment :**



Endpoint

- **Primary Endpoint**

  Major Adverse Cardiovascular Events (MACE)

  1. Death from cardiovascular cause
  2. Non fatal myocardial infarction
  3. Unstable angina pectoris
  4. Heart failure
  5. Stroke
  6. Other cardiovascular events

  requiring hospitalization

- **Secondary Endpoints**

  - Revascularization
  - New-onset diabetes mellitus

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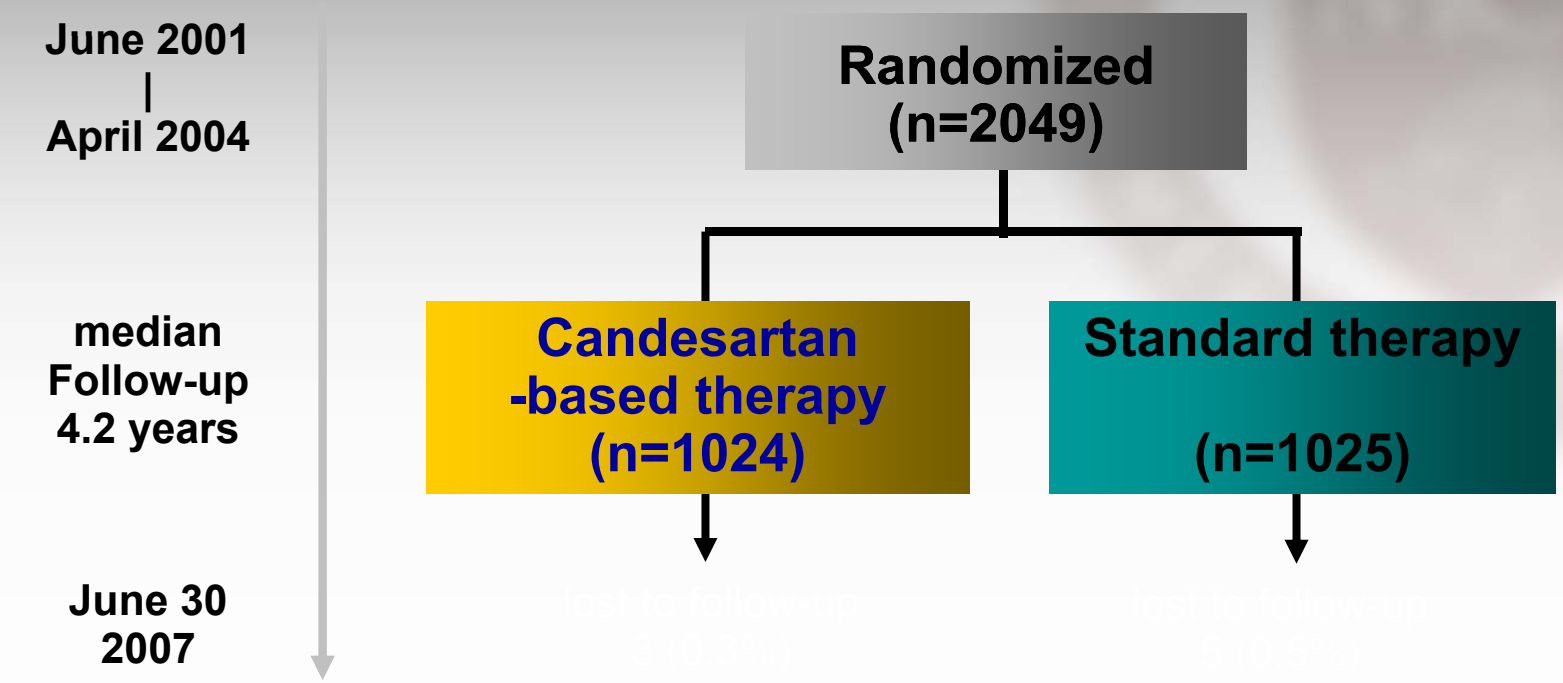
Flow Diagram for the Trial



Statistical consideration

- Sample size of 2,049 with an 80% power to detect a 20% risk reduction at two-tailed 5%.
- Stratified, permuted-block randomization.
- The intention-to-treat approach.

Patient Characteristics (1)

	Candesartan (n=1024)	Standard (n=1025)
Age	65 ± 9	65 ± 9
Women	186 (18%)	219 (21%)
BMI (Kg/m^2)	25 ± 3	25 ± 3
SBP (mmHg)	135 ± 19	136 ± 18
DBP (mmHg)	76 ± 12	76 ± 12
treated Hypertension	933 (91%)	960 (94%)
Heart Rate (beats/min)	69 ± 11	69 ± 10
Diabetes	379 (37%)	401 (39%)
Hypercholesterolemia	604 (59%)	612 (60%)
Smoking	401 (39%)	377 (37%)
Cerebrovascular disease	111 (11%)	94 (9%)
Atrial fibrillation	58 (6%)	77 (8%)

Patient Characteristics (2)

	Candesartan (n=1024)	Standard (n=1025)
ACS	346 (34%)	378 (37%)
Stable CAD	678 (66%)	647 (63%)
Previous MI	406 (40%)	373 (36%)
previous PCI	852 (83%)	844 (82%)
previous CABG	124 (12%)	112 (11%)
No. of diseased vessels ≤1	585 (57%)	583 (57%)
≥2	439 (43%)	442 (43%)
NYHA I/II/III/IV(%)	78 / 18 / 2 / 2	81 / 15 / 2 / 2
Ejection Fraction (%)	54 ± 11	55 ± 11
CRP (median : mg/L)	2 [1-4]	2 [1-4]
Ccr (mL/min)	63 ± 20	62 ± 19

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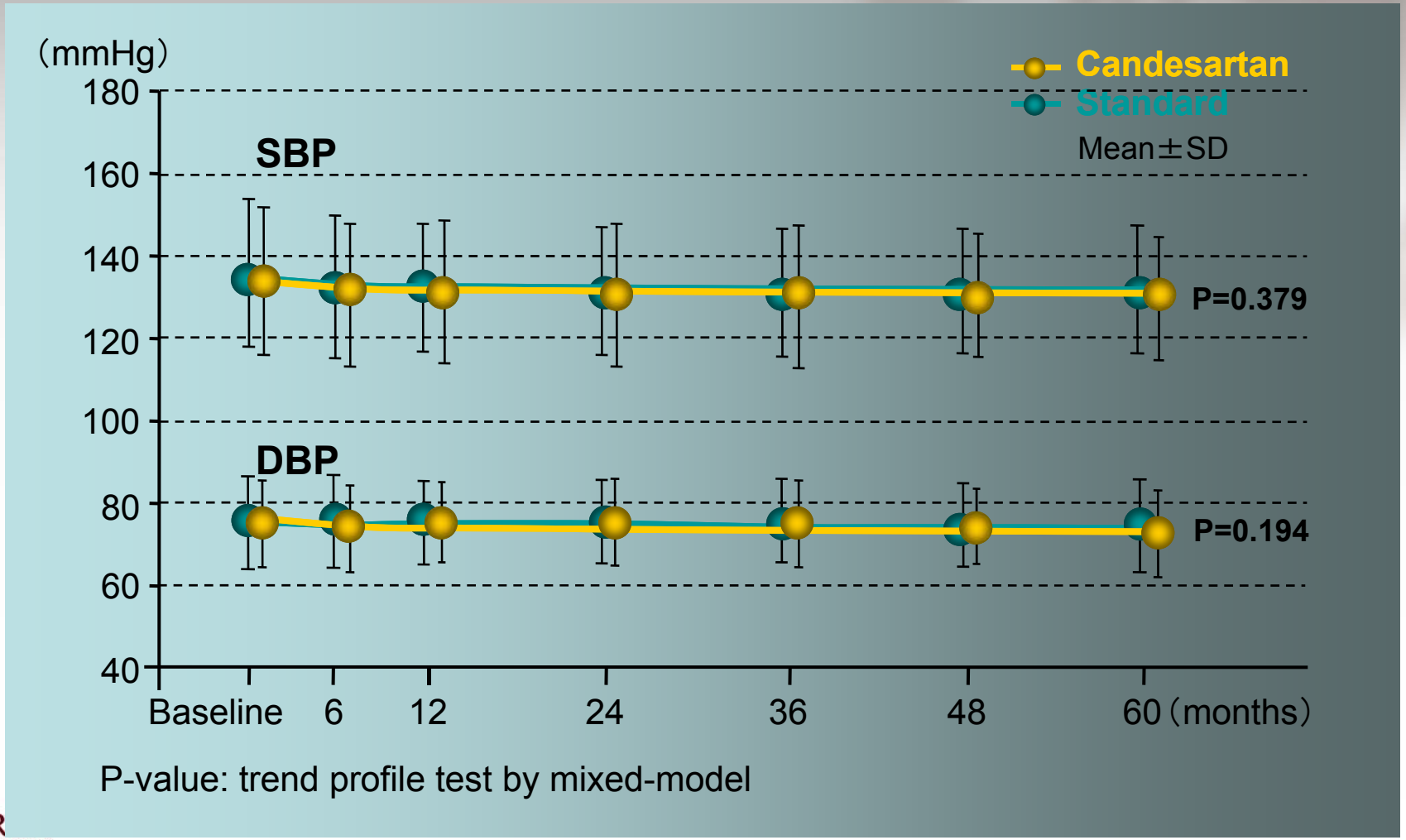
Medications at Randomization

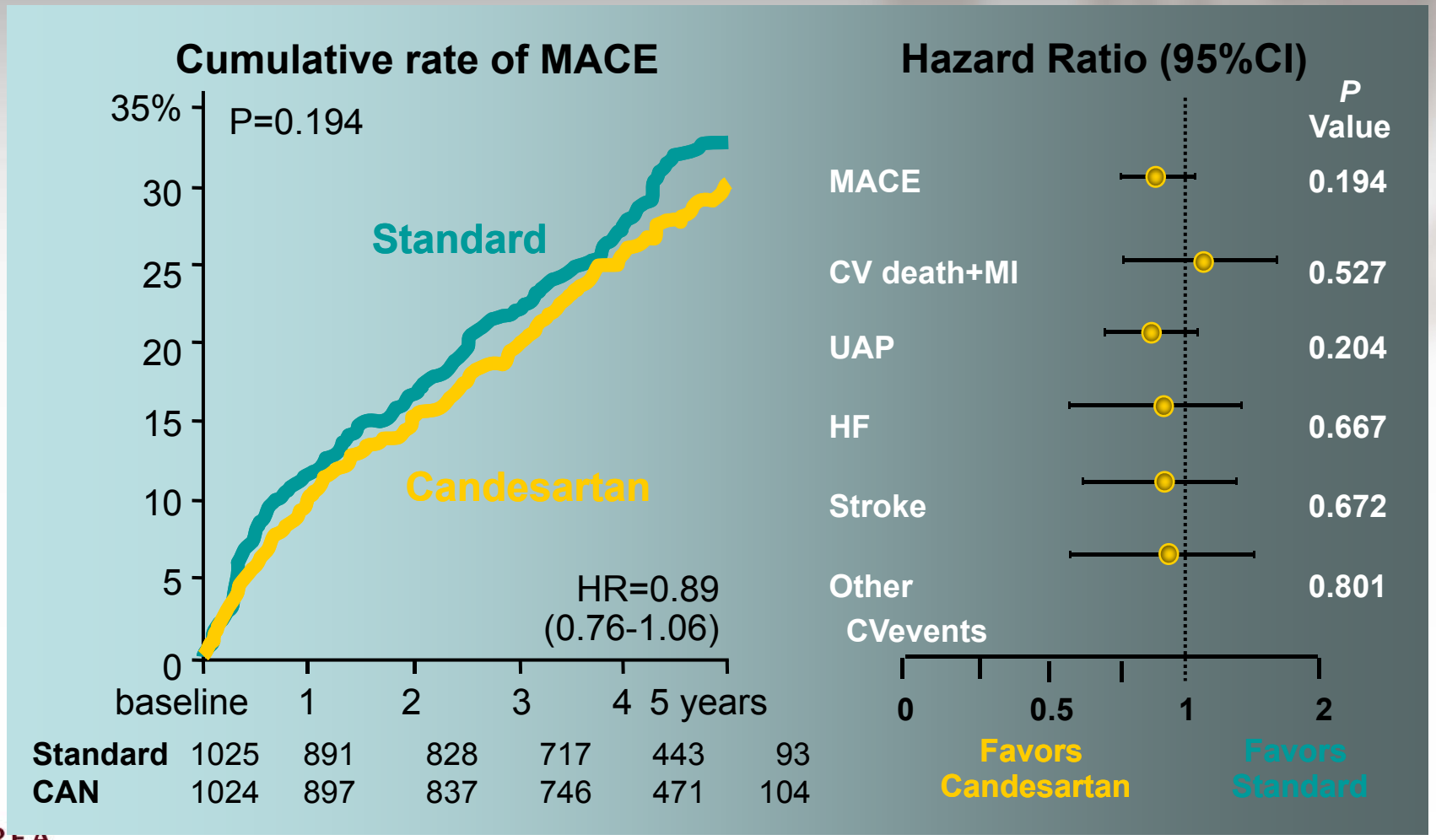
	Candesartan (n=1024)	Standard (n=1025)
Candesartan < 8mg/day	771 (75%)	not allowed
Candesartan ≥ 8mg/day	253 (25%)	
ACEis	not allowed	723 (71%)
Calcium channel blockers	457 (45%)	574 (56%)
Beta blockers	464 (45%)	506 (49%)
Diuretics	103 (10%)	82 (8%)
Statins	459 (45%)	447 (44%)
Nitrates	503 (49%)	526 (51%)
Aspirin	948 (93%)	935 (91%)

Blood Pressure Changes

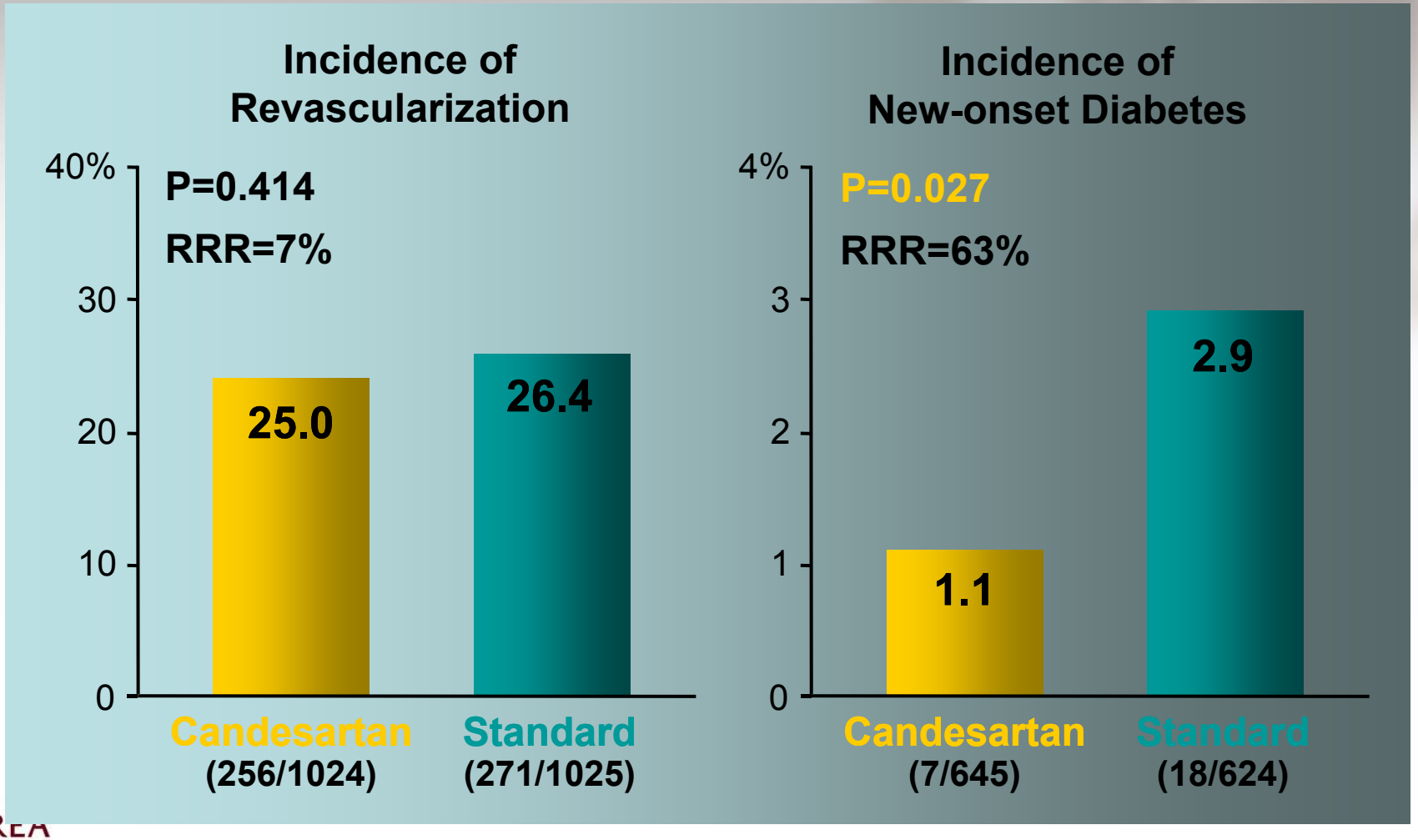


P-value: trend profile test by mixed-model

Primary Endpoint



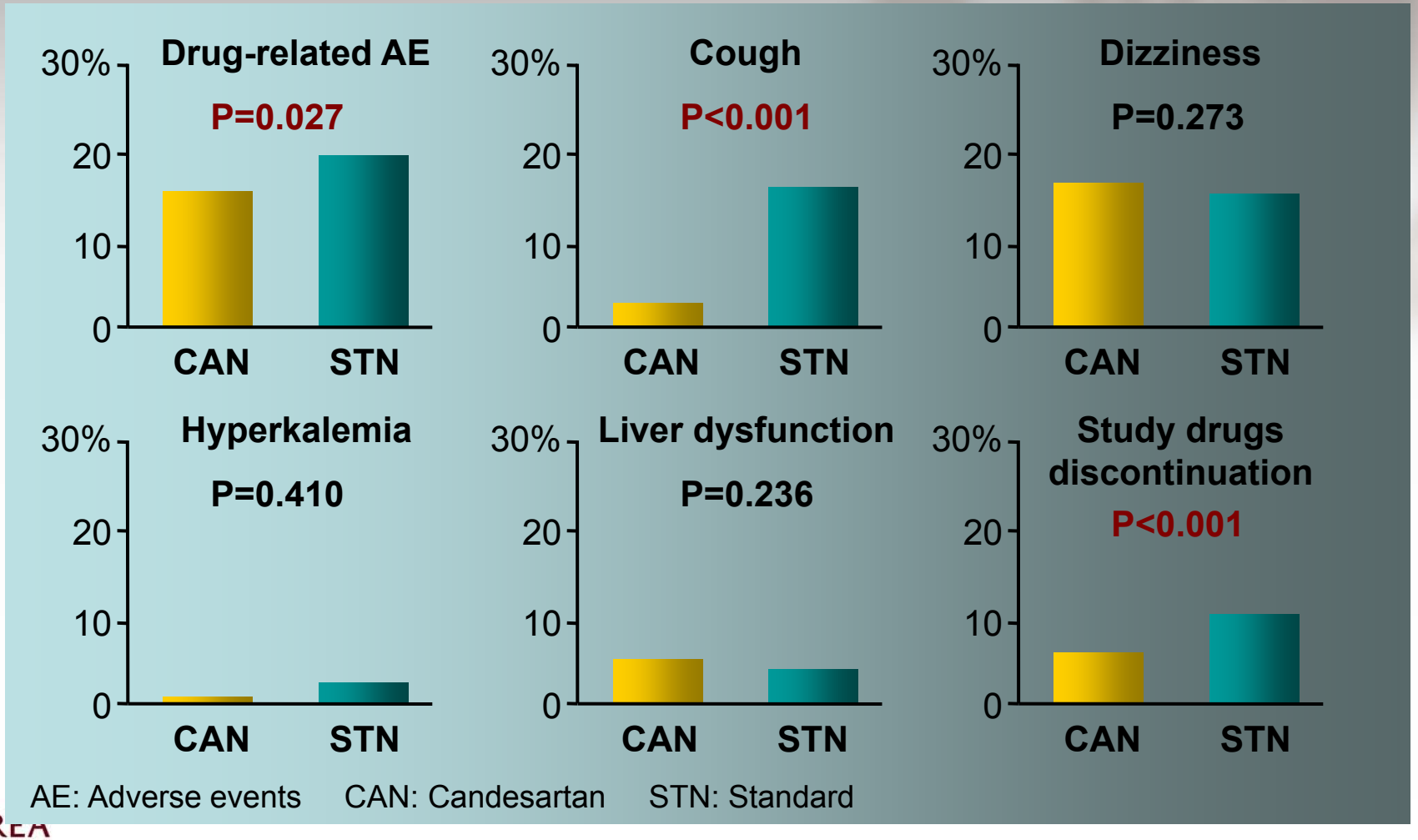
Secondary Endpoint



Candesartan vs Standard with ACEi

	Candesartan (n=1024)	ACEi (n=723)	HR [95%CI]	*P* value
Primary endpoint				
MACE	264 (25.8%)	203 (28.1%)	0.90 [0.75-1.08]	0.24
CV death + MI	57 (5.6%)	40 (5.5%)	1.01 [0.67-1.51]	0.96
UAP	151 (14.7%)	117 (16.2%)	0.90 [0.70-1.14]	0.38
HF	40 (3.9%)	35 (4.8%)	0.80 [0.51-1.26]	0.34
Stroke	45 (4.4%)	38 (5.3%)	0.83 [0.54-1.27]	0.39
other CV events	35 (3.4%)	27 (3.7%)	0.91 [0.55-1.50]	0.70
Secondary endpoints				
revascularization	256 (25.0%)	192 (26.6%)	0.92 [0.77-1.12]	0.41
New-onset DM	7/645 (1.1%)	12/418 (2.9%)	0.37 [0.15-0.94]	0.04

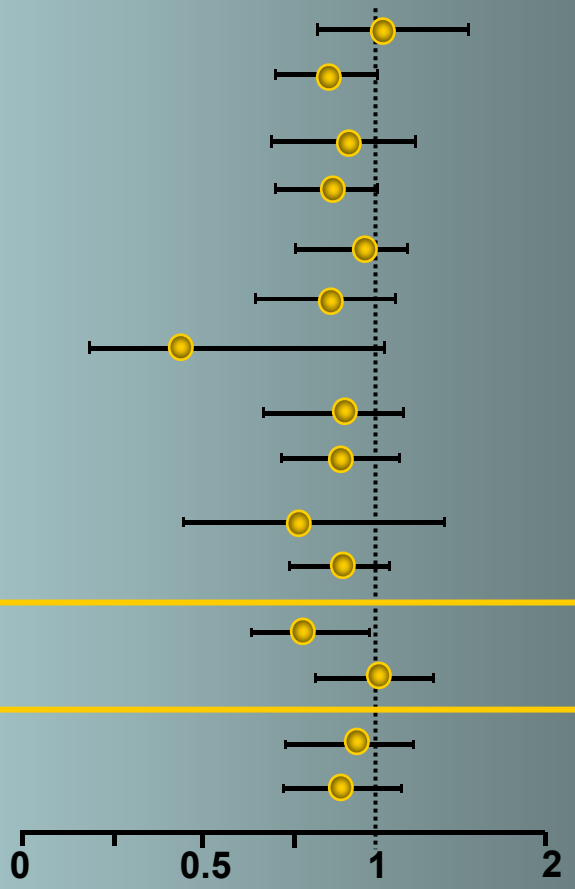
Secondary Endpoint



AE: Adverse events CAN: Candesartan STN: Standard

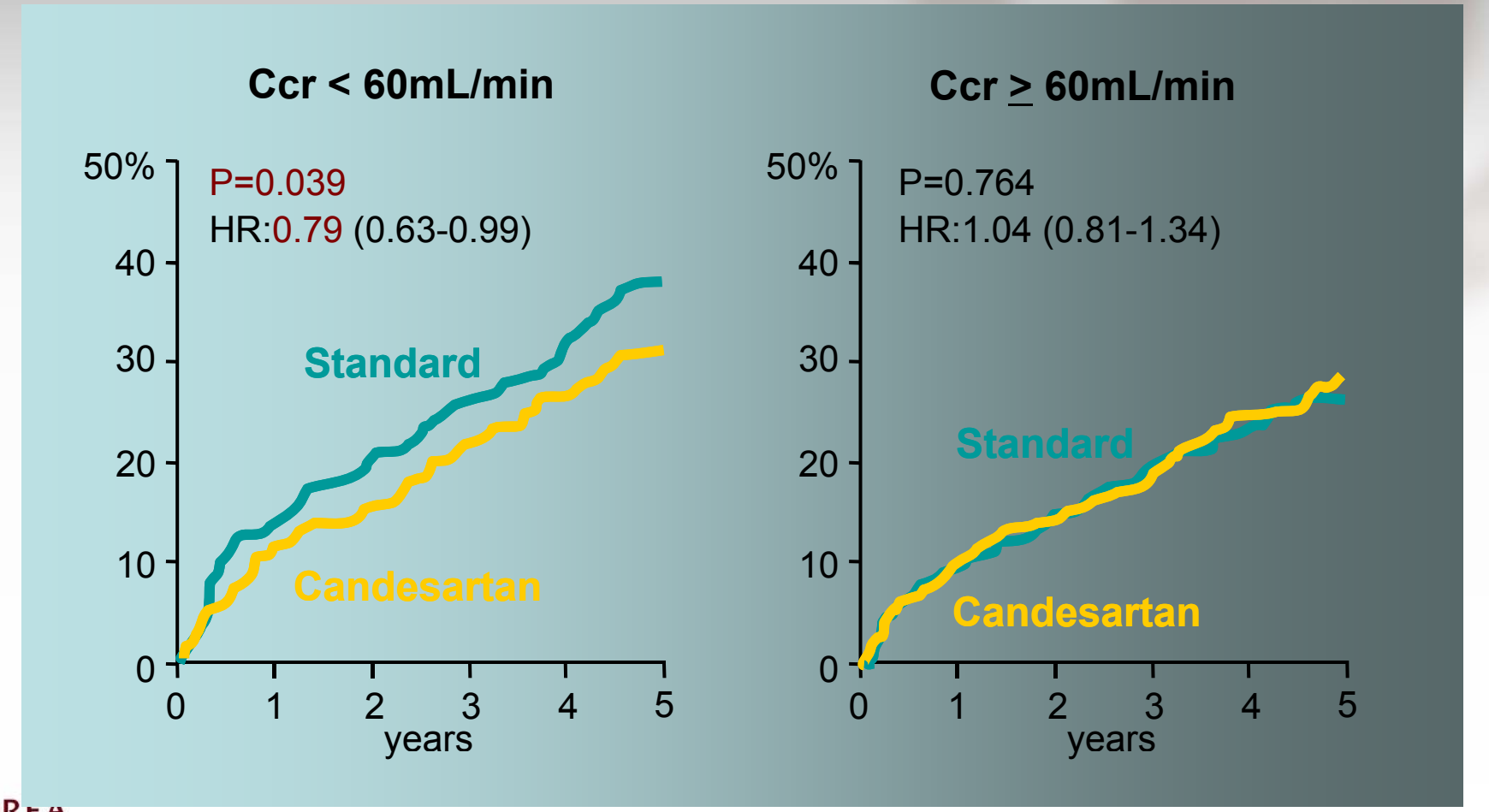
Subgroup analysis for MACE

		Hazard Ratio	*P*-Value	*P*-value for Interaction
Women		1.05	0.80	0.361
Men		0.88	0.11	
Age	<65	0.93	0.61	0.749
	≥65	0.88	0.22	
BMI	<25	0.97	0.76	0.143
	≥25 <30	0.87	0.30	
	≥30	0.45	0.07	
ACS	Yes	0.91	0.48	0.962
	No	0.90	0.31	
EF	≤35	0.78	0.40	0.584
	>35	0.90	0.24	
Ccr	**<60***	**0.79**	**0.04**	0.113
	≥60	1.04	0.76	
CRP	<2	0.94	0.63	0.768
	≥2	0.90	0.36	



* : median

Subgroup analysis by renal function (MACE)



Summary

In comparison with standard therapy, Candesartan-based therapy

- reduced the incidence of MACE by 11%, while not statistically significant.
- reduced the incidence of new-onset DM by 63%.
- caused a lower incidence of drug-related AE.
- significantly reduced the incidence of MACE by 21% in patients with impaired renal function.

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Conclusion

- Candesartan-based therapy produced comparable effects to Non-ARB-based standard therapy and was well tolerated in CAD patients with hypertension.

- Furthermore, candesartan significantly reduced the incidence of new-onset DM.

- The present study provides evidence to support the rationale for candesartan-based therapy in CAD patients,particularly in those with chronic kidney disease.

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Conclusions

- Candesartan and Amlodipine equally reduce the number of CV events in high-risk hypertensive patients under strict BP control.
- Candesartan-based therapy produced comparable effects to Non-ARB-based standard therapy and was well tolerated in CAD patients with hypertension.
- Candesartan is more beneficial than Amlodipine and ACEI for hypertensive patients with chronic kidney disease or obesity, and may be preferable for patients with metabolic syndrome.

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제1회 임상의사를 위한 최신 심장학 Core Review

KOALA Symposium

(KOrea Guro cArdiovascuLAr Center)

일시 2008. 5.10(토) 14:00~18:30 **장소** 고려대학교 구로병원 대강당

AGENDA

→ 고혈압 Recent Advances in Treatment of Hypertension

- 새로운 고혈압 치료기법
- 대사증후군 동반 고혈압의 치료전략
- 폐성 고혈압의 진단과 치료의 최신지견

→ 고지혈증/동맥경화증 Update in Atherosclerosis Managemen

- 최근 발표된 의미 있는 임상연구 결과
- 노인과 일반인에서 고지혈증 치료의 차이
- 'The lower the better' 모든 환자들에서 적용해도 좋은가?

→ 관상동맥/말초혈관 질환 Controversies in Coronary Heart Disease

- 안정형 협심증 환자에서 약물치료는 중재시술치료 보다 예후가 나쁜가?
- 동맥경화증의 치료에 맞춤형의학은 현실화 될 것인가?
- 약물 용출성 스텐트 시술 후 항혈소판 치료는 언제까지 해야 하나 ?
- 말초혈관질환 치료의 최신지견–혈관질환 Clinic / Wound Center 를 중심으로

→ 심부전 Essentials in Heart Failure

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→ 심부전 Essentials in Heart Failure

- 심부전 약물 치료의 실제: 약제의 선택, 용량, 사용순서 그리고 병합
- 심부전 환자가 다른 질환도 있다면? 피해야 할 약은?
- 심부전 환자의 예후 인자

The mechanism of prevention of DM by inhibition of the RAS

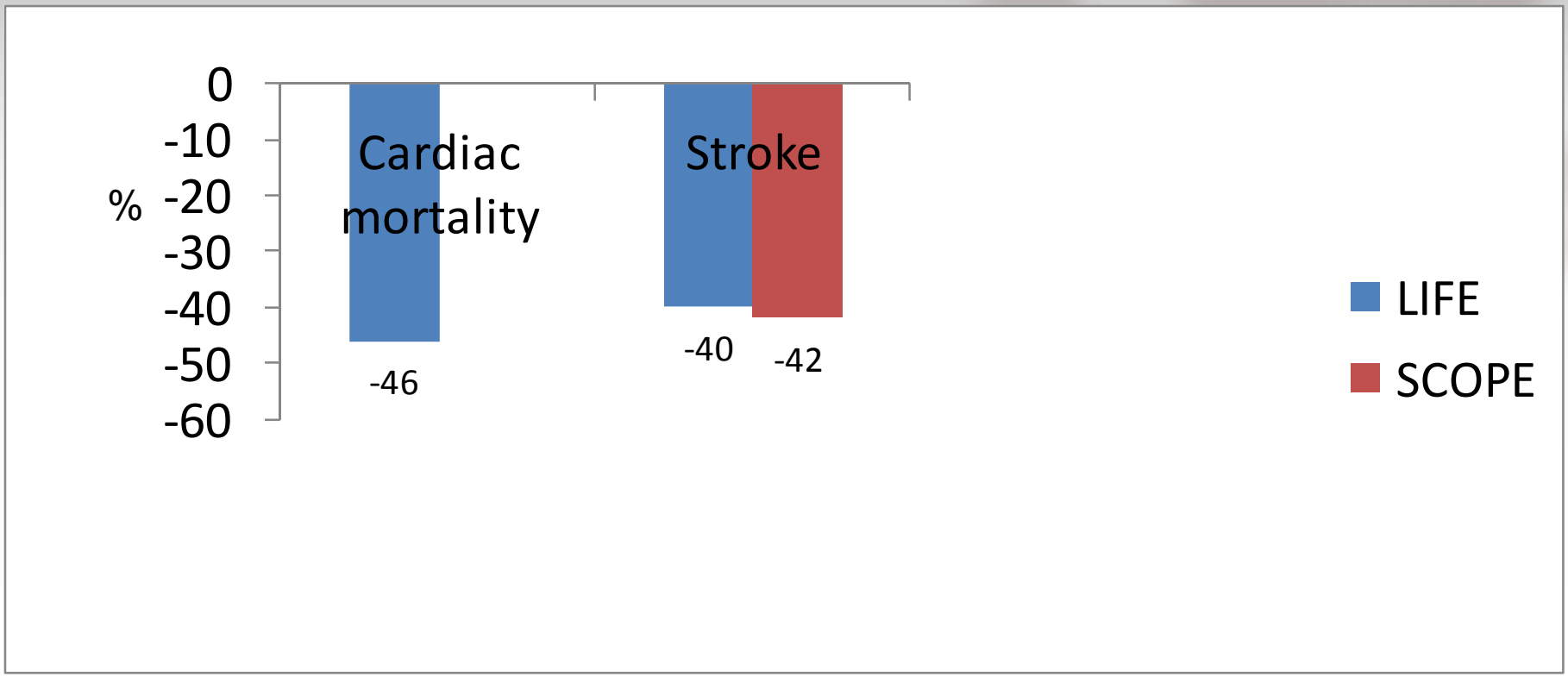
- Hemodynamic benefits

  - antagonizing the Ang II–mediated hypoperfusion of skeletal muscle or pancreatic islet cells. *Circulation 2004;110:*1507–1512

- Direct inhibitory effects of angiotensin II on insulin signaling and glucose transport *Am J Cardiol 2003;91(suppl):30H–37H*

- Reduction in islet fibrosis and increased B-cell mass, by decreasing oxidative stress, apoptosis, and profibrotic pathways *J Hypertens 2005;23:463– 473.*

Isolated systolic hypertension



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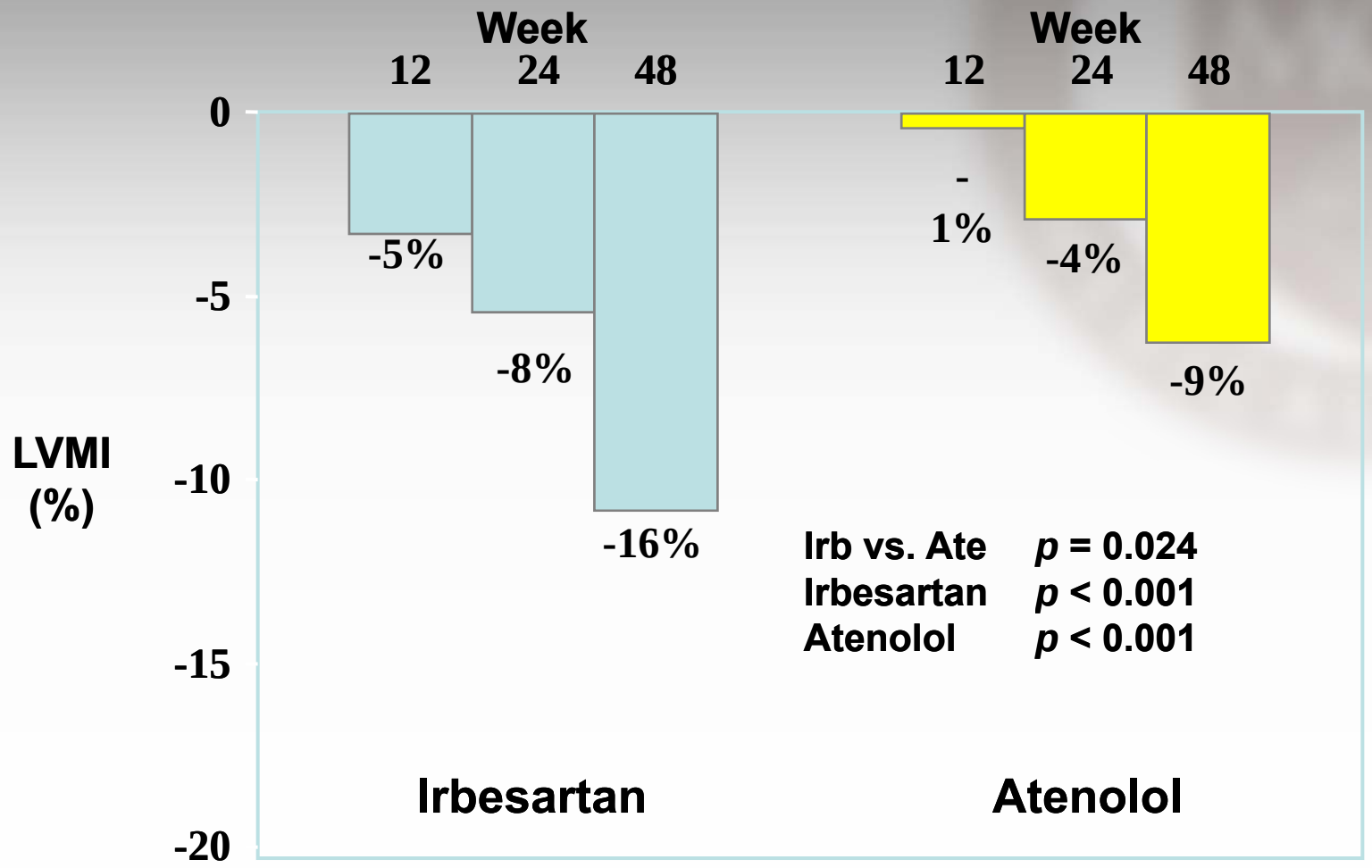
Irbesartan vs. atenolol in hypertension & LVH: LVMI reduction



Malmqvist K, Kahan T et al. *J Hypertens* 2001:19(6);1167-76.

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Predictors of new-onset atrial fibrillation

- Hypertension
- Left ventricular mass and hypertrophy
- Left atrial enlargement
- Congestive heart failure and valvular and coronary heart disease
- Heart rate below 72 beats/min (PIUMA study, Val-HeFT trial)
- Aging (>70세 → 1.5배), Male (1.5배)
- Diabetes
- BNP level