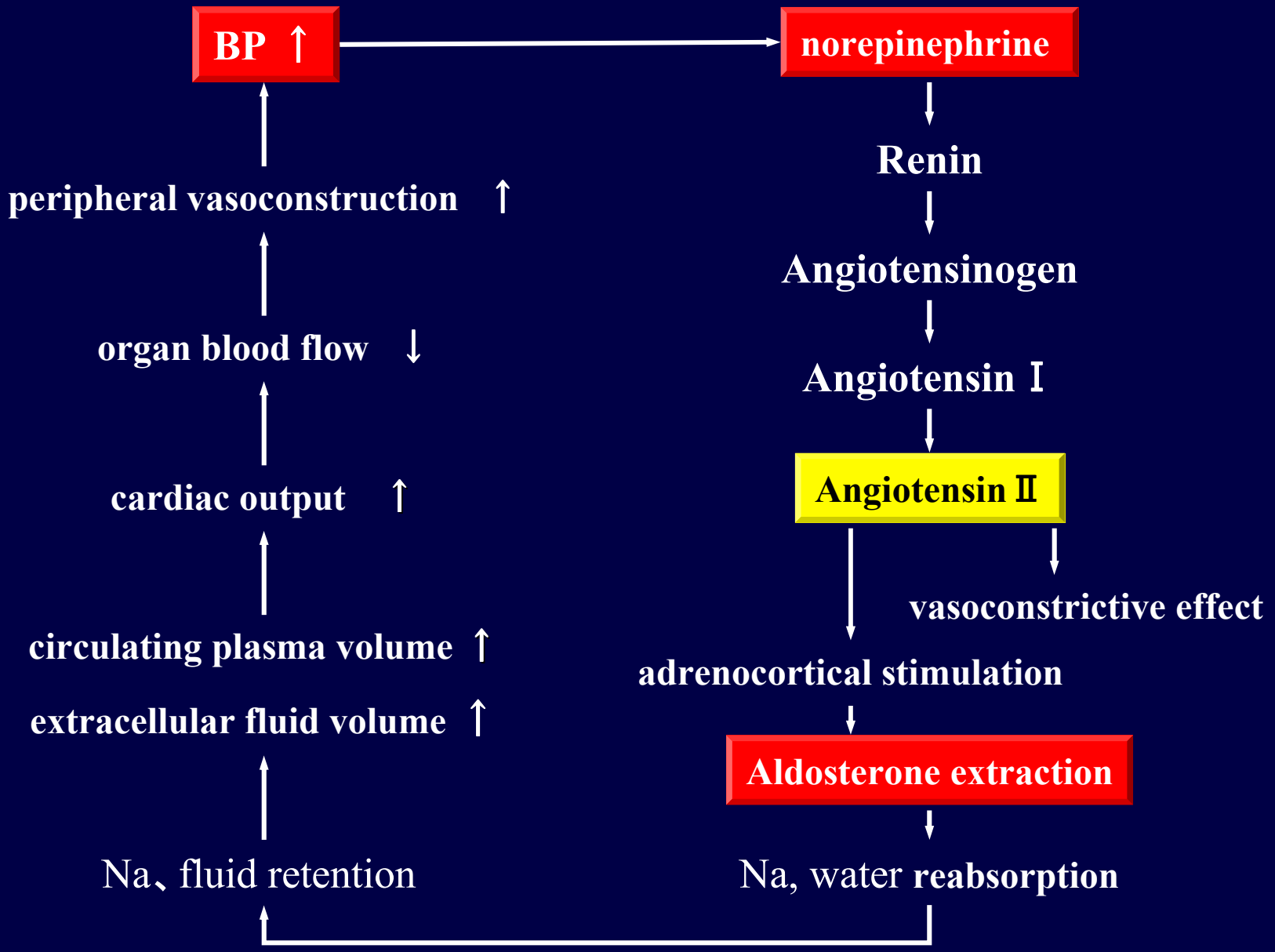
JIKEI HEART Study

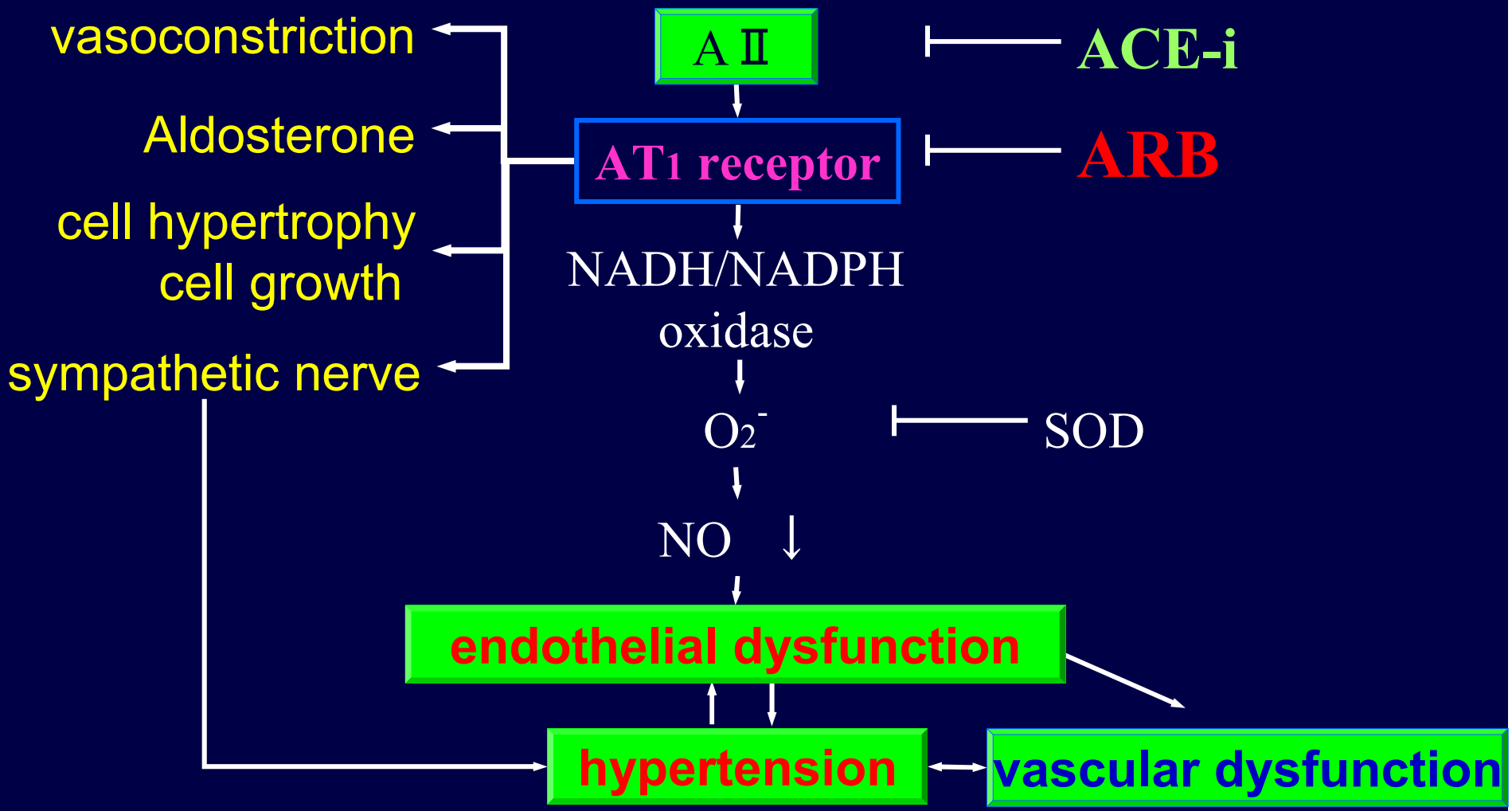
Japanese Investigation of Kinetic Evaluation In Hypertensive Event And Remodeling Treatment Study

Lancet 2007, 369

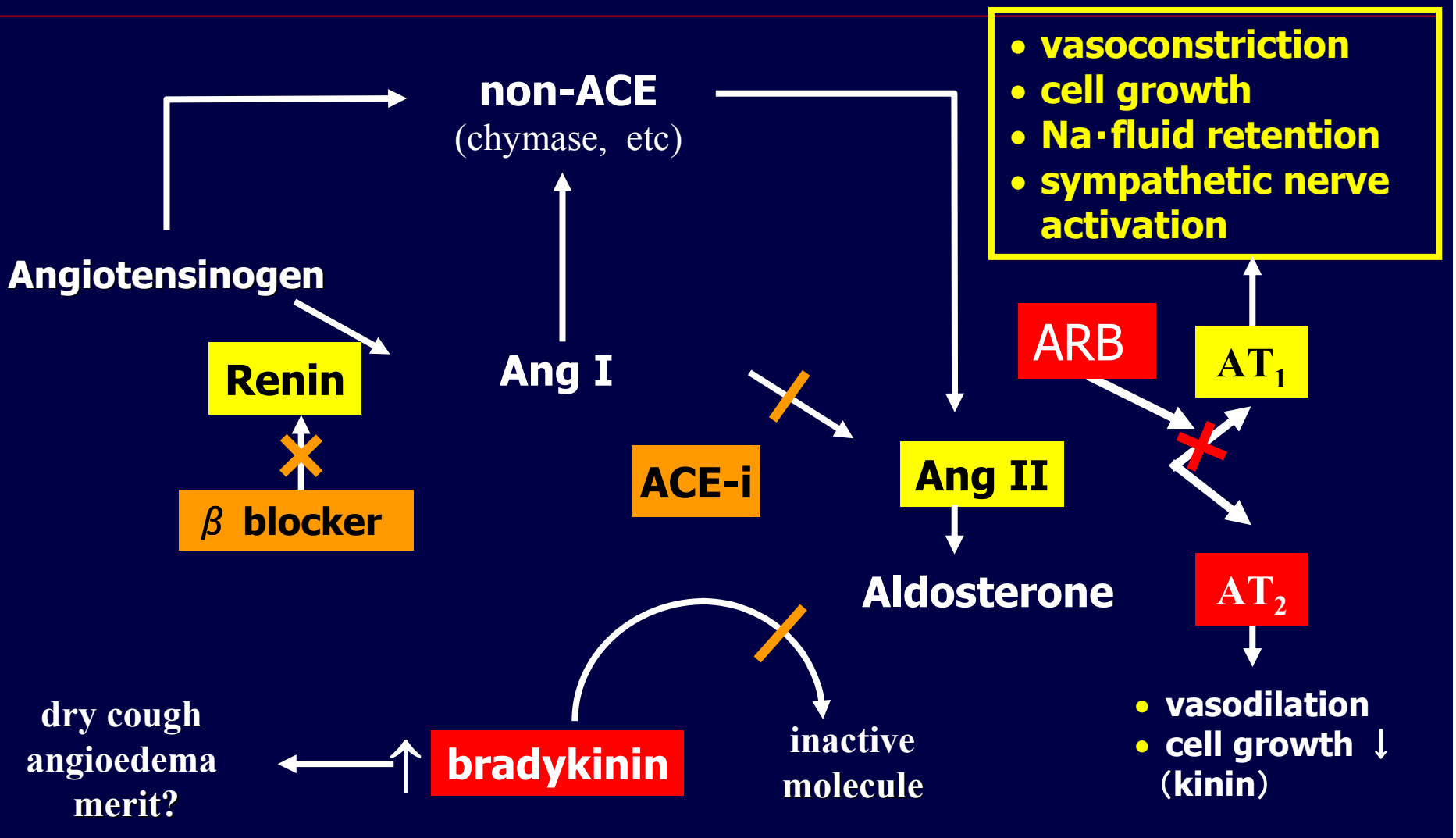
Hypertension and neurohormonal factor



Angiotensin II and endothelial dysfunction



Renin-Angiotensin-Aldosterone System



Study Design

- Study hypothesis:
  - Valsartan will improve morbidity and mortality when added to conventional therapies in Japanese patients with hypertension and cardiovascular disease

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Endpoint

- Primary endpoint:
  - Composite of CV mortality and morbidity
    - Stroke or TIA, MI, hospitalisation for CHF or angina pectoris, dissecting aneurysm of the aorta, lower limb arterial obstruction, doubling of serum creatinine or transition to dialysis

- Secondary endpoint:
    - Death from any cause, left ventricular hypertrophy, changes in ECG, proteinuria, B-type natriuretic peptide (BNP), heart failure symptoms, heart failure syndrome, blood pressure and heart rate.

Mochizuki S : Cardiovasc Drugs Ther 18 305-309, 2004

JIKEI HEART Study

- Investigator initiated and conducted
- Prospective, randomized, open-label, blinded endpoint（PROBE）
- 3,081 Japanese patients with high blood pressure, coronary heart disease and/or heart failure
- Valsartan vs Non-ARB-based therapy to achieve aggressive BP target of 130/80 mmHg

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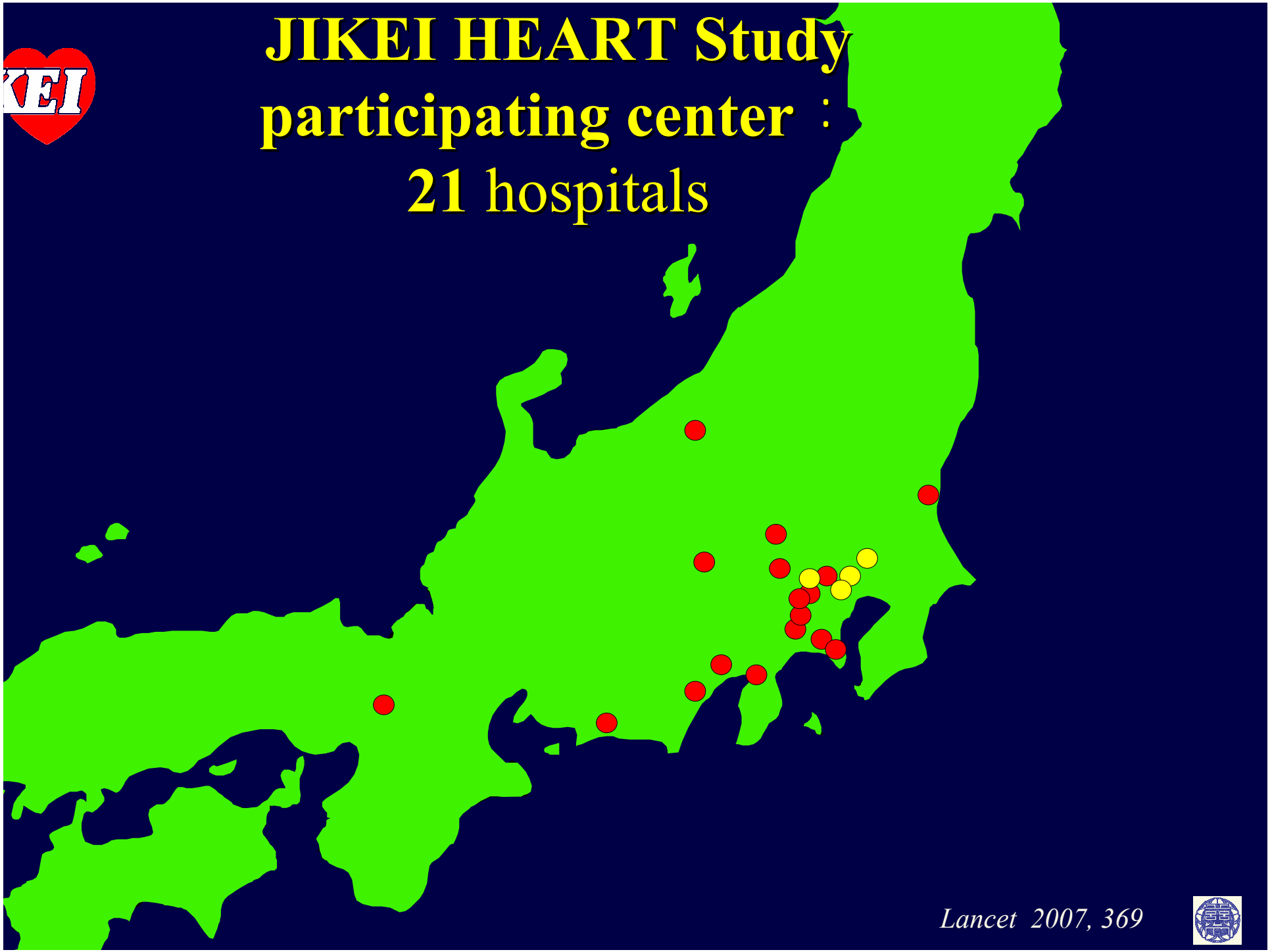
JIKEI HEART Study
participating center：
21 hospitals
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Exclusion criteria

- acute coronary syndrome or myocardial infarction within 6 manths
- any cerebrovascular event within 3 months
- serum creatinin higher than 3.0mg/dL
- potassium higher than 5mmol/L
- treatment with an angiotensin receptor blocker 4 weeks or less before randomization
- judgment by the physician that participation was unwise on the basis of patient characteristics and drug safety

Mochizuki S : Cardiovasc Drugs Ther 18 305-309, 2004

Treatment schedule

Medications at baseline

Medication	Valsartan group (n=1,541)	non-ARB group (n=1,540)
CCB	1,041(68%)	1,011(66%)
ACE-I	548(36%)	525(34%)
β-blocker	486(32%)	502(33%)
α-blocker	74(5%)	93(6%)
Thiazide	29(2%)	39(3%)
Antialdosterone agent	52(3%)	64(4%)
other diuretics	117(8%)	126(8%)
Statin	461(30%)	490(32%)
Fibrate	42(3%)	37(2%)

-4
Week

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Baseline characteristics

Medical history	Valsartan group (n=1,541)	Non-ARB group (n=1,540)
Hypertension	1,358（88%）	1,341（87%）
Coronary heart disease	514（33%）	522（34%）
Heart failure	176（11%）	174（11%）
Hyperlipidaemia	812（53%）	813（53%）
Diabetes mellitus	315（20%）	314（20%）

Data are means.

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Baseline characteristics

Clinical characteristics	Valsartan arm (n=1,541)	Non-ARB arm (n=1,540)
Female	521(34%)	517(34%)
Age(years)	65(10)	65(10)
Body-mass index(kg/cm^2)	24(3)	24(3)
Current smoker	259(17%)	262(17%)
Systolic blood pressure(mmHg)	139.2(11.4)	138.8(10.6)
Diastolic blood pressure(mmHg)	81.4(10.5)	81.4(10.8)
Heart rate(beats/min)	71(11)	71(11)

Data are means.

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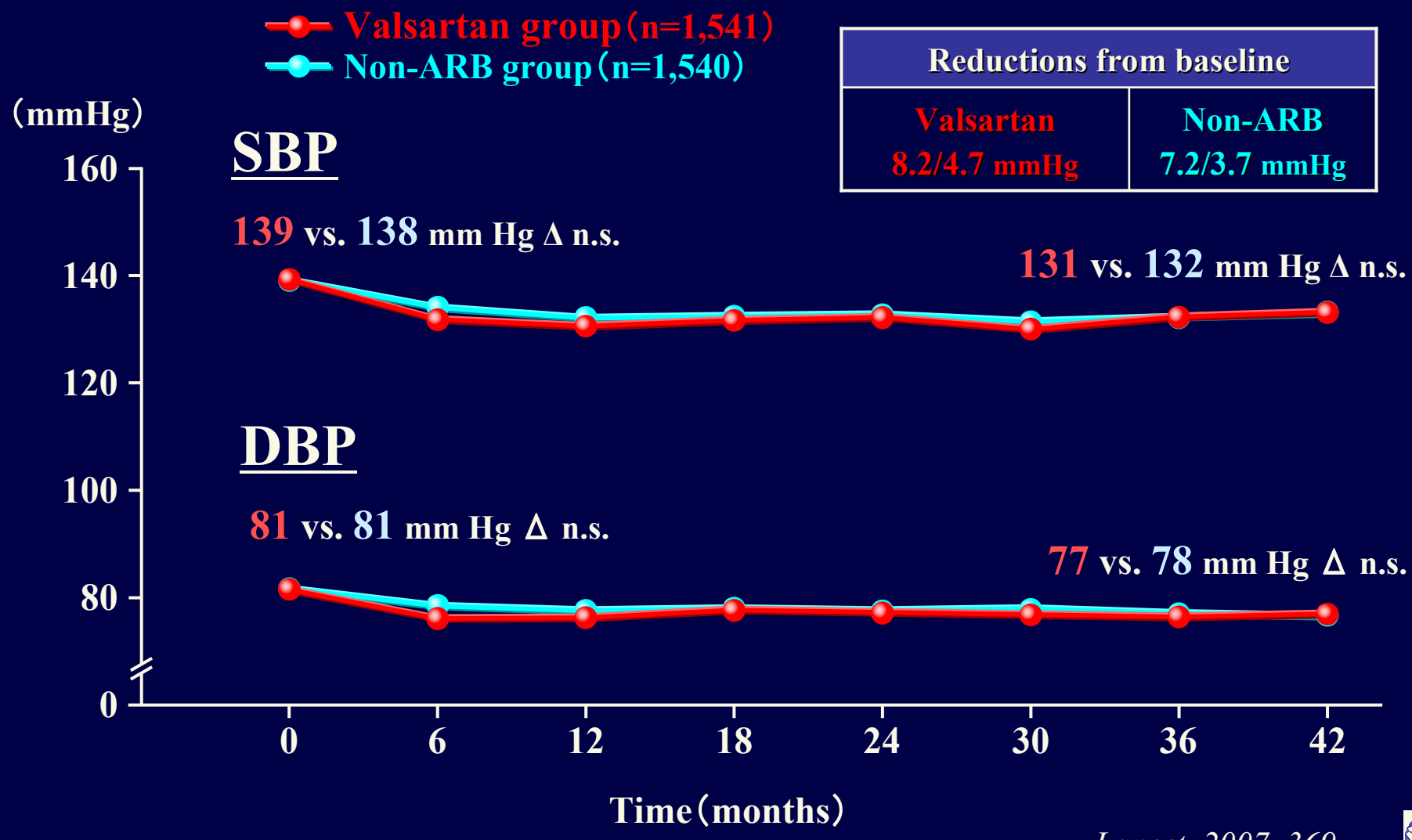
Blood pressure results



Reductions from baseline	
Valsartan 8.2/4.7 mmHg	Non-ARB 7.2/3.7 mmHg

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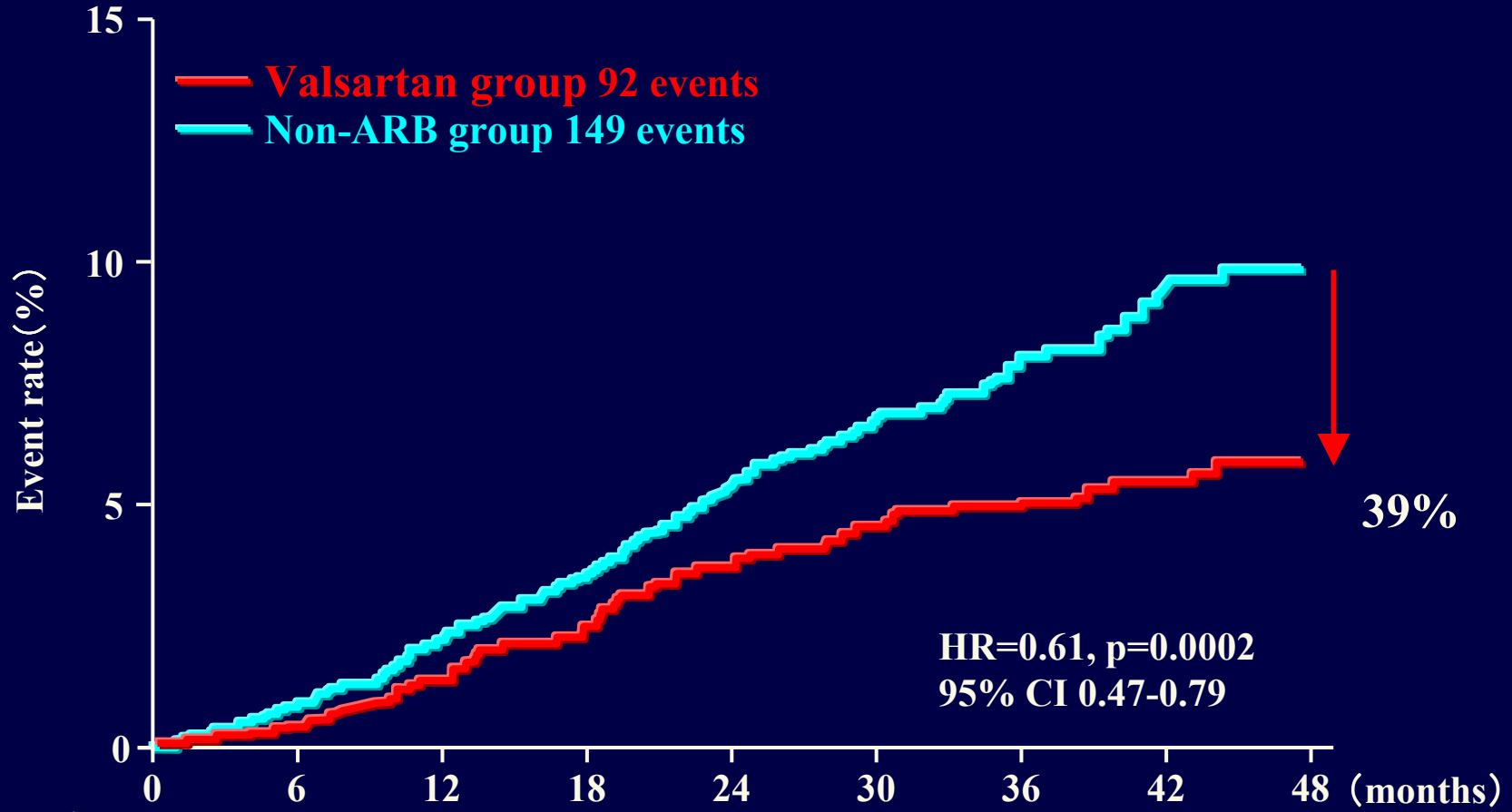
Primary endpoint



Number at risk									
Valsartan	1,541	1,504	1,441	1,257	1,092	855	689	368	368
Non-ARB	1,540	1,502	1,447	1,262	1,075	835	657	344	343

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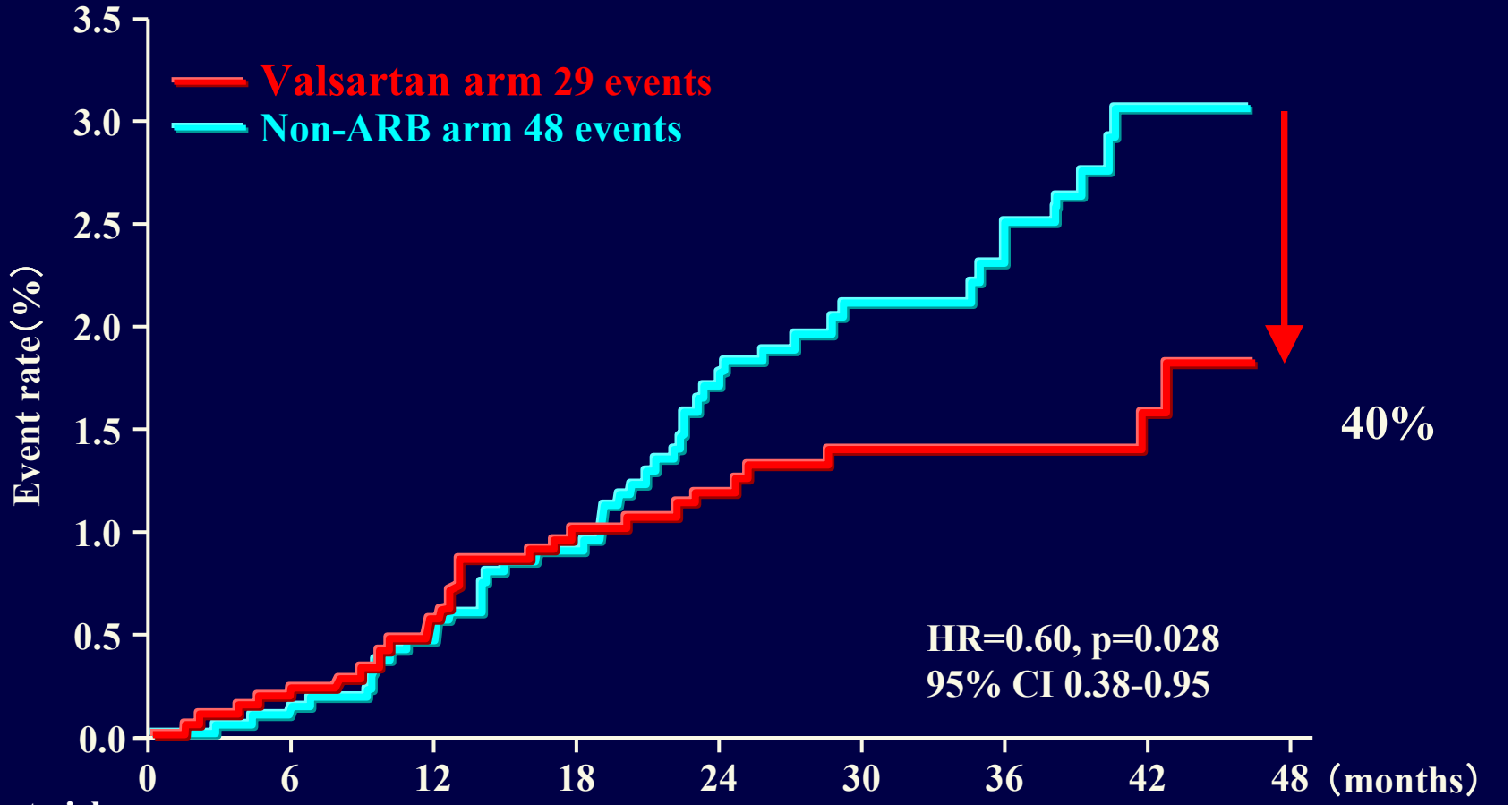
New or recurrent stroke



Number at risk

Valsartan	1,541	1,504	1,442	1,258	1,093	855	689	368	368
Non-ARB	1,540	1,502	1,450	1,266	1,079	836	656	343	343

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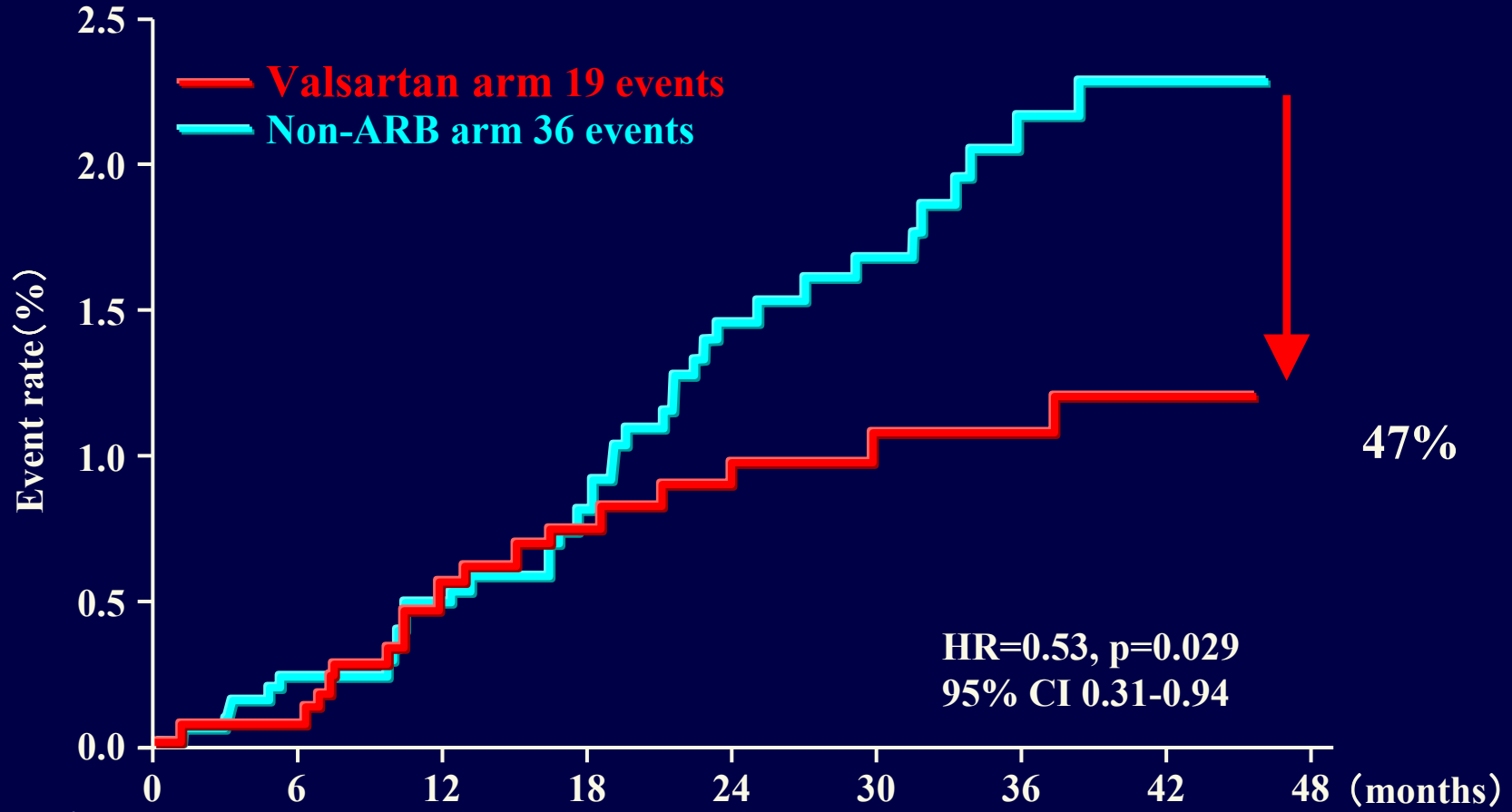
Hospitalization for heart failure



Number at risk									
Valsartan	1,541	1,504	1,441	1,257	1,093	856	690	369	368
Non-ARB	1,540	1,502	1,448	1,265	1,077	837	657	343	343

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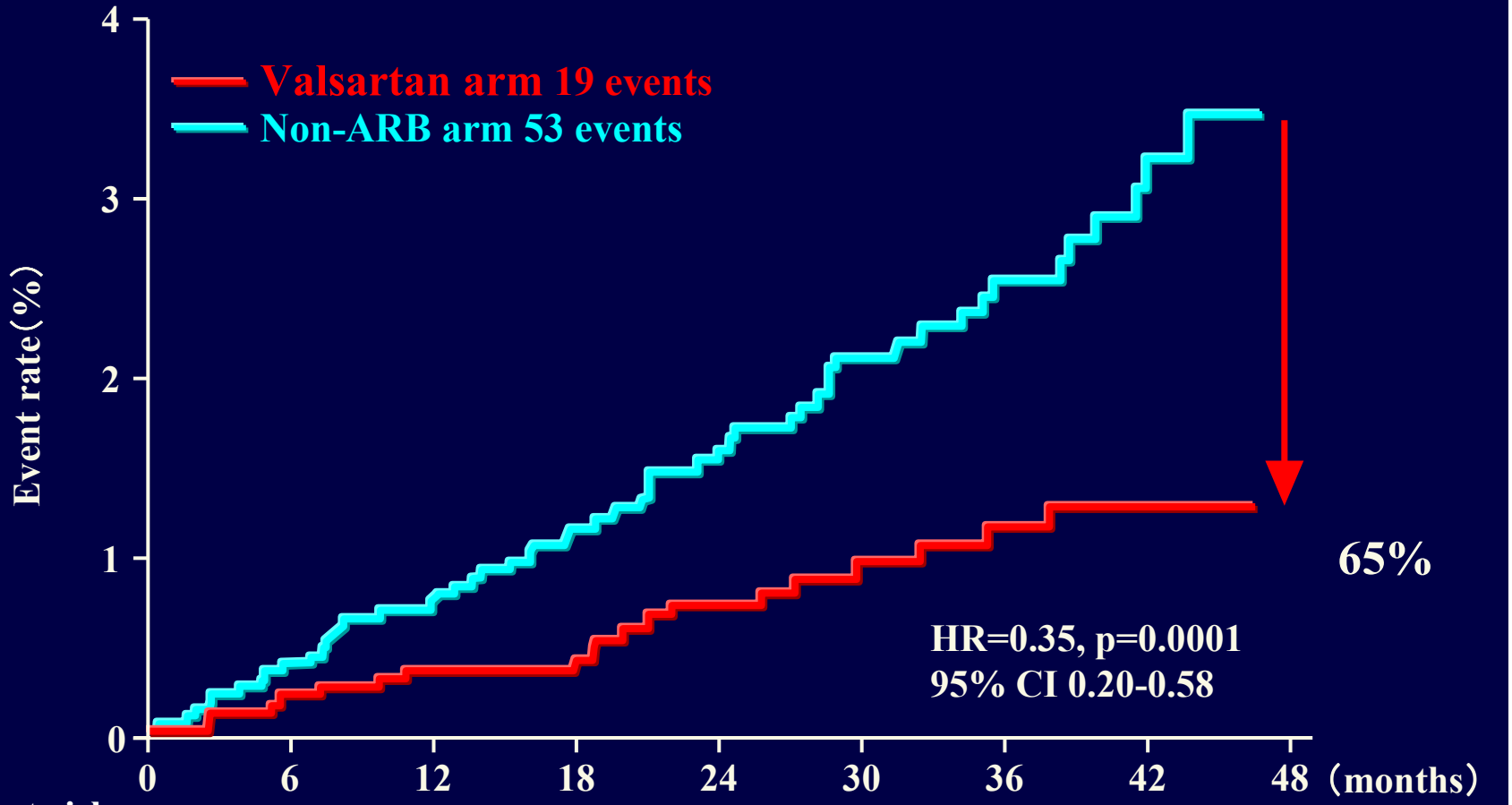
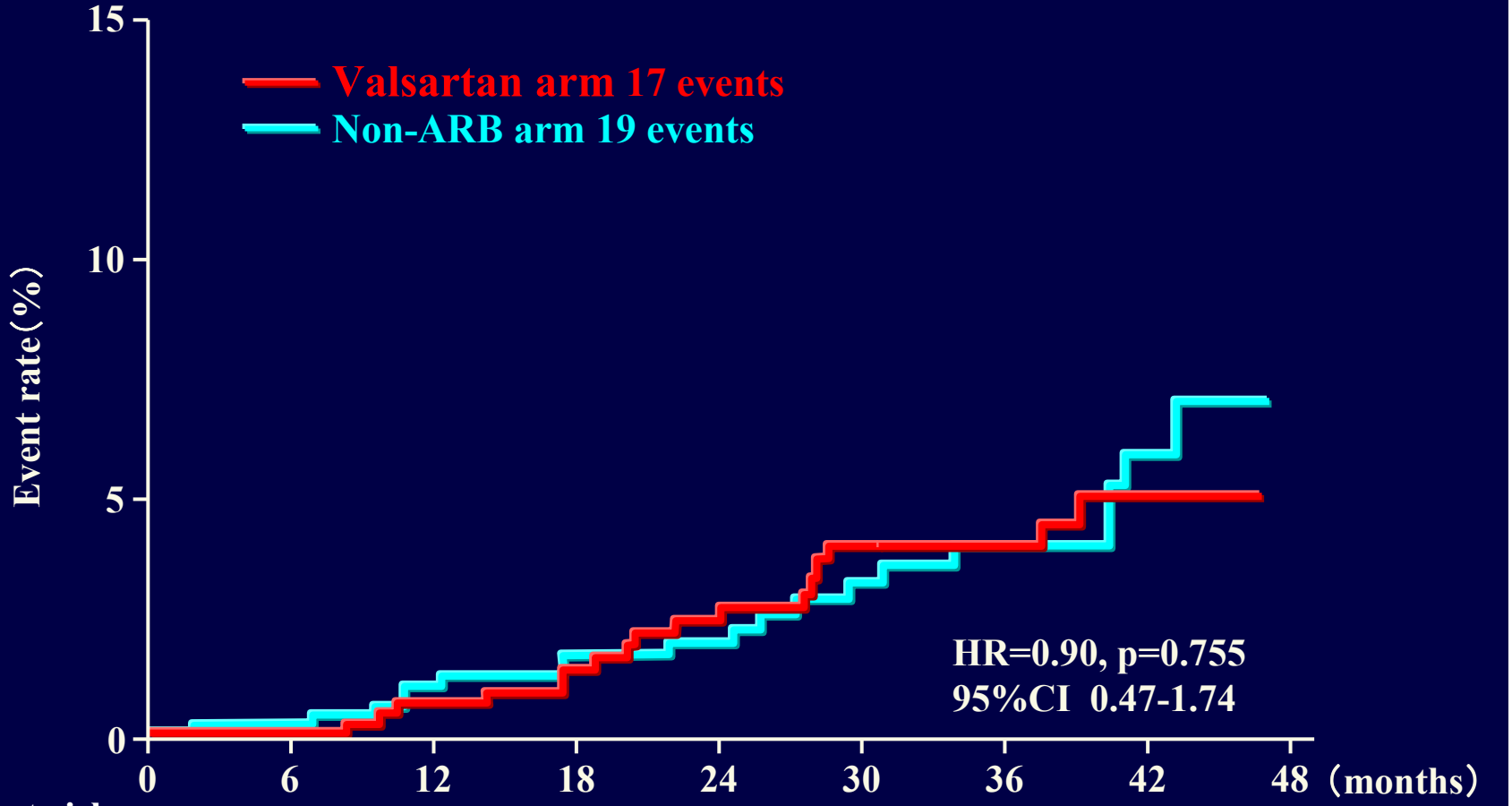
Hospitalization for angina pectoris



Number at risk									
Valsartan	1,541	1,504	1,441	1,257	1,092	855	689	368	368
Non-ARB	1,540	1,504	1,450	1,265	1,078	837	658	343	343

Lancet 2007, 369

New or recurrent acute myocardial infarction



Number at risk									
Valsartan	1,541	1,504	1,441	1,257	1,092	855	689	368	368
Non-ARB	1,540	1,504	1,452	1,267	1,081	839	658	344	343

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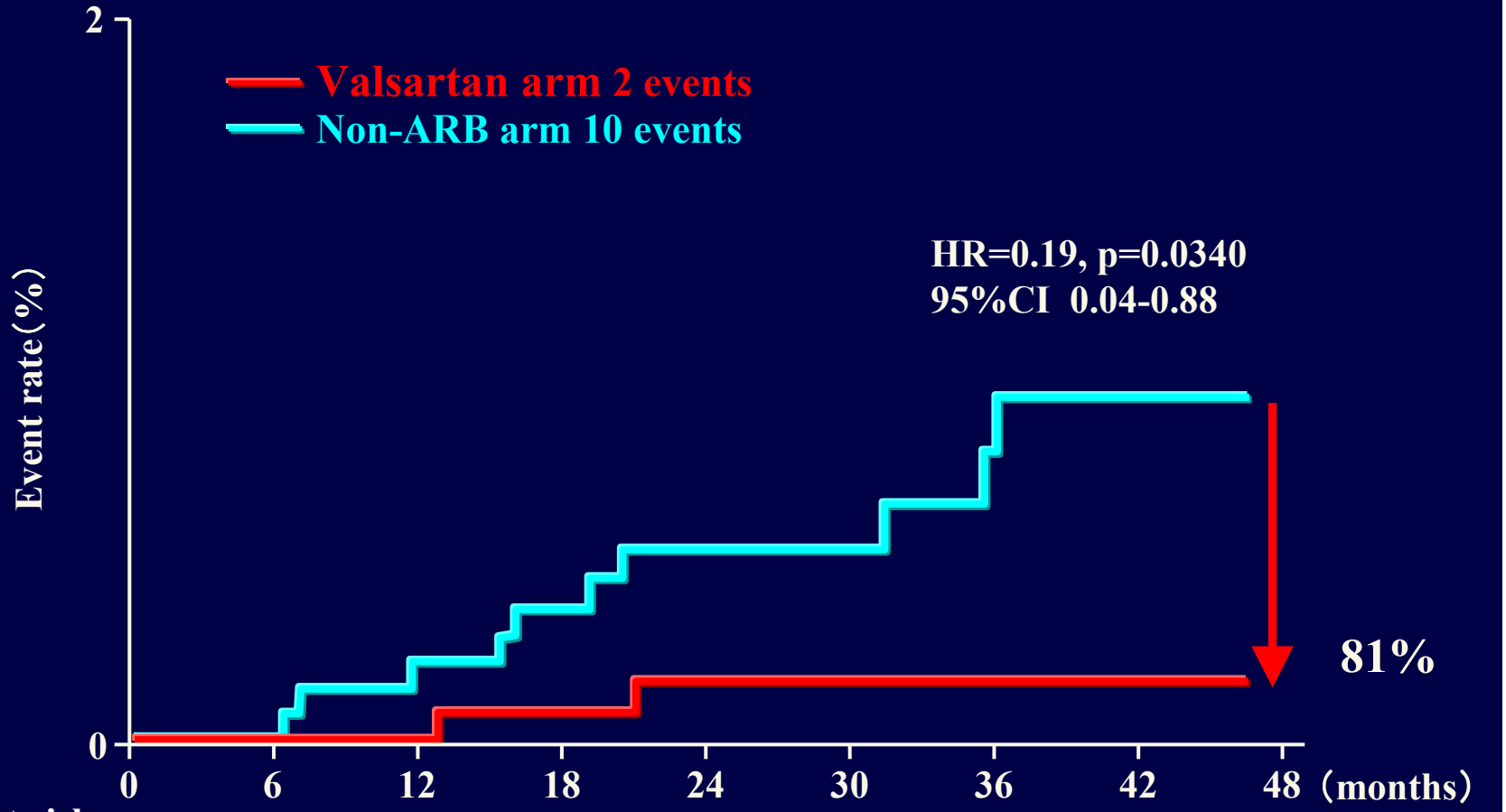
Dissecting aortic aneurysm



Number at risk									
Valsartan	1,541	1,504	1,441	1,257	1,092	855	689	368	368
Non-ARB	1,540	1,502	1,447	1,262	1,075	835	657	344	343

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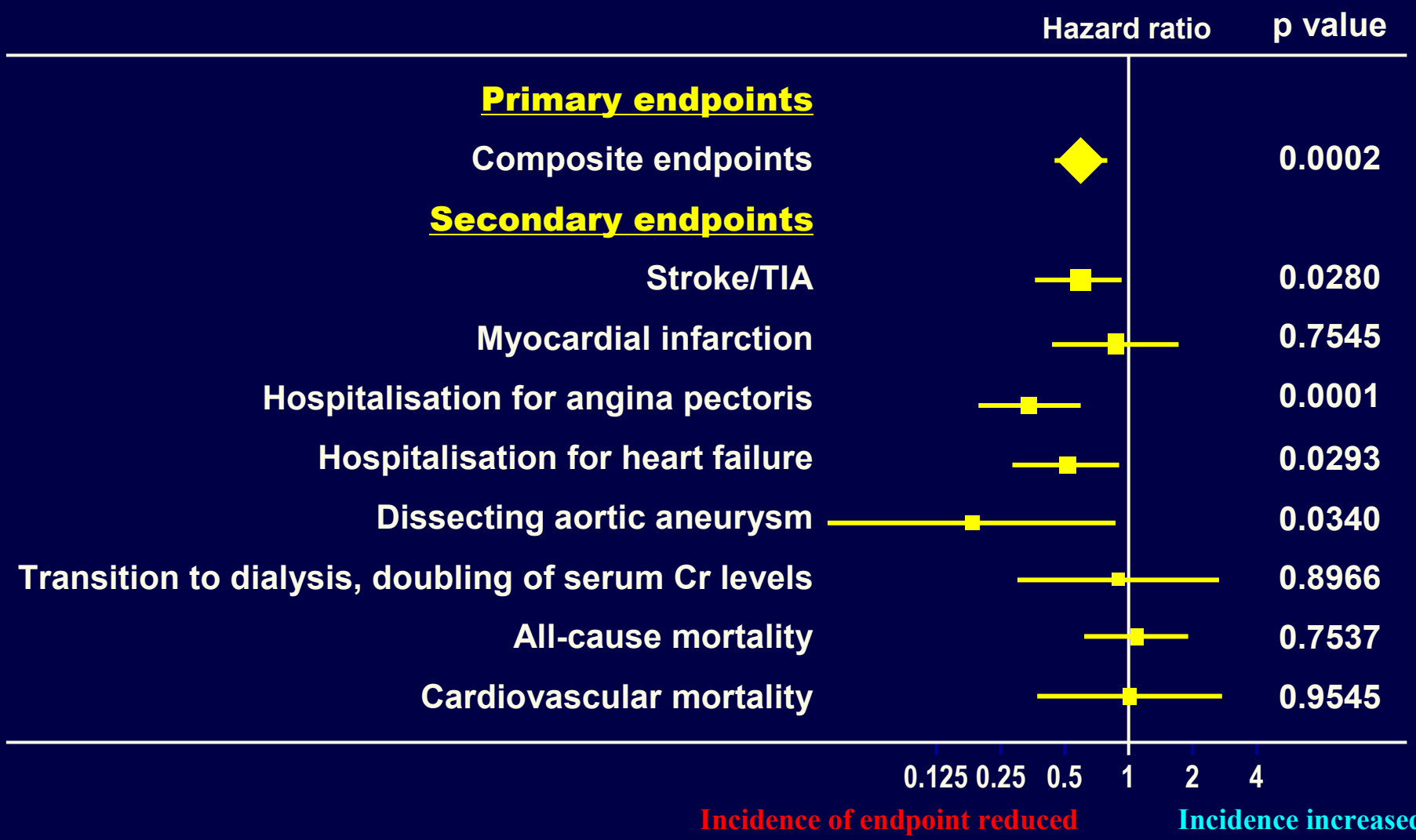
Effect of treatment on endpoints



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Clinical relevance

- For the first time, the clinical benefits of valsartan added to the benefits from blood pressure control, are extended to an Asian population
- The JIKEI Heart Study results are highly relevant to clinical practice
- We have to consider not only aggressive blood pressure control but also which blood pressure drug is the best choice to prevent outcomes

Study organization

- **Executive Committee**

  Chair

  Seibu Mochizuki
  (The Jikei University School of Medicine)

  Björn Dahlöf
  (Sahlgrenska University Hospital, Sweden)

Study organization

- **Endpoint Committee**

  Masatsugu Horiuchi（Chair, Ehime University）

  Junichi Yamazaki（Toho University）

  Hiromi Rakugi（Osaka University）

- **Safety Committee**

  Shigeru Kageyama（Chair）

  Tetsuo Sato, Masato Matsushima, Shigeto Murakami,

  all from The Jikei University School of Medicine.

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Division of Cardiology, Mitaka Hospital - Tatsuo Yamazaki.

Division of Cardiology, ,Higashiyama Takeda Hospital - Izuru Masuda.

Division of Cardiology, Sagamino Central Hospital - Takaaki Iwai.

Division of Cardiology, Seirei-Mikatagahara

- Sousuke Miyazawa, Hideki Kajiwara, Tohru Sugiura.

Dose-adjusted* number of AHT medications

		Baseline	Month 6	Month 12	Month 24	End of study
Valsartan	Val	0	0.93	0.93	0.93	0.95
	Non-ARB	0	0	0	0	0
ACE-I	Val	0.42	0.38	0.38	0.33	0.29
	Non-ARB	0.48	0.50	0.60	0.56	0.58
CCB	Val	0.81	0.79	0.70	0.67	0.67
	Non-ARB	0.76	0.89	0.87	0.87	0.95
ß blocker	Val	0.23	0.22	0.23	0.20	0.20
	Non-ARB	0.18	0.19	0.21	0.21	0.22
Diuretics	Val	0.07	0.11	0.07	0.07	0.06
	Non-ARB	0.07	0.14	0.17	0.20	0.17
all AHT medications	Val	1.79	2.69	2.55	2.55	2.41
	Non-ARB	1.79	2.11	2.39	2.39	2.44

* Dose of each individual drug adjusted in % of standard dose of that drug in Japan.

Mechanism of ARB

Stroke

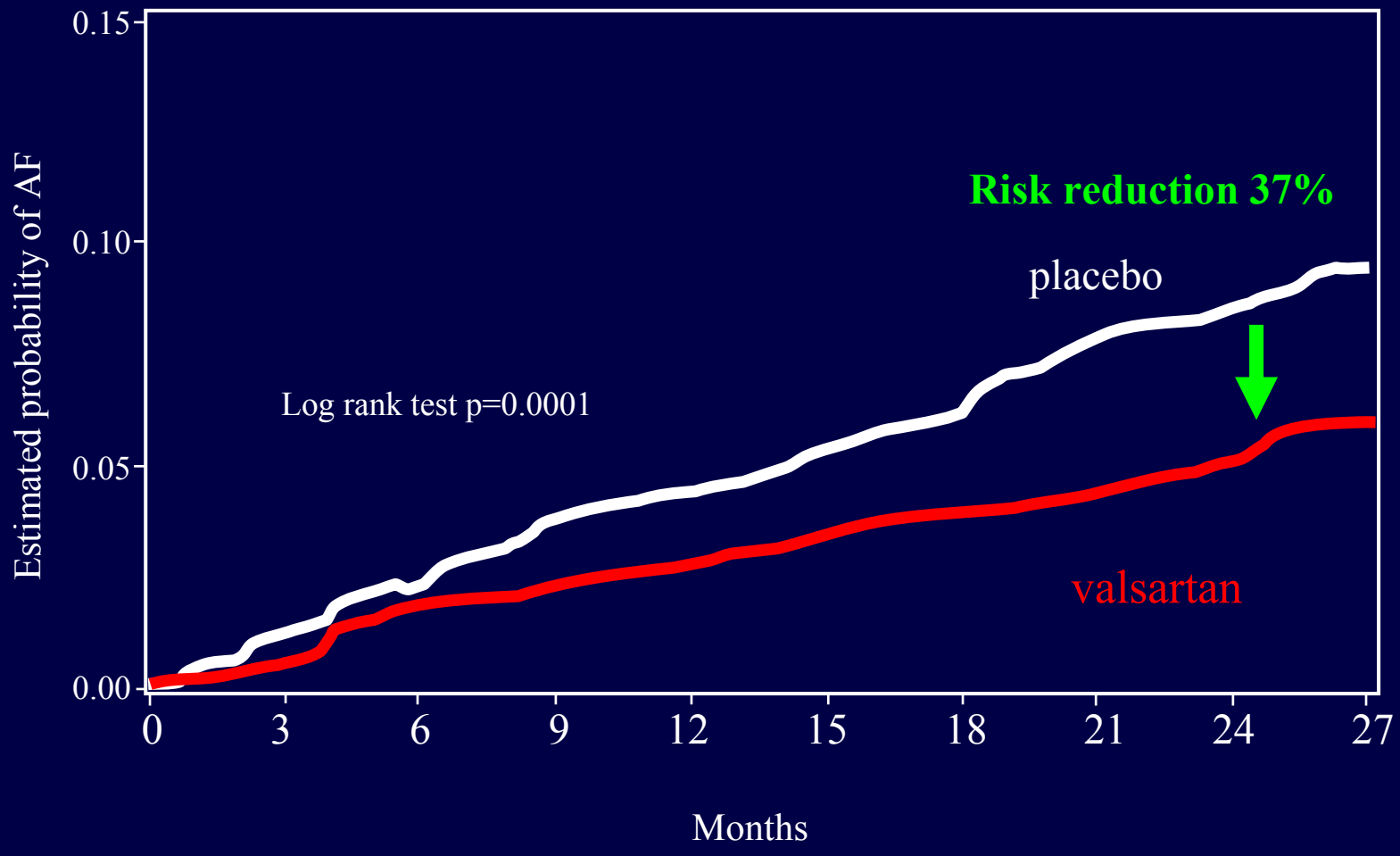
Valsartan reduces the incidence of atrial fibrillation in patients with heart failure

Result from the Valsartan Heart Failure Trial (Val-HeFT)

Maggioni AP, Latini R, Carson PE, Singh SN, Barlera S, Glazer R, Masson S, Cere E, Tognoni G, Cohn JN; Val-HeFT Investigators.

Maggioni A P et al. Am Heart J 149(3): 548-557,2005

Atrial fibrillation（Kaplan-Meier curve）



Maggioni A P et al. Am Heart J 149(3): 548-557,2005

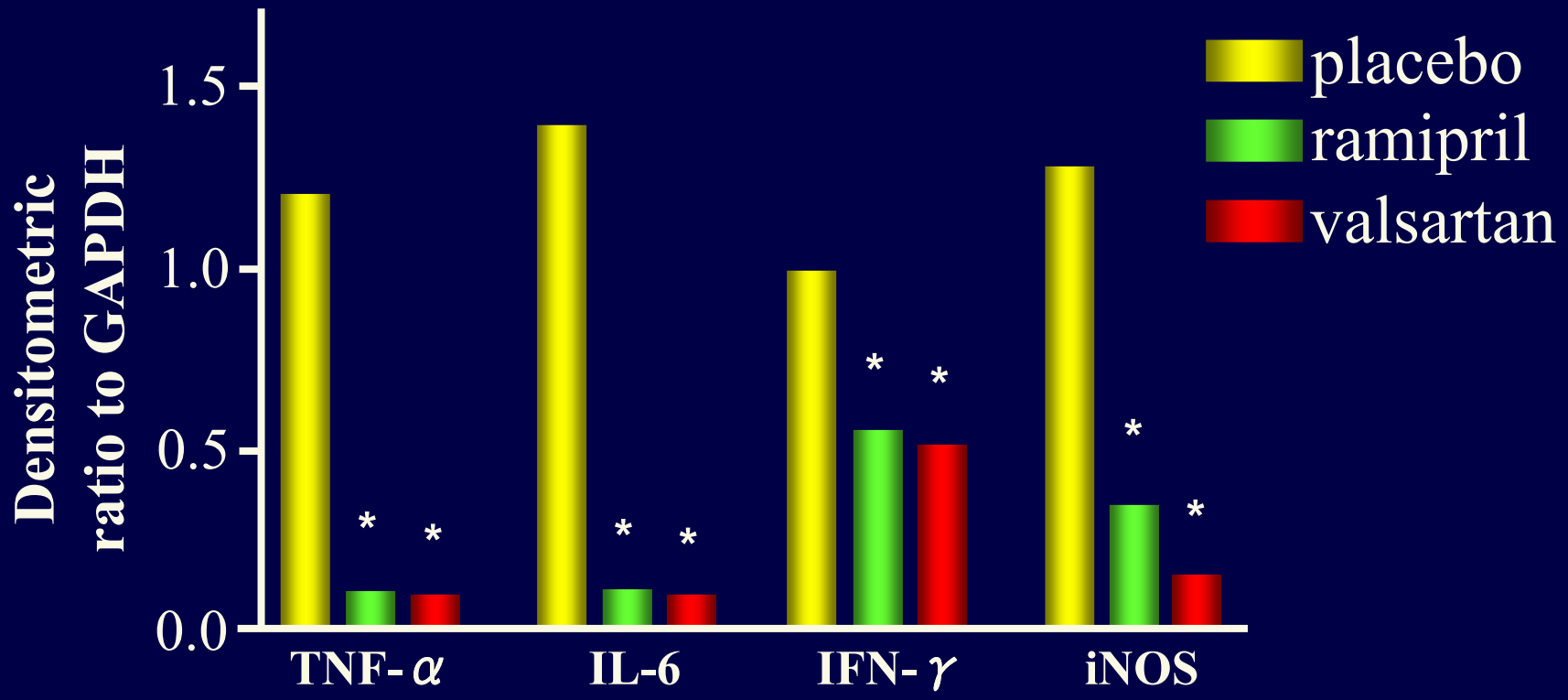
Angina pectoris

Cardiac Angiotensin II Participates in Coronary Microvessel Inflammation of Unstable Angina and Strengthens the Immunomediated Component

Gian Gastone Neri Serneri, Maria Boddi, Pietro Amedeo Modesti, Mirella Coppo, Ilaria Cecioni, Thomas Toscano, Maria Letizia Papa, Manuela Bandinelli, Gian Franco Lisi, Mario Chiavarelli

Circ Res 94:1630-1637,2004

Expression of mRNAs for GAPDH, TNF-α, IL-6, IFN-γ, and iNOS in Unstable Angina biopsy specimens



*P<0.01 vs placebo

Serneri G G N et al. *Circ Res* 94:1630-1637,2004

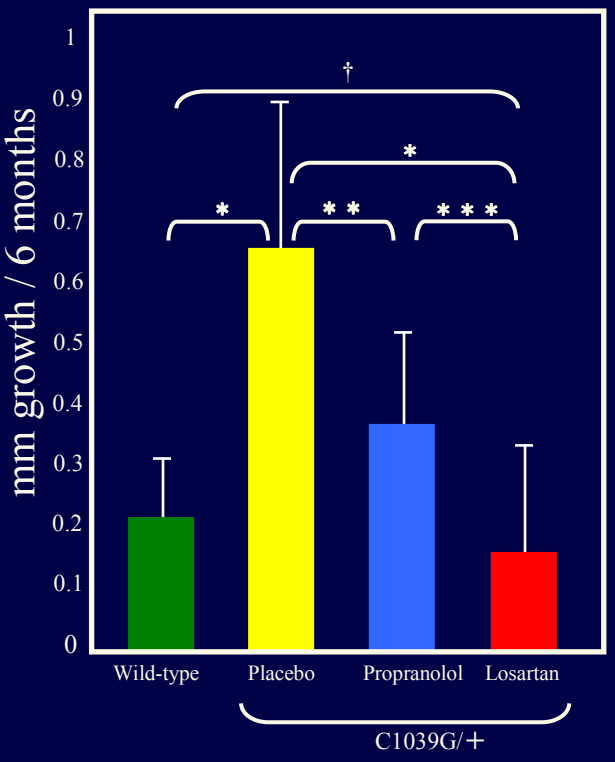
Dissecting aortic aneurysm

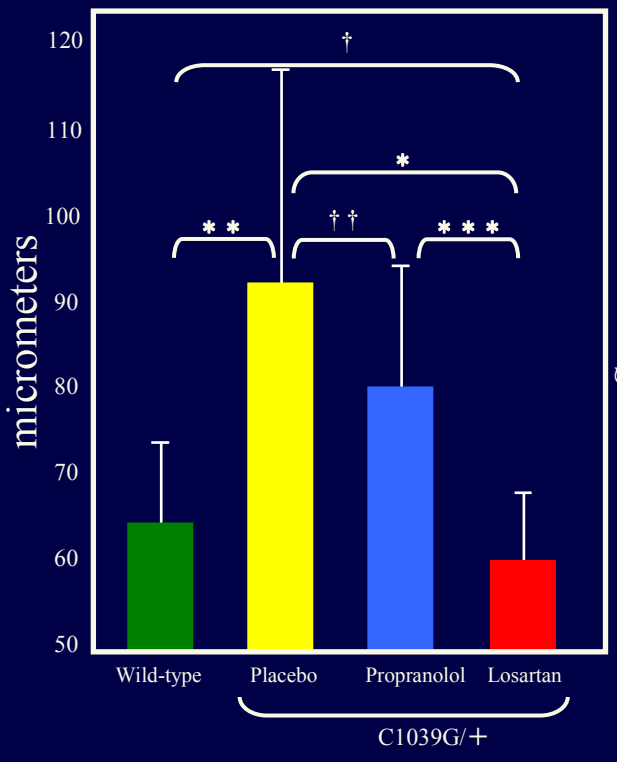
Losartan, an AT1Antagonist, Prevents Aortic Aneurysm in a Mouse Model of Marfan Syndrome

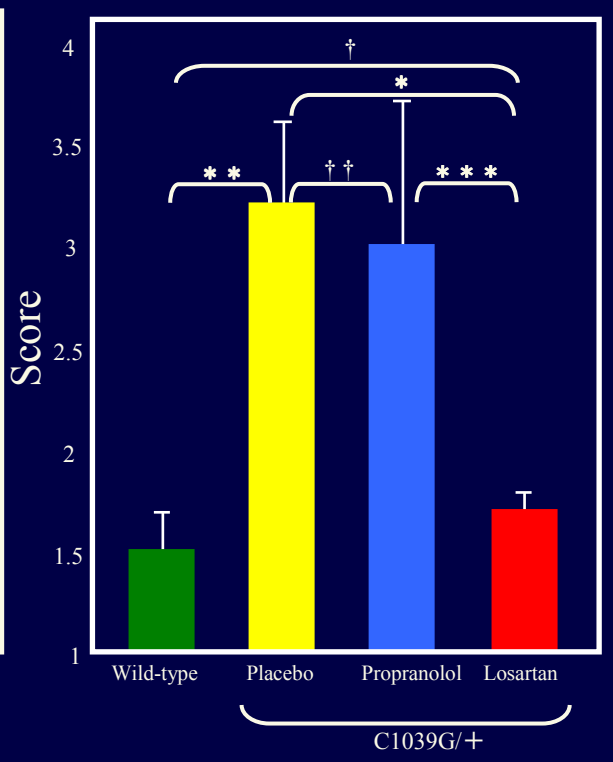
Jennifer P. Habashi,Daniel P. Judge, Tammy M. Holm, Ronald D. Cohn,
Bart L.Loeys, Timothy K. Cooper, Loretha Myers, Erin C. Klein,
Guosheng Liu, Carla Calvi, Megan Podowski, Enid R. Neptune,
Marc K. Halushka, Djahida Bedja,Kathleen Gabrielson, Daniel B. Rifkin,
Luca Carta, Francesco Ramirez,David L. Huso, Harry C. Dietz

Science 312:117-121,2006

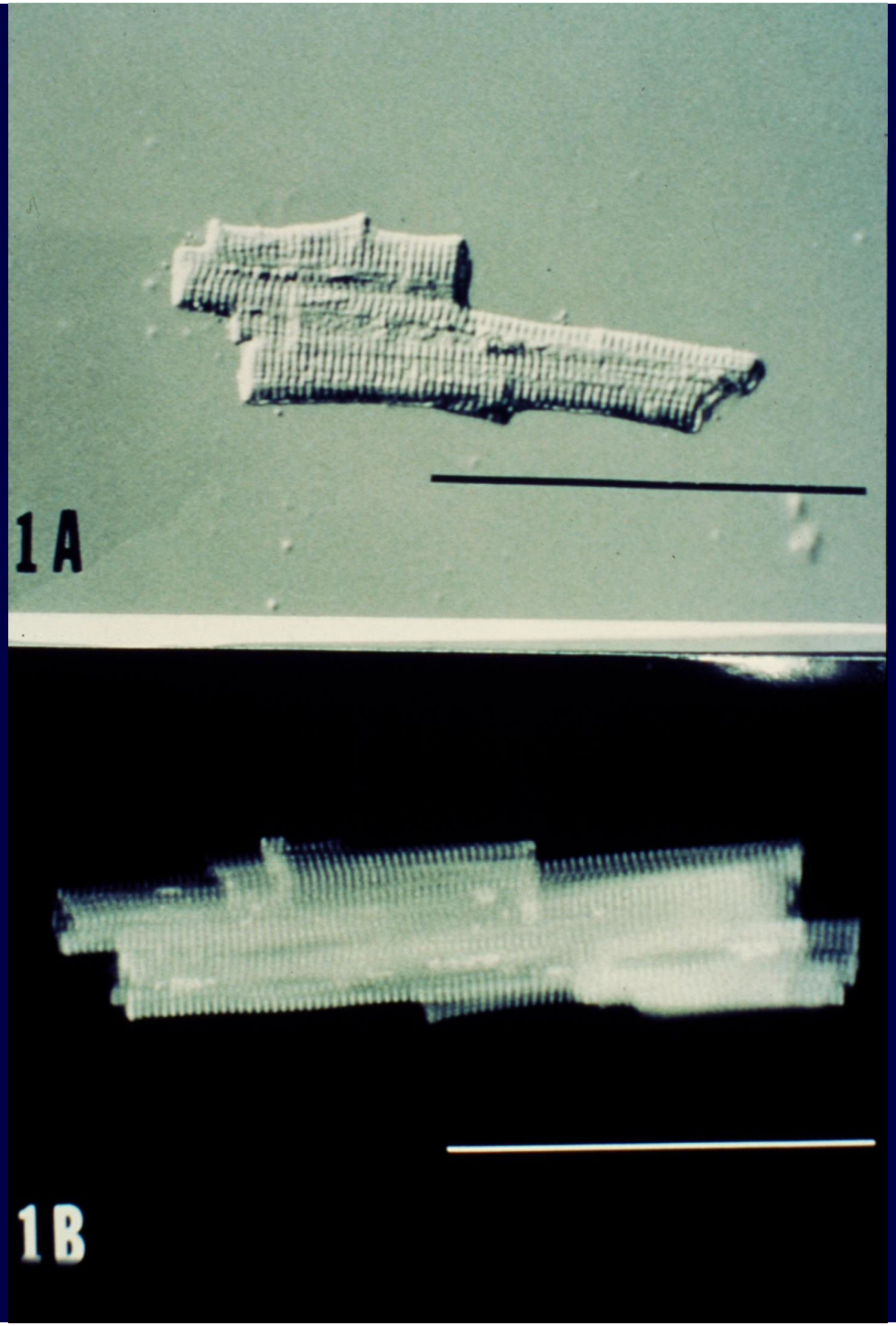
Prevents Aortic Aneurysm in a Mouse Model of Marfan Syndrome





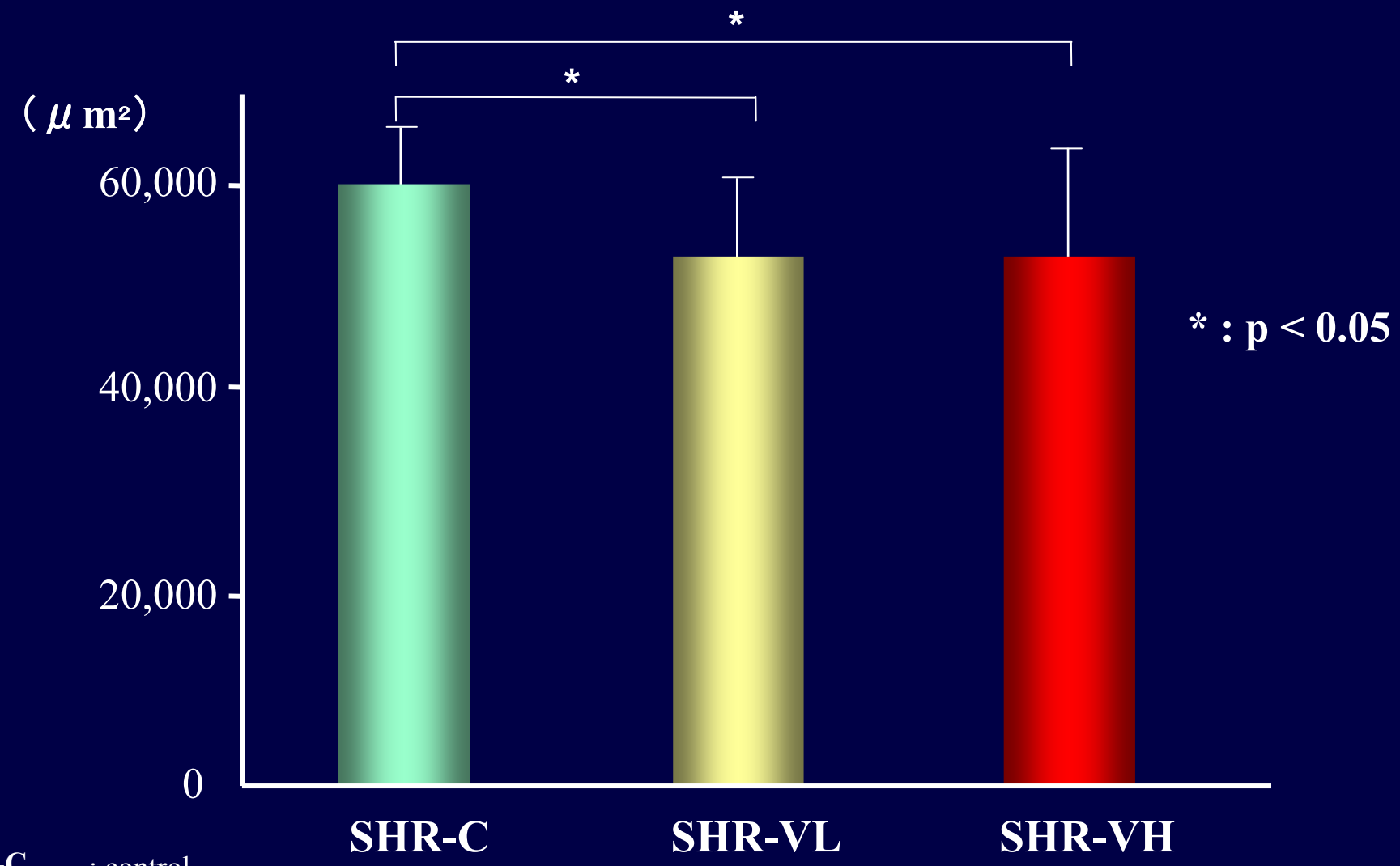


Habashi J et al. Science 312:117-121,2006


1A
1B

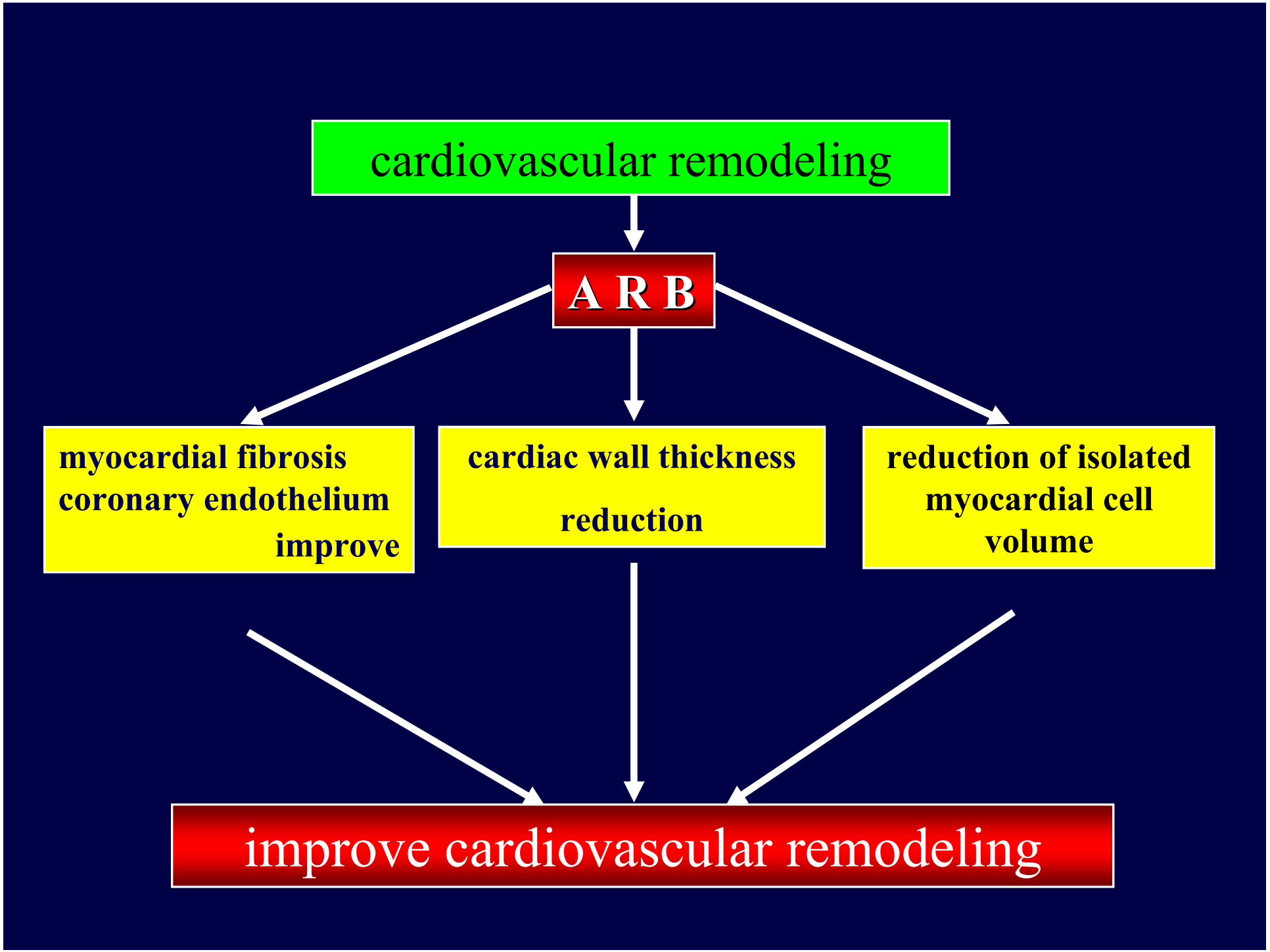
Coulter Channelyzer (Model C-256)

Change of LV myocardial cell volume in Spontaneous Hypertensive Rat（SHR）

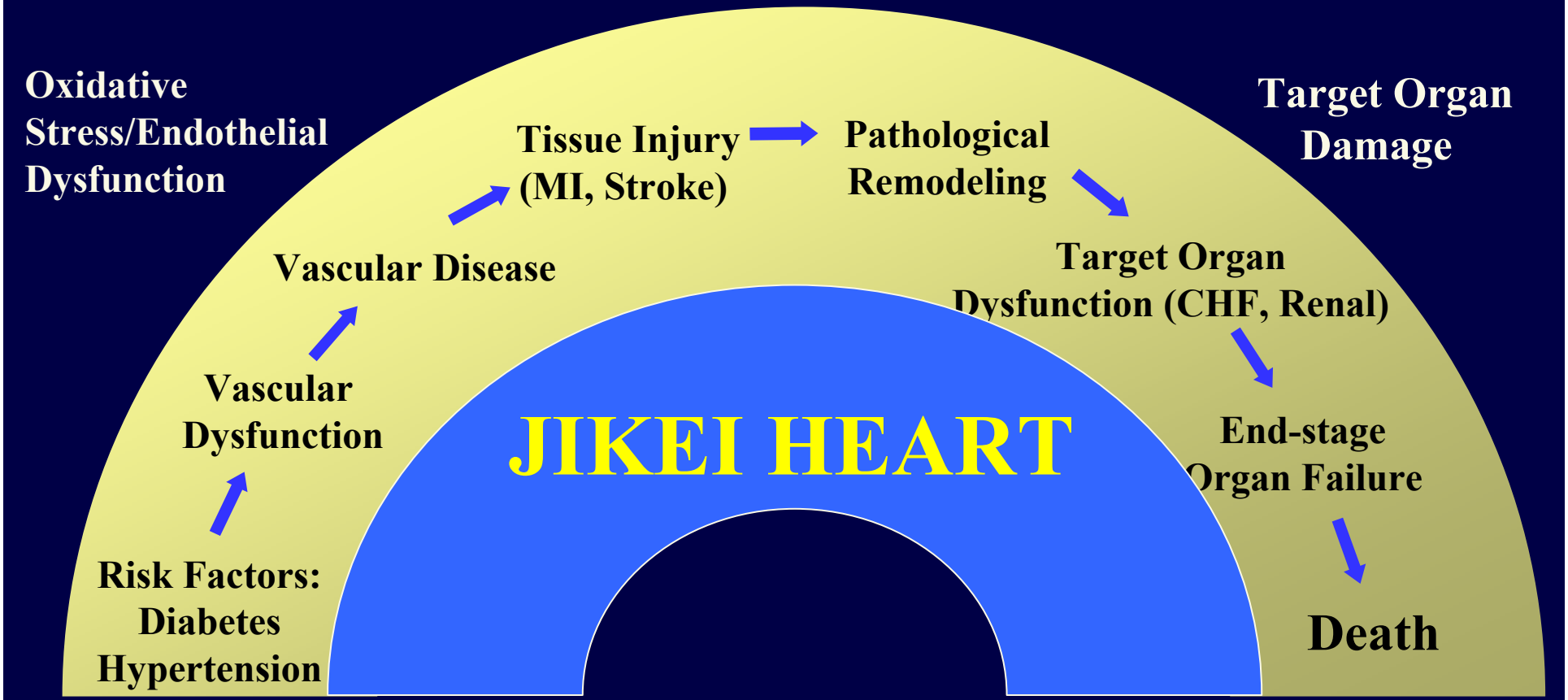


SHR-C : control
SHR-VL : low dose valsartan
SHR-VH : high dose valsartan

Onodera T et al. Prog Med 20 : 1222-1224, 2000


cardiovascular remodeling
A R B
myocardial fibrosis coronary endothelium improve
cardiac wall thickness reduction
reduction of isolated myocardial cell volume
improve cardiovascular remodeling

JIKEI HEART Study in CV Continuum



Adapted from Dzau V, Braunwald E *Am Heart J* 121:1244-163, 1991