Cardiac Protection across the cardiac continuum

Dong-Ju Choi, MD, PhD
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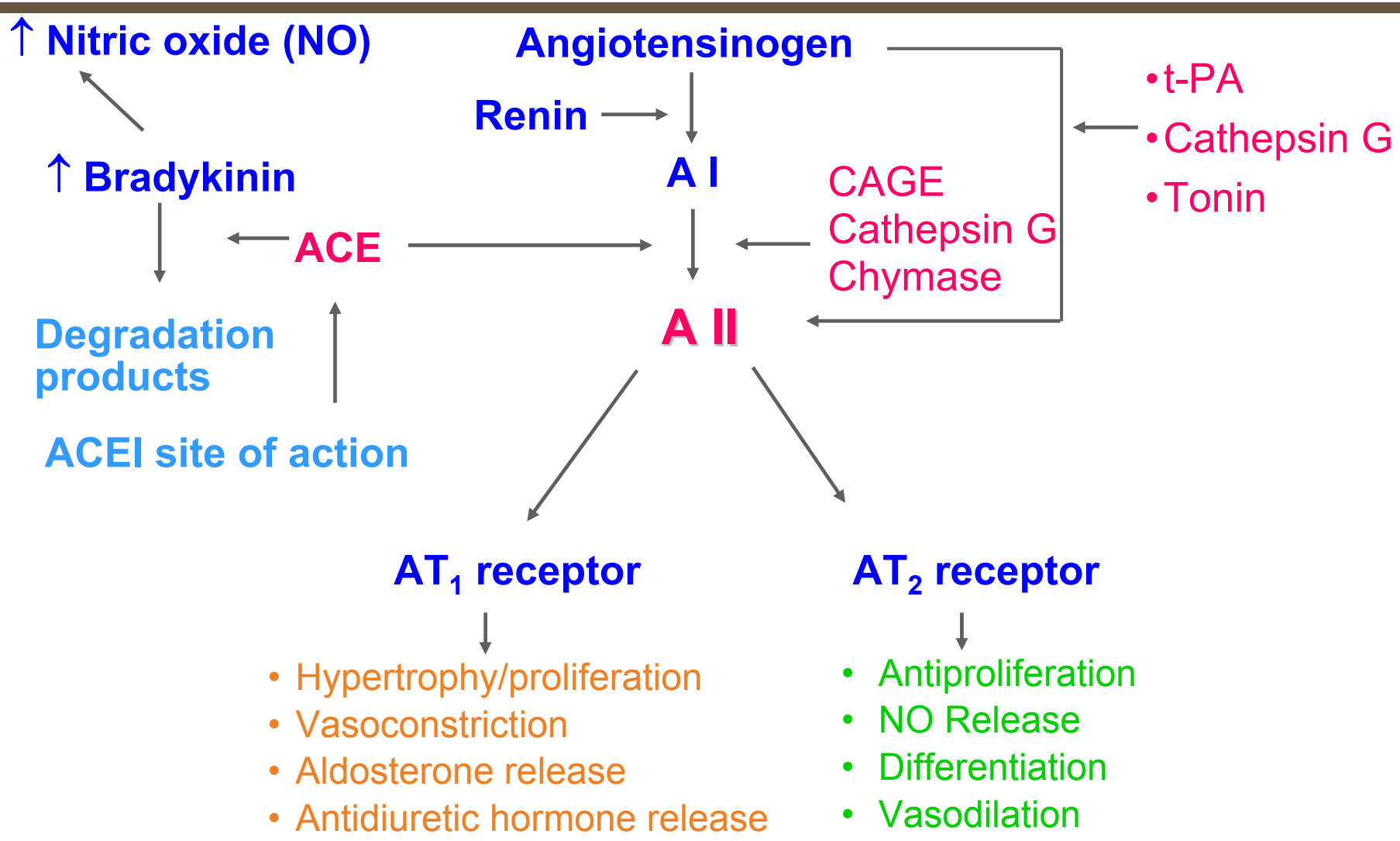
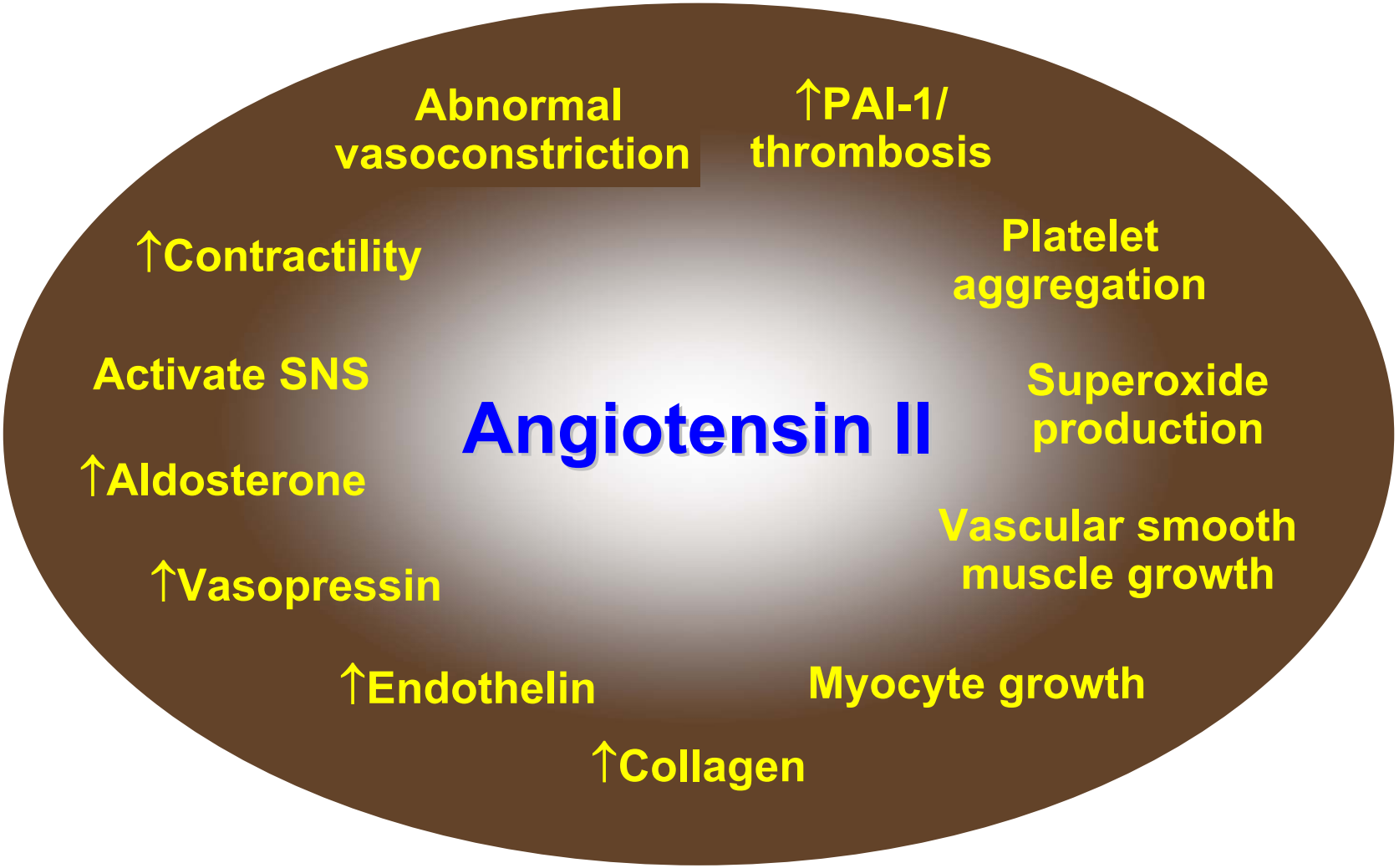
Renin Angiotensin Cascade



de Gasparo M, et al. Hypertension. Pathophysiology, Diagnosis, and Management. 2nd ed. New York, NY: Raven Press; 1995:1695–1720.

Dzau VJ. J Hypertens. 1989;7:933-936.

Pathophysiologic Effects of Angiotensin II



Burnier M, Brunner HR. *Lancet*. 2000;355:637–645.

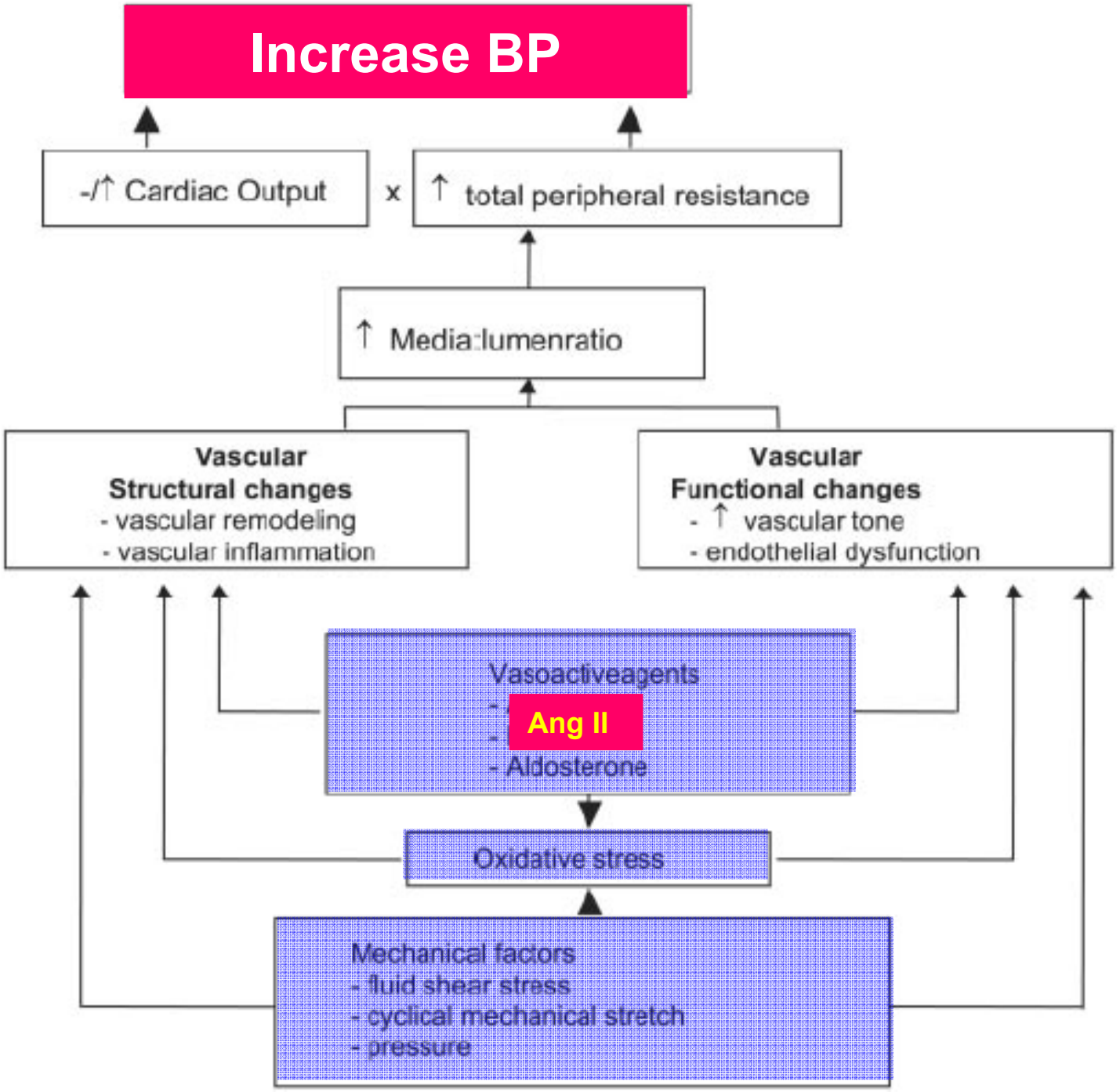
Adverse Effects of RAS on CV System

Vascular change

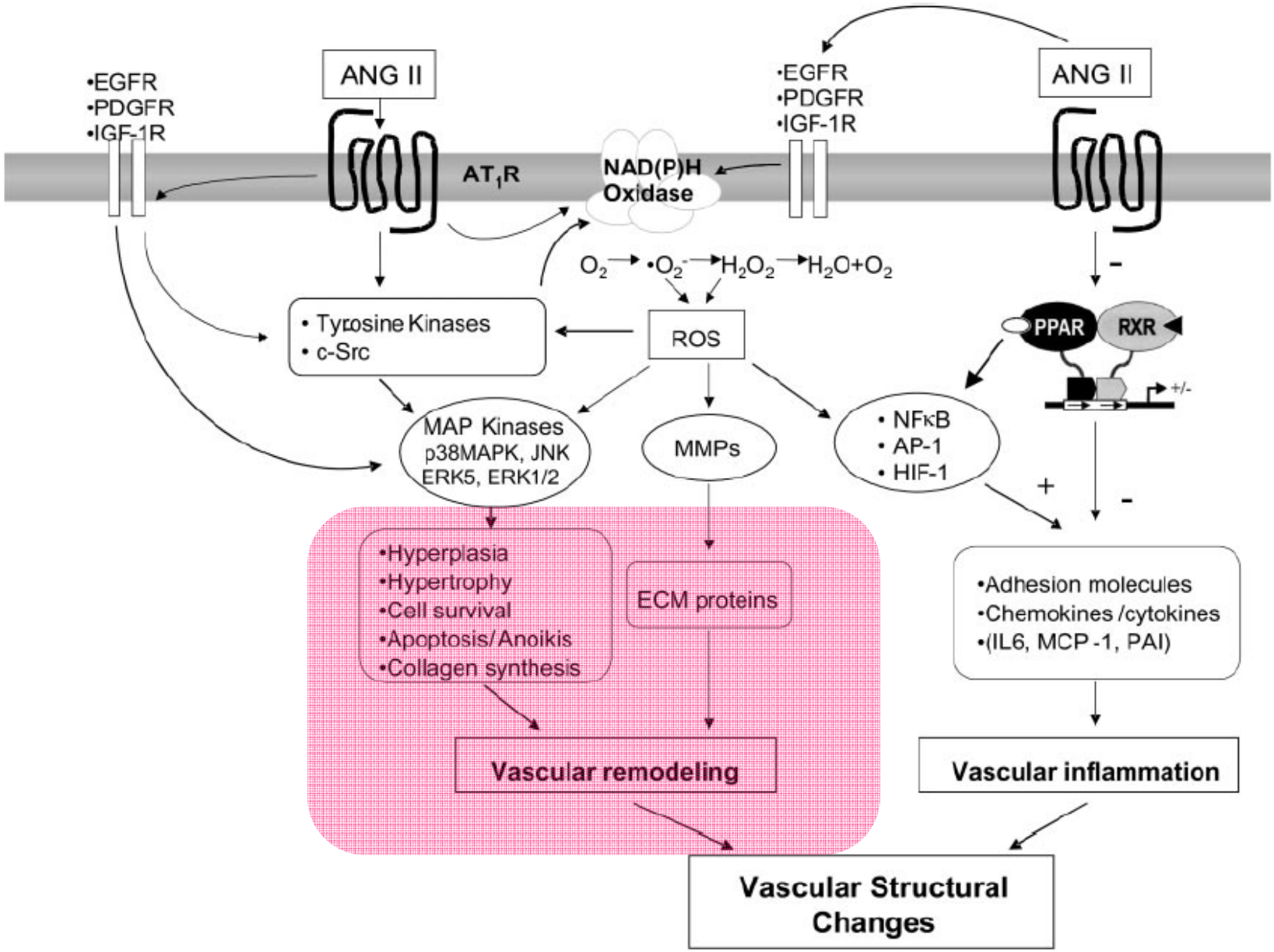
1. Vascular remodeling
2. Endothelial dysfunction
3. Inflammation

Myocardial damage

1. Myocyte sequestration
2. Myocyte isolation


Increase BP
-/↑ Cardiac Output
x
↑ total peripheral resistance
↑ Media:lumenratio
Vascular
Structural changes
- vascular remodeling
- vascular inflammation
Vascular
Functional changes
- ↑ vascular tone
- endothelial dysfunction
Vasoactiveagents
-
-
- Aldosterone
Ang II
Oxidative stress
Mechanical factors
- fluid shear stress
- cyclical mechanical stretch
- pressure

Vascular Remodeling



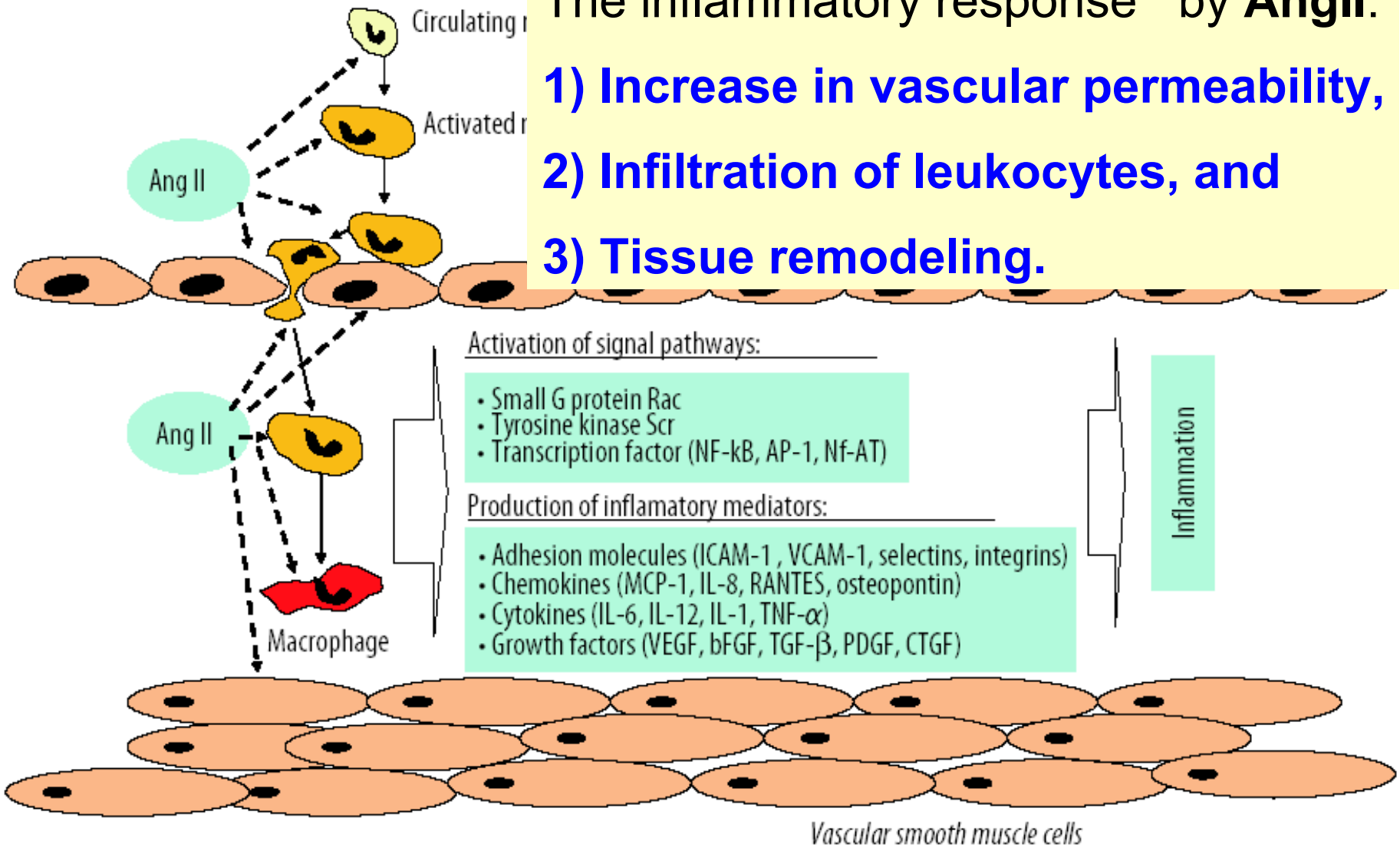
AngII-induced Inflammation

The inflammatory response by **AngII**:

1) Increase in vascular permeability,

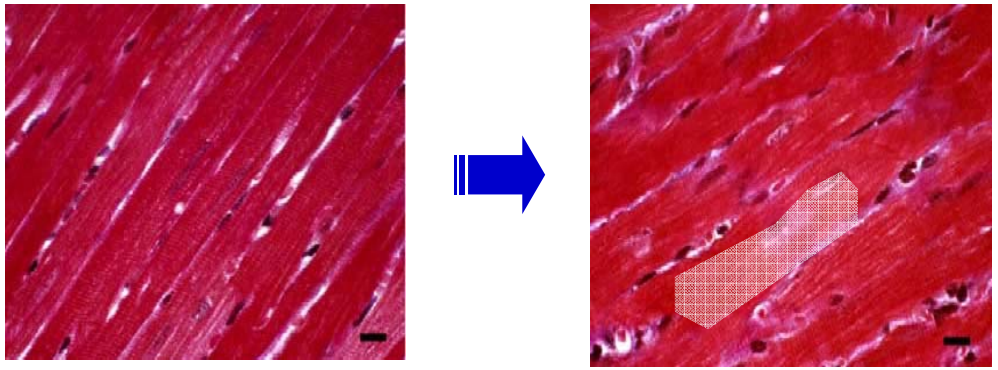
2) Infiltration of leukocytes, and

3) Tissue remodeling.

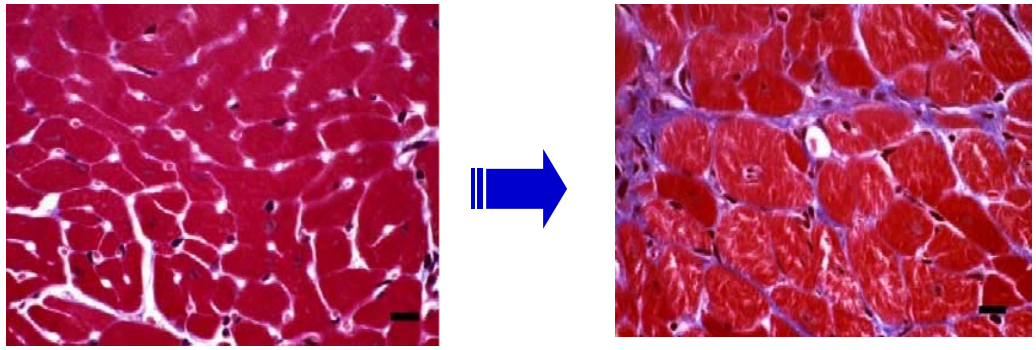


Myocardial Damage by RAS

1. Myocyte sequestration
   - **Hypertrophy**
   - **Apoptosis**
   - **Necrosis**



2. Myocyte isolation
   - **Interstitial fibrosis**
   - **Conduction disturbance**



Blocking RAS is critical to prevent

1. Vascular change

   (Vascular remodeling, endothelial dysfunction and inflammation)

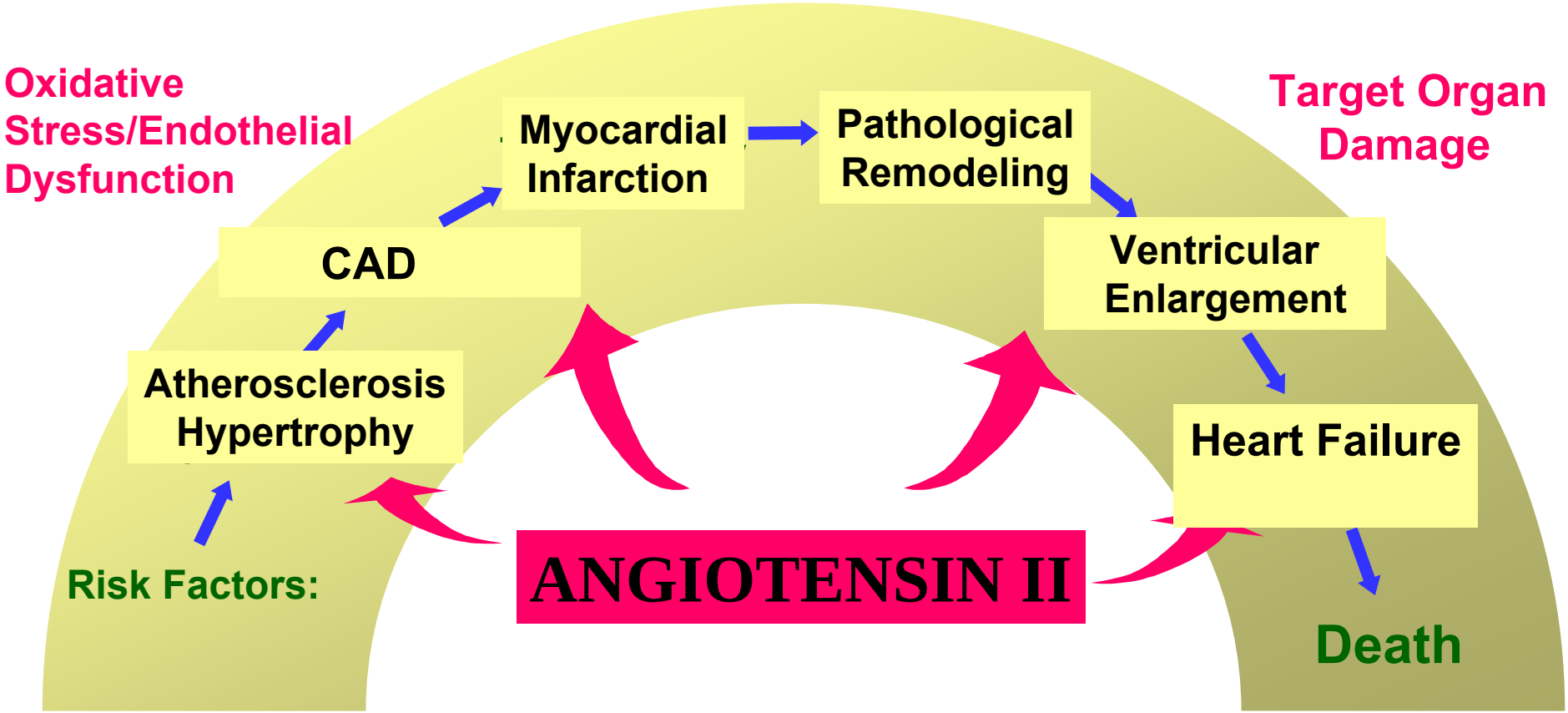
   and

2. Myocardial damage

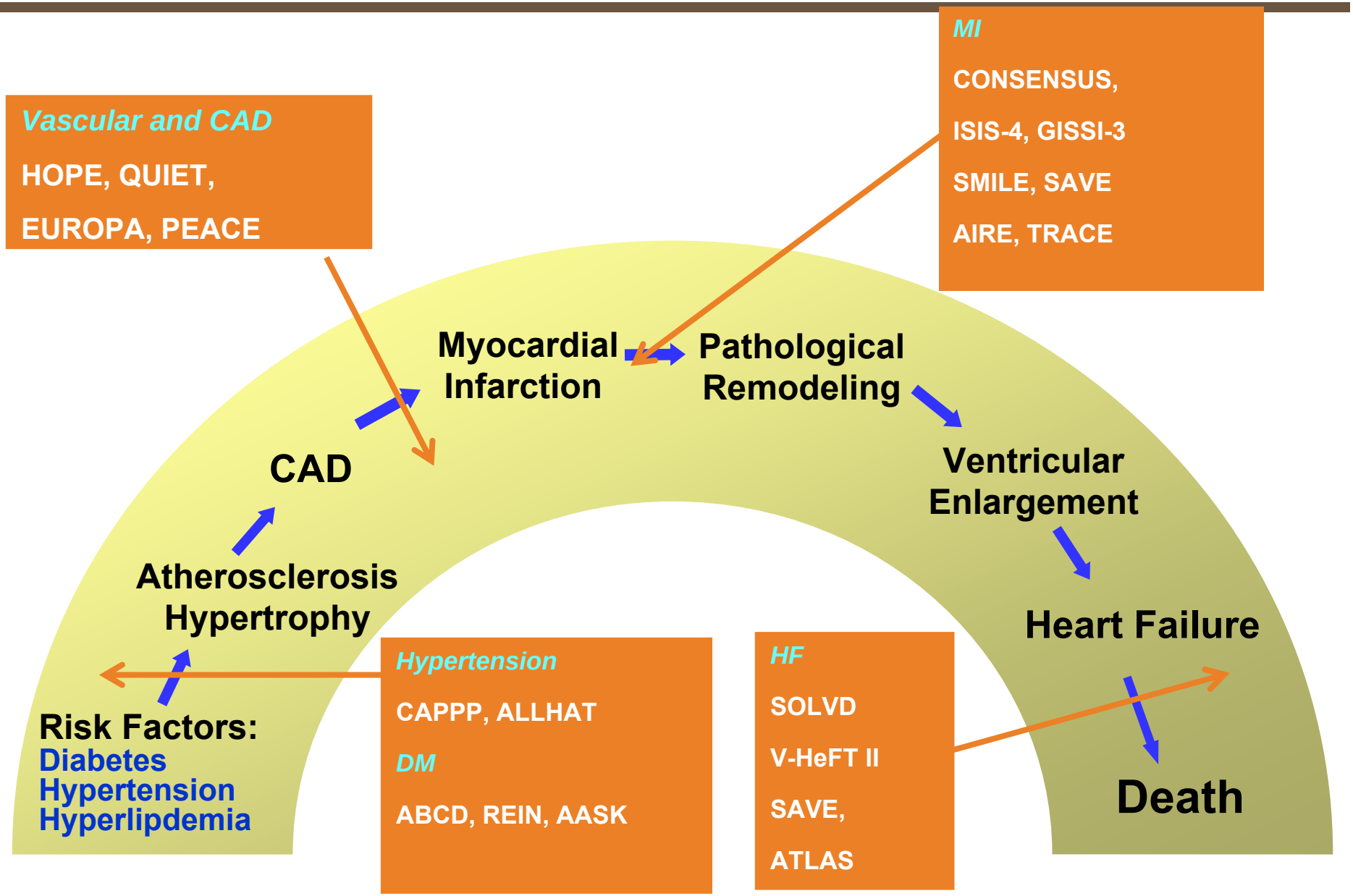
   (Myocyte sequestration and myocyte isolation)

The Cardiovascular Continuum:

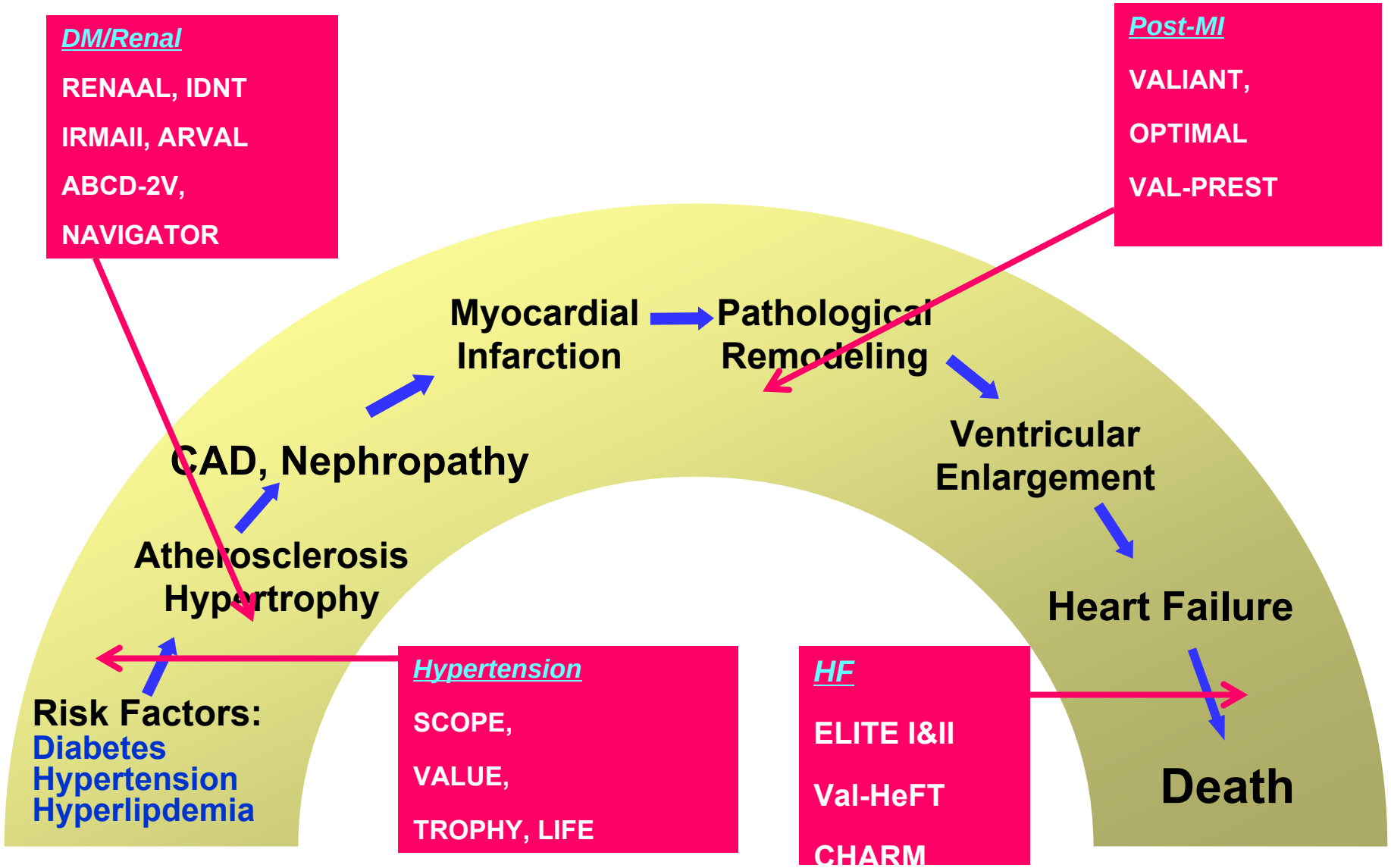
Mechanisms and Mediators



Clinical Trials with ACE inhibitors



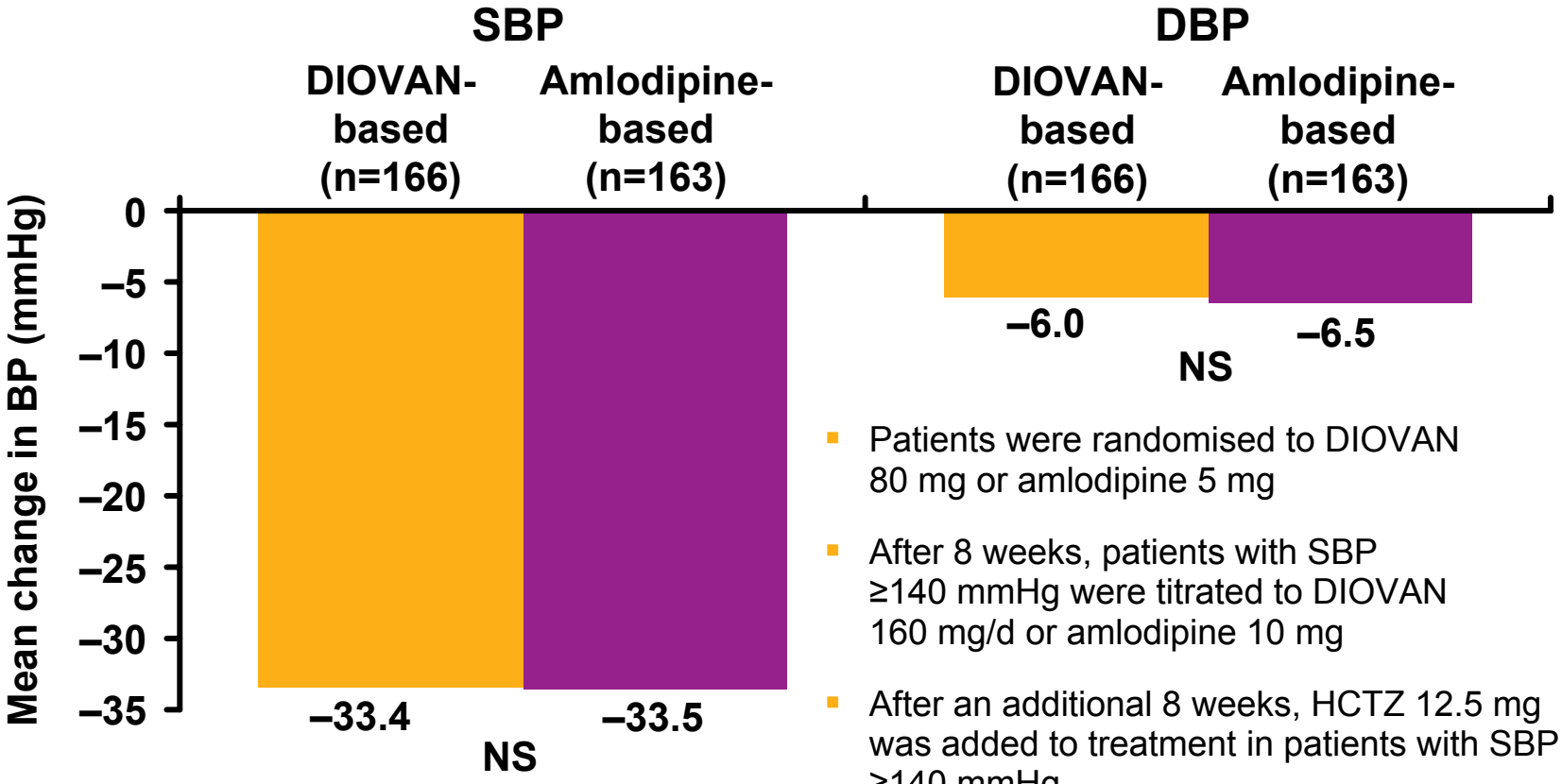
Clinical Trials with ARB



Val-Syst Trial:

Powerful Double-digit BP Reductions with Valsartan-based Therapy in Patients with ISH Aged 60–80

Randomised, double-blind, titration to effect study of patients (aged 60–80 years) with ISH: 24 weeks' treatment



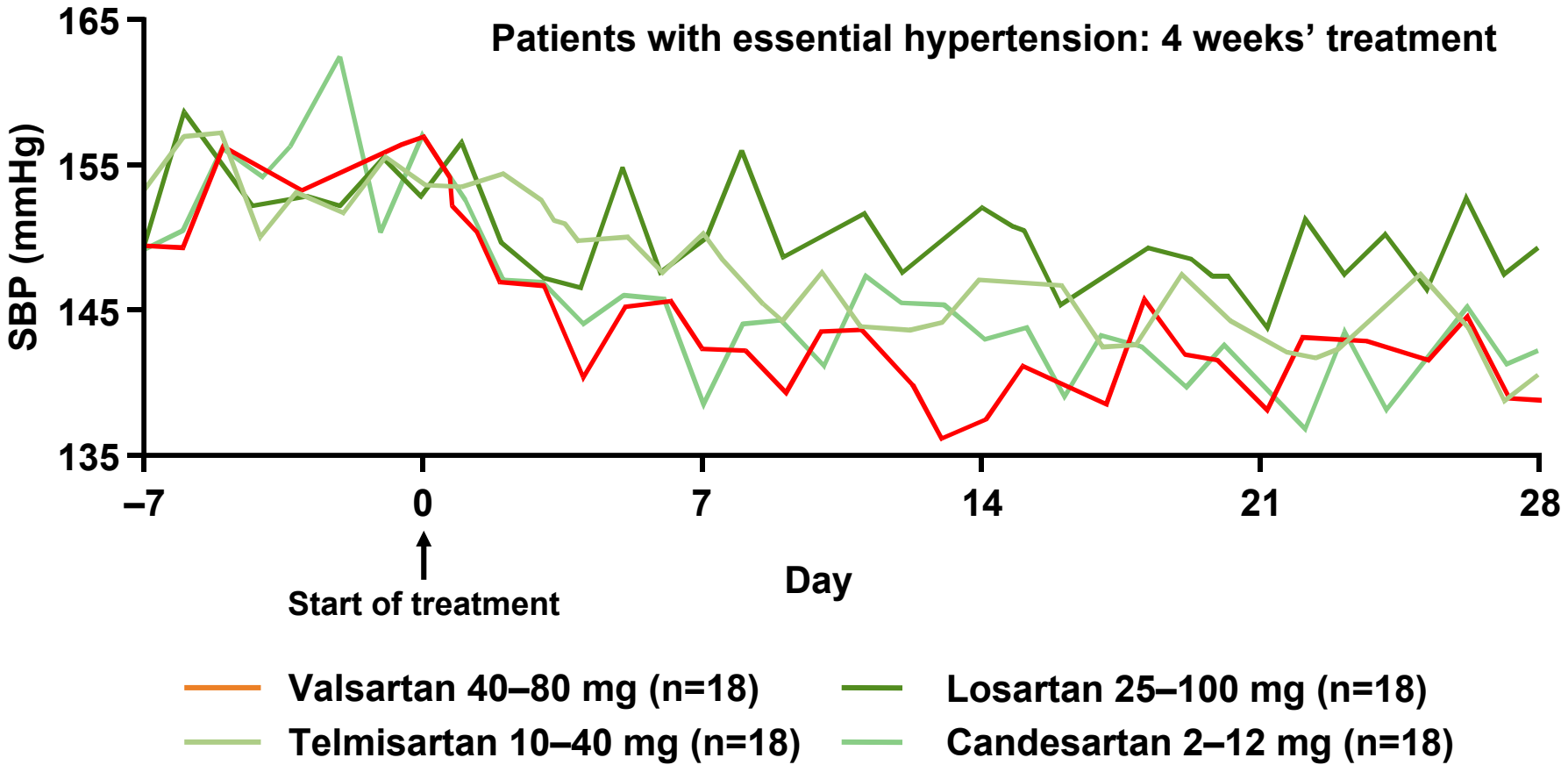
- Patients were randomised to DIOVAN 80 mg or amlodipine 5 mg
- After 8 weeks, patients with SBP ≥140 mmHg were titrated to DIOVAN 160 mg/d or amlodipine 10 mg
- After an additional 8 weeks, HCTZ 12.5 mg was added to treatment in patients with SBP ≥140 mmHg

Val-Syst: Valsartan in Isolated Systolic Hypertension (ISH);
Per protocol population data shown;
NS = not significant

Clin Ther 2003;25:2765–80

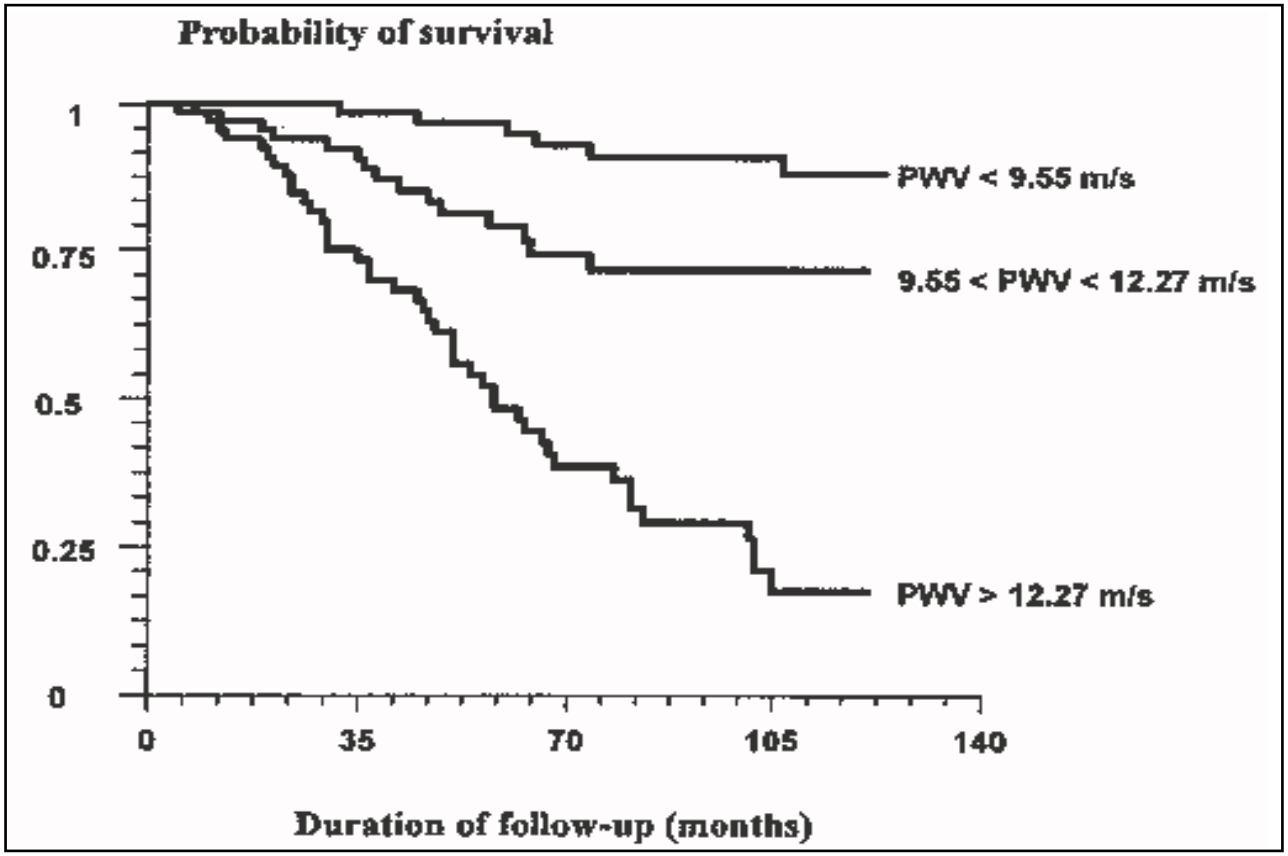
Time Course of Morning BP Changes Mediated by ARBs

Morning home BP



Clin Exp Hypertens 2005;27:477–89

The role of arterial stiffness

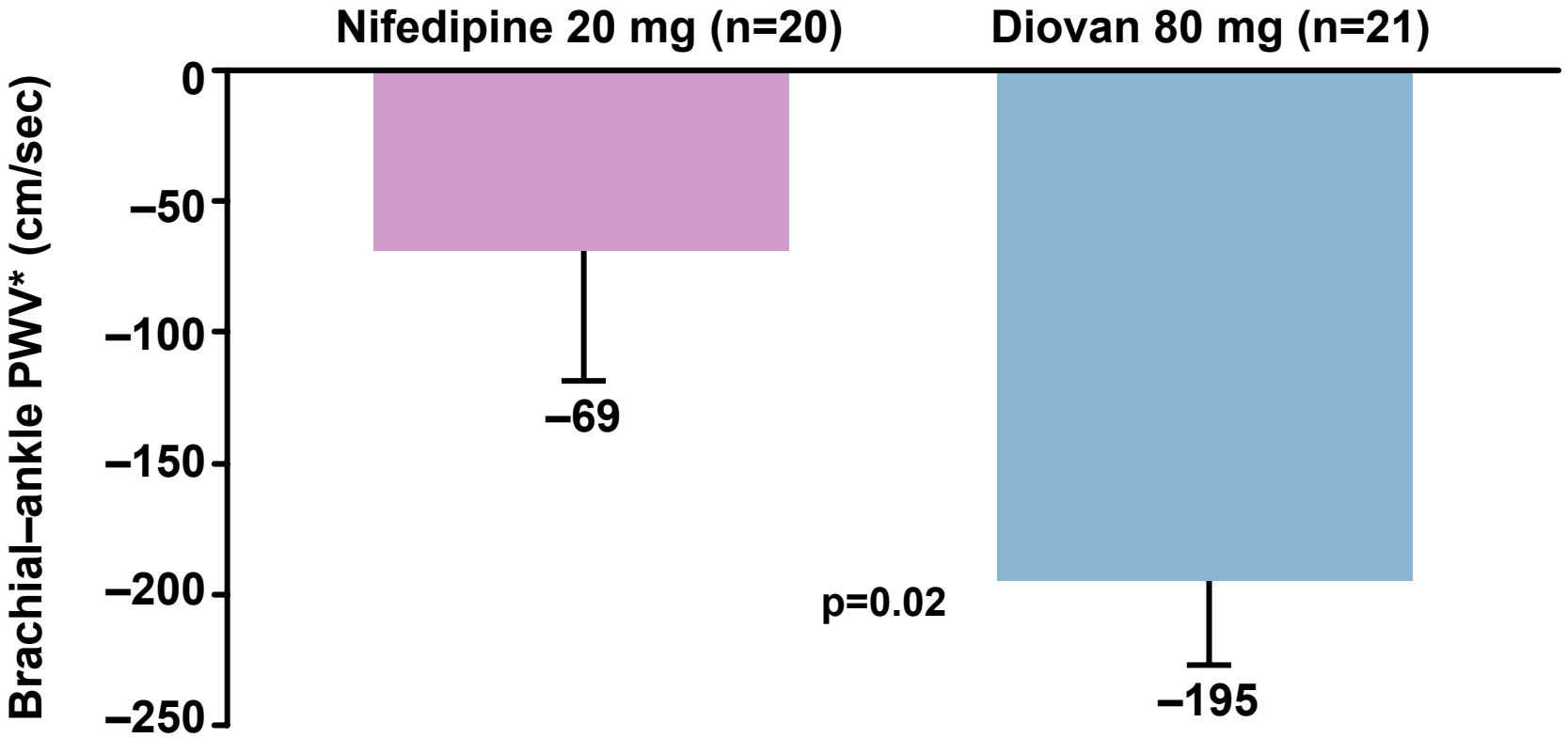


- The **role of arterial stiffness** as the **major cause of cardio-vascular risk** can be seen in recent outcome data.
- **Pulse Wave Velocity**
- **aortic pulse wave velocity** on entry was used to stratify arterial stiffness in a cohort of ESRD patients into tertiles
- 1st tertile has almost normal results; 3rd tertile has 6x risk of "all cause' mortality

Clin Exp Hypertens. 2004 Oct-Nov;26(7-8):689-99

Reduces Arterial Stiffness

Randomised study of patients with hypertension: 3 months' treatment

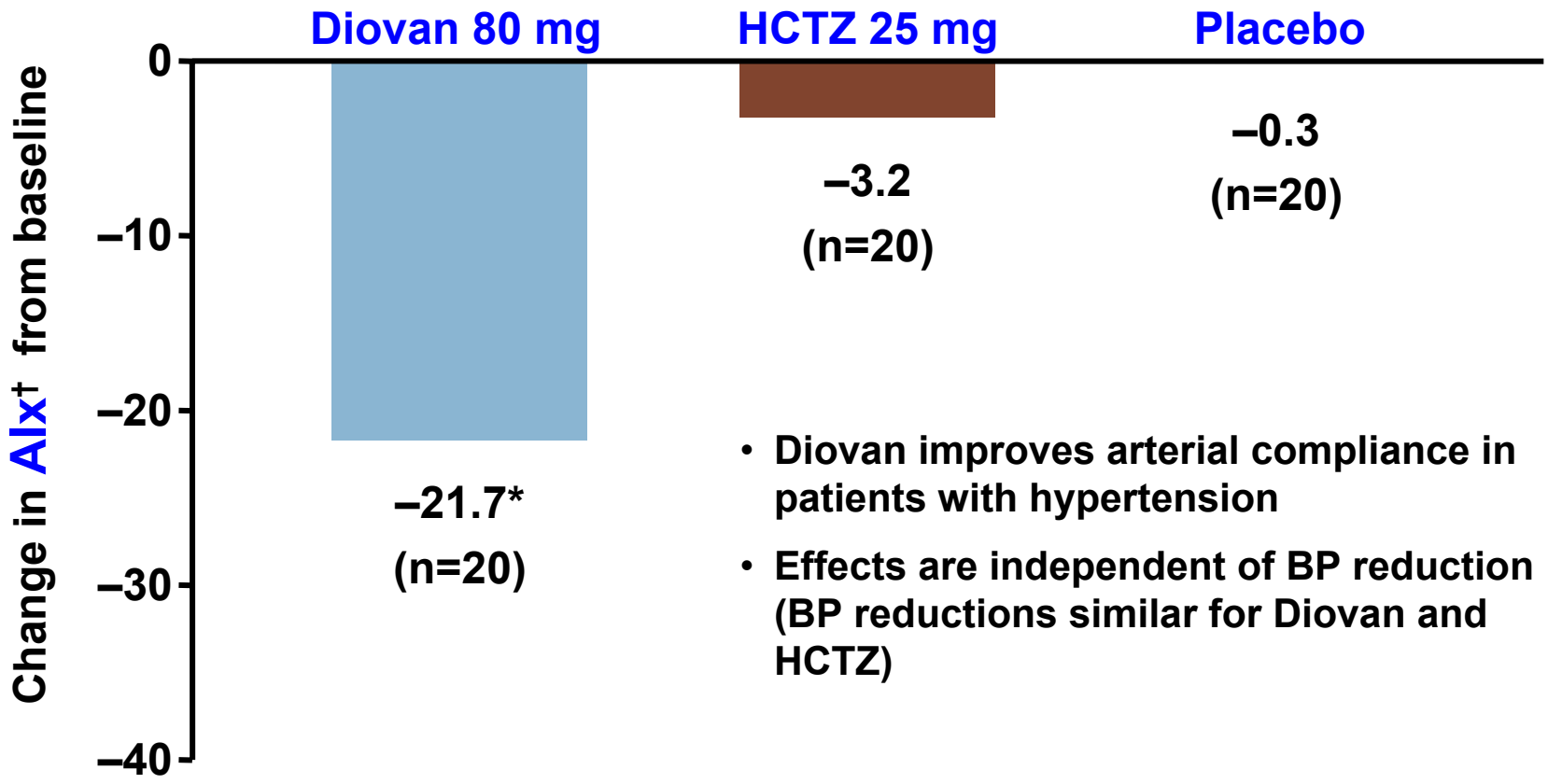


***Brachial-ankle pulse wave velocity (PWV), a measure for systemic arterial stiffness**

Am J Hypertens 2004;17:1050–5

Reduces Arterial Stiffness

Randomised, double-blind, parallel-group design study of patients with essential hypertension: 6 weeks' treatment



- Diovan improves arterial compliance in patients with hypertension
- Effects are independent of BP reduction (BP reductions similar for Diovan and HCTZ)

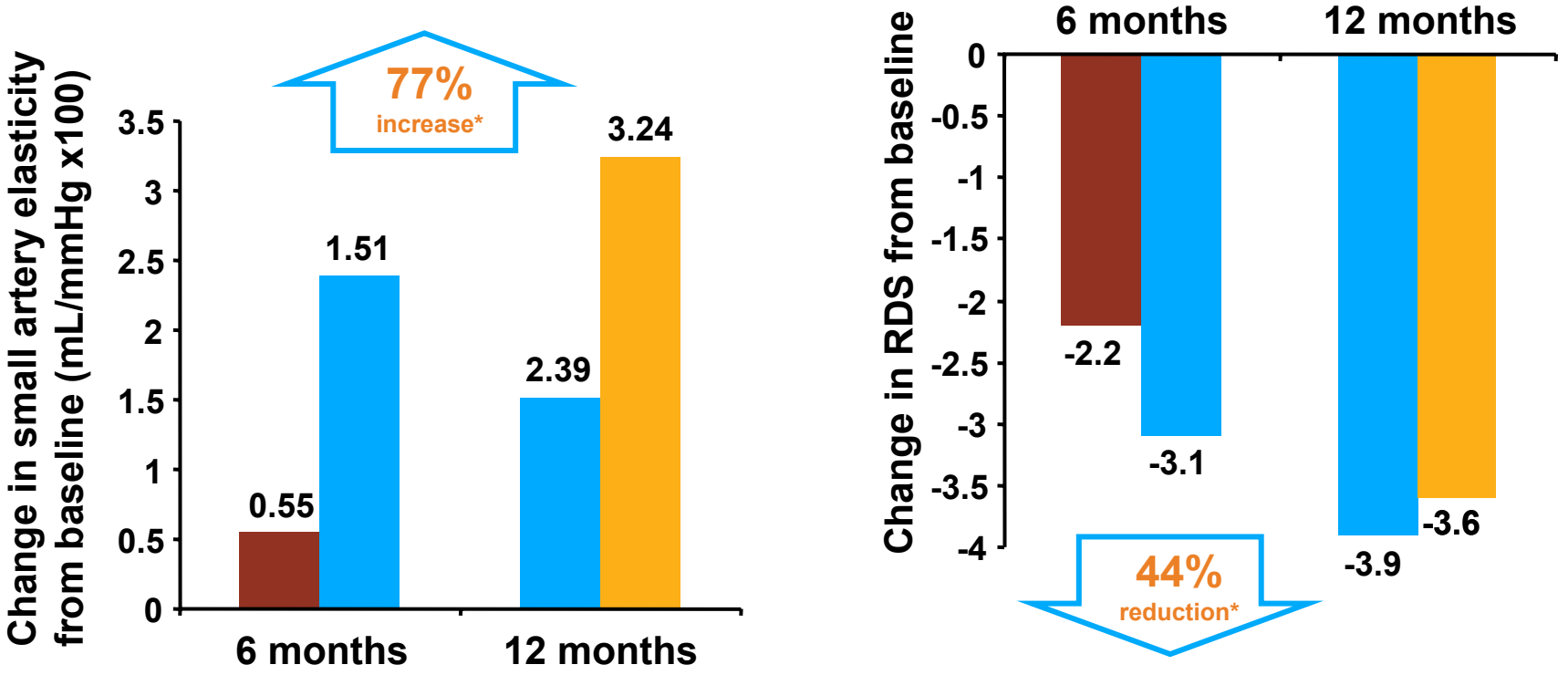
†Augmentation index (AIx), a measure of arterial function

*p<0.01 vs HCTZ and vs placebo

J Hypertens 2002;20:2423–8

DETECTIV : Valsartan Increases Small Artery Elasticity in Asymptomatic Risk Patients with High CV Risk

Results from a 12-month study in 76 asymptomatic patients# with RDS ≥6 and controlled BP and cholesterol levels (DETECTIV study)



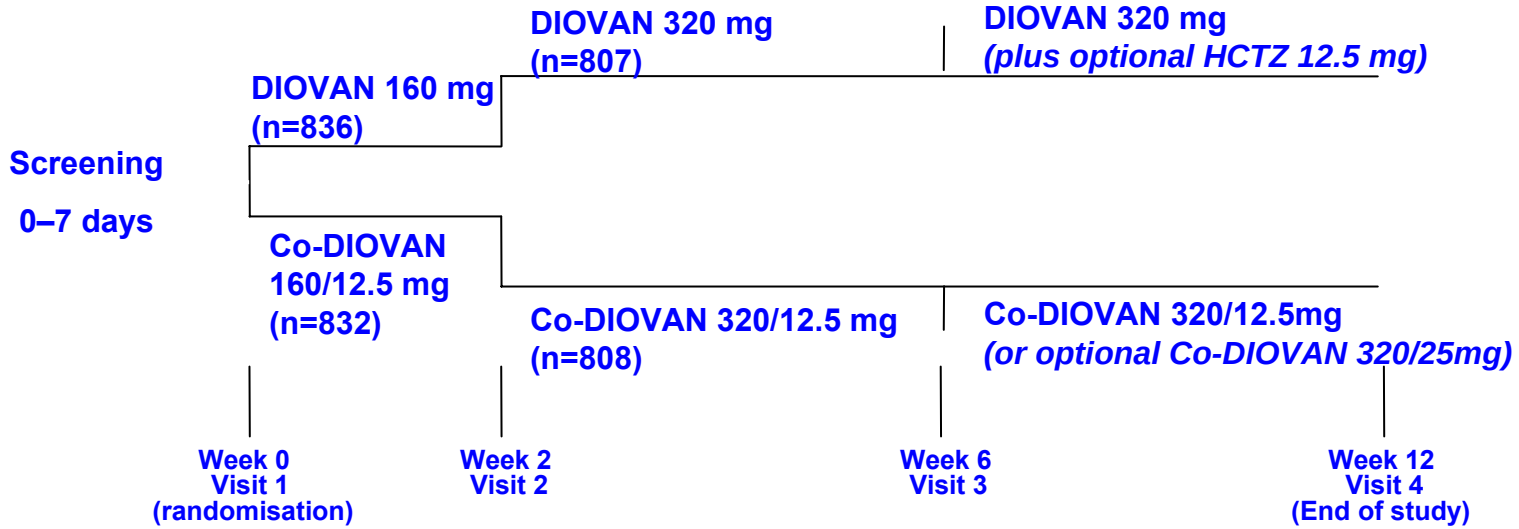
#Individuals completing the study with or without antihypertensive or lipid lowering medications, BP <140/90 mmHg; *p<0.000; RDS=Rasmussen Disease Score

Duprez et al.

JACC 2007;50:published online

Val-MARC: Managing BP Aggressively and Evaluating Reductions in hsCRP

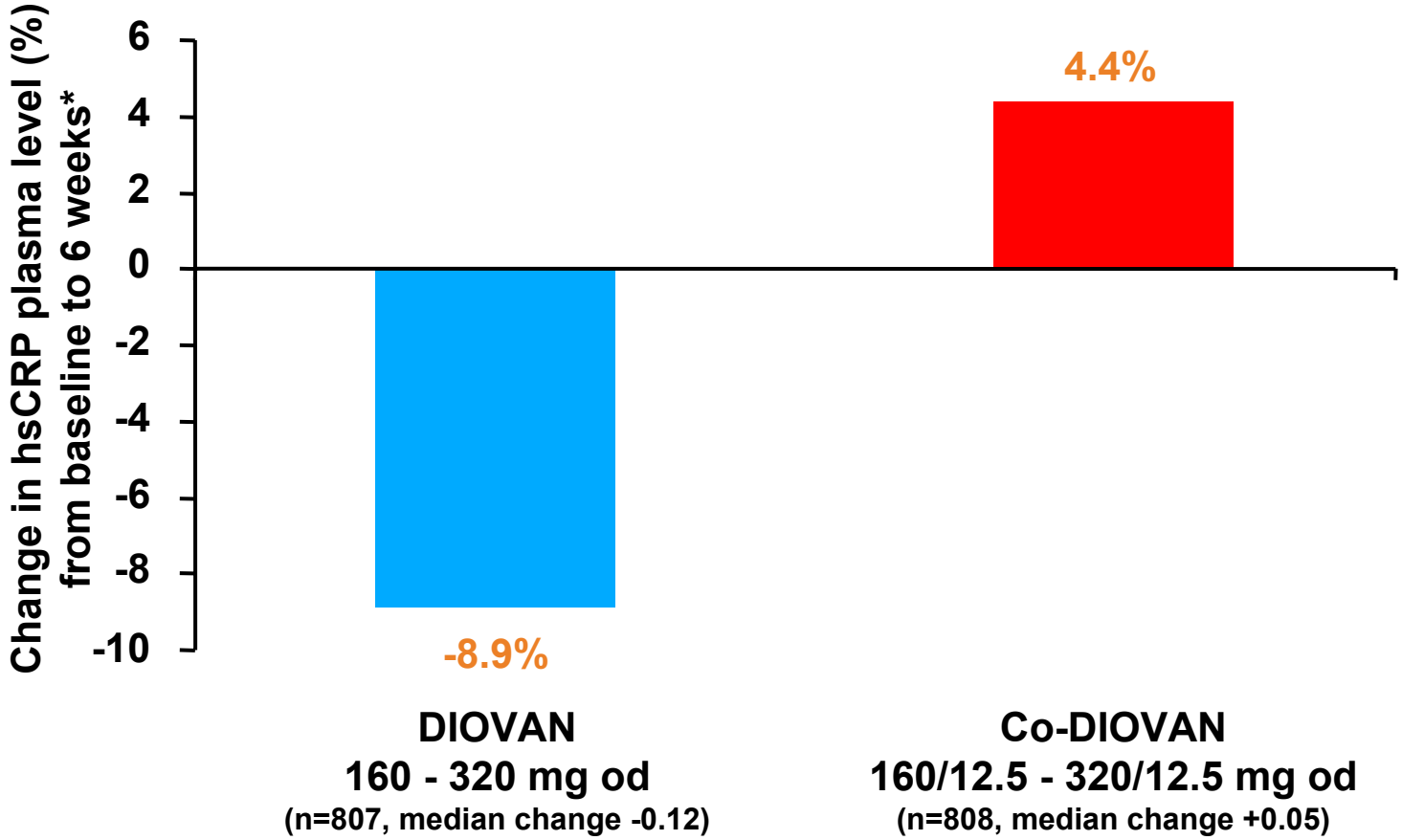
- Multicentre, open-label, randomised, parallel-group study of patients with Stage II hypertension
- Objectives, to determine:
  - If BP reduction with DIOVAN/Co-DIOVAN is effective at reducing hsCRP levels
  - If there is a difference between moderate and aggressive BP reduction in terms of hsCRP change
- Primary endpoints:
  - Change in SBP from baseline to Week 6 with DIOVAN vs Co-DIOVAN
  - Change in hsCRP from baseline to Week 6 with DIOVAN vs Co-DIOVAN
  - Change in hsCRP from baseline to Week 12 in the overall group



Hypertension 2006;48:73-79

Val-MARC : DIOVAN Reduces hsCRP Levels Independent of Blood Pressure Reduction

Results from a 6-week study* in 1,615 patients with stage II HTN#
(Val-MARC study)

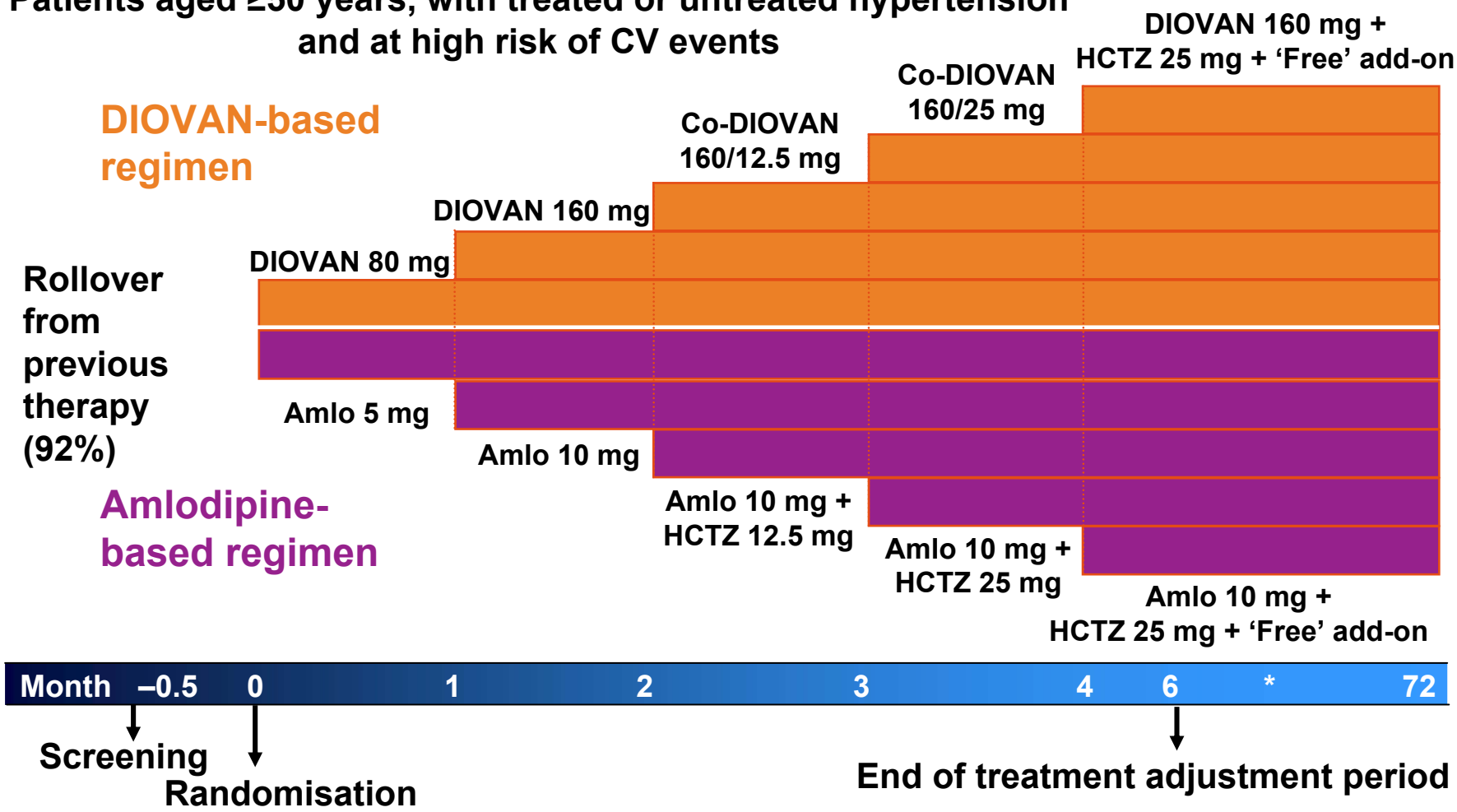


#SBP ≥160 mmHg or DBP ≥100 mmHg, patients completing the study; *Study duration 12 weeks, after 6 weeks of treatment, HCTZ 12.5 mg/day allowed at discretion in both groups to reach BP <140/90 mmHg); p<0.001 for DIOVAN vs. Co-DIOVAN

Ridker et al. *Hypertension* 2006;48:73-79

VALUE: Elective Titration to Target BP(<140/90 mmHg)

Patients aged ≥50 years, with treated or untreated hypertension and at high risk of CV events

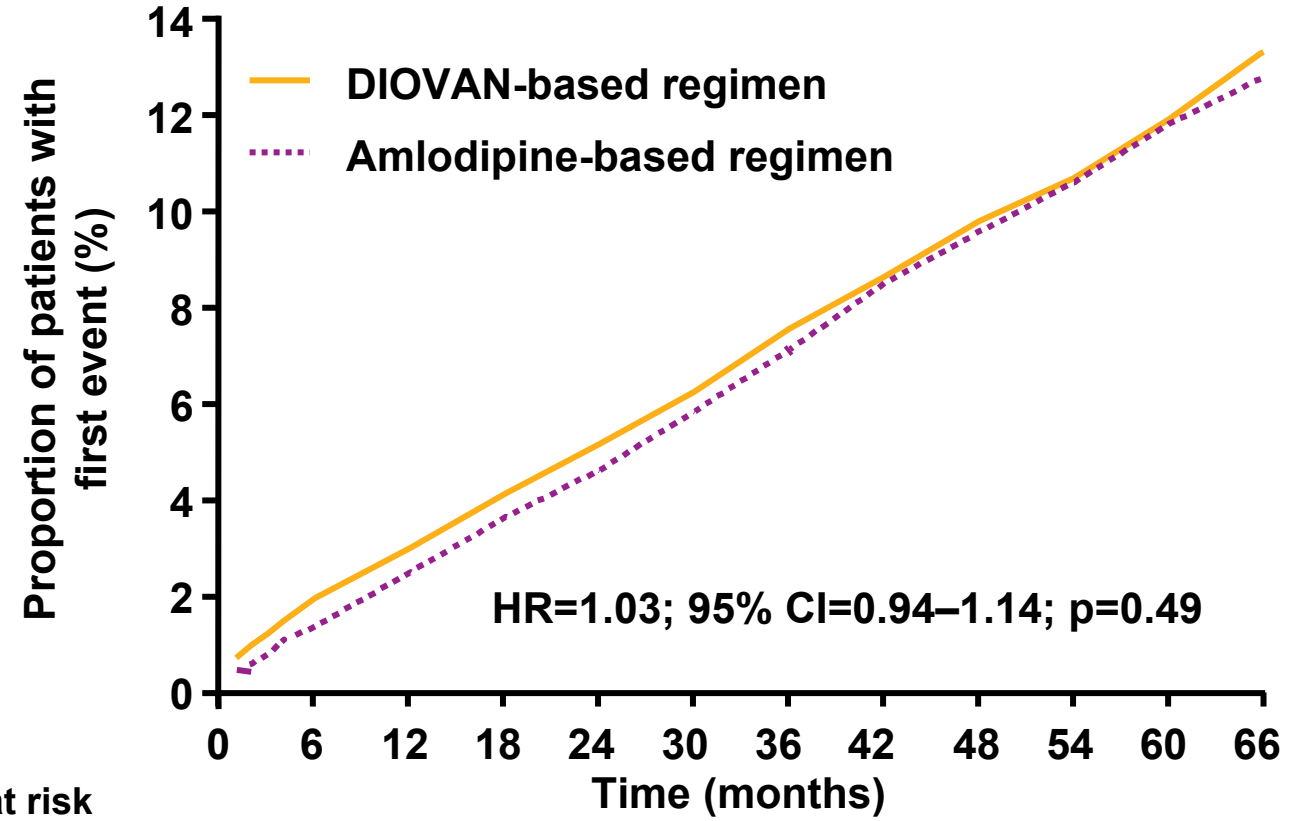


*Patient visits every 6 months for Months 6–72; Amlo = amlodipine

Lancet 2004;363:2022–31

VALUE:

Rate of Cardiac Events Did not Differ Between the Vasarta and Amlodipine Groups



Number at risk												
DIOVAN	7,649	7,459	7,407	7,250	7,085	6,906	6,732	6,536	6,349	5,911	3,765	1,474
Amlodipine	7,596	7,469	7,424	7,267	7,117	6,955	6,772	6,576	6,391	5,959	3,725	1,474

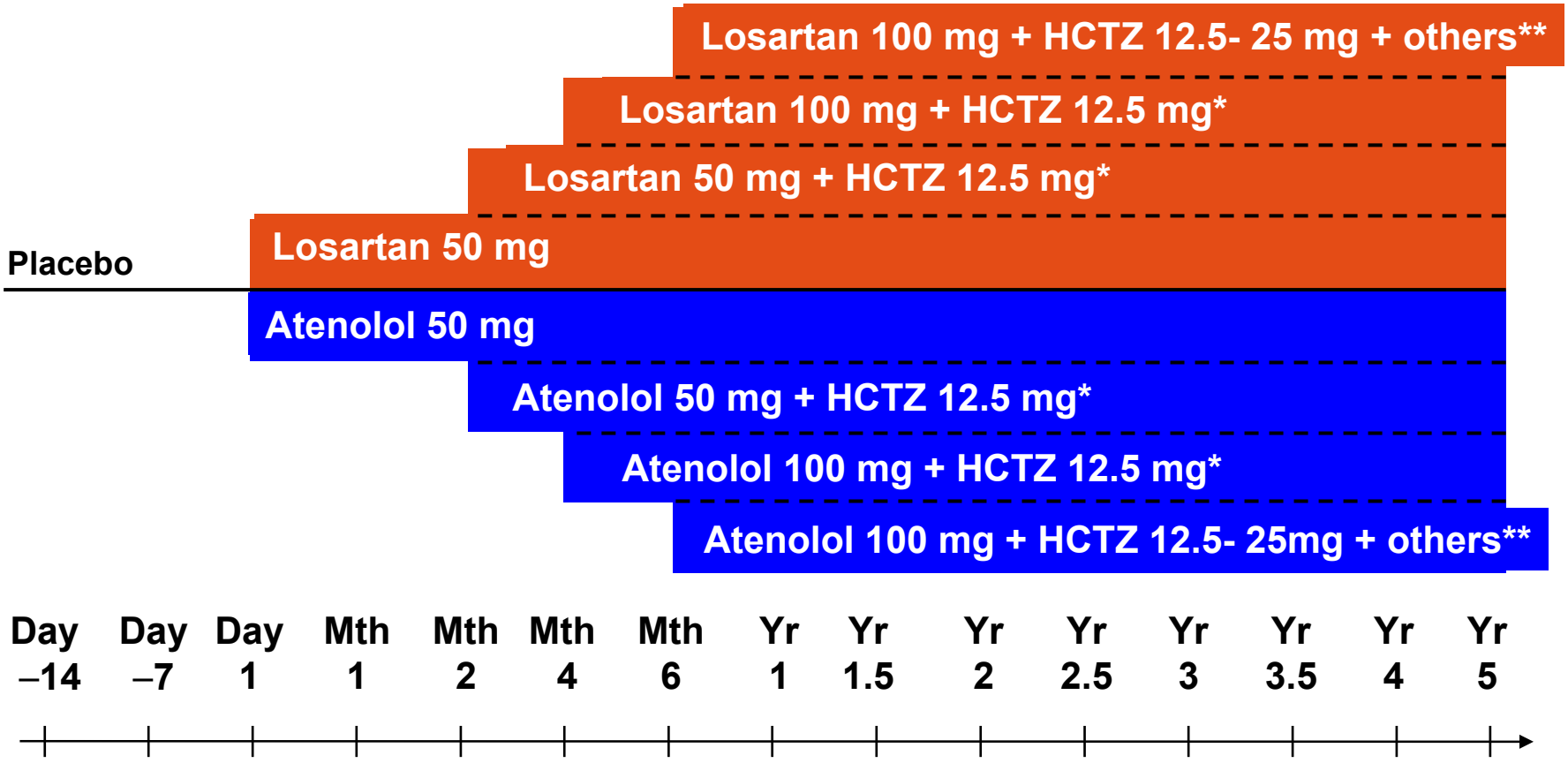
Lancet 2004;363:2022–31

LIFE :

The Losartan Intervention For Endpoint Reduction in Hypertension Study

Patients aged ≥55 years, with treated or untreated hypertensionand at high risk of CV events

*** Titration to target blood pressure: <140 / 90 mmHg**

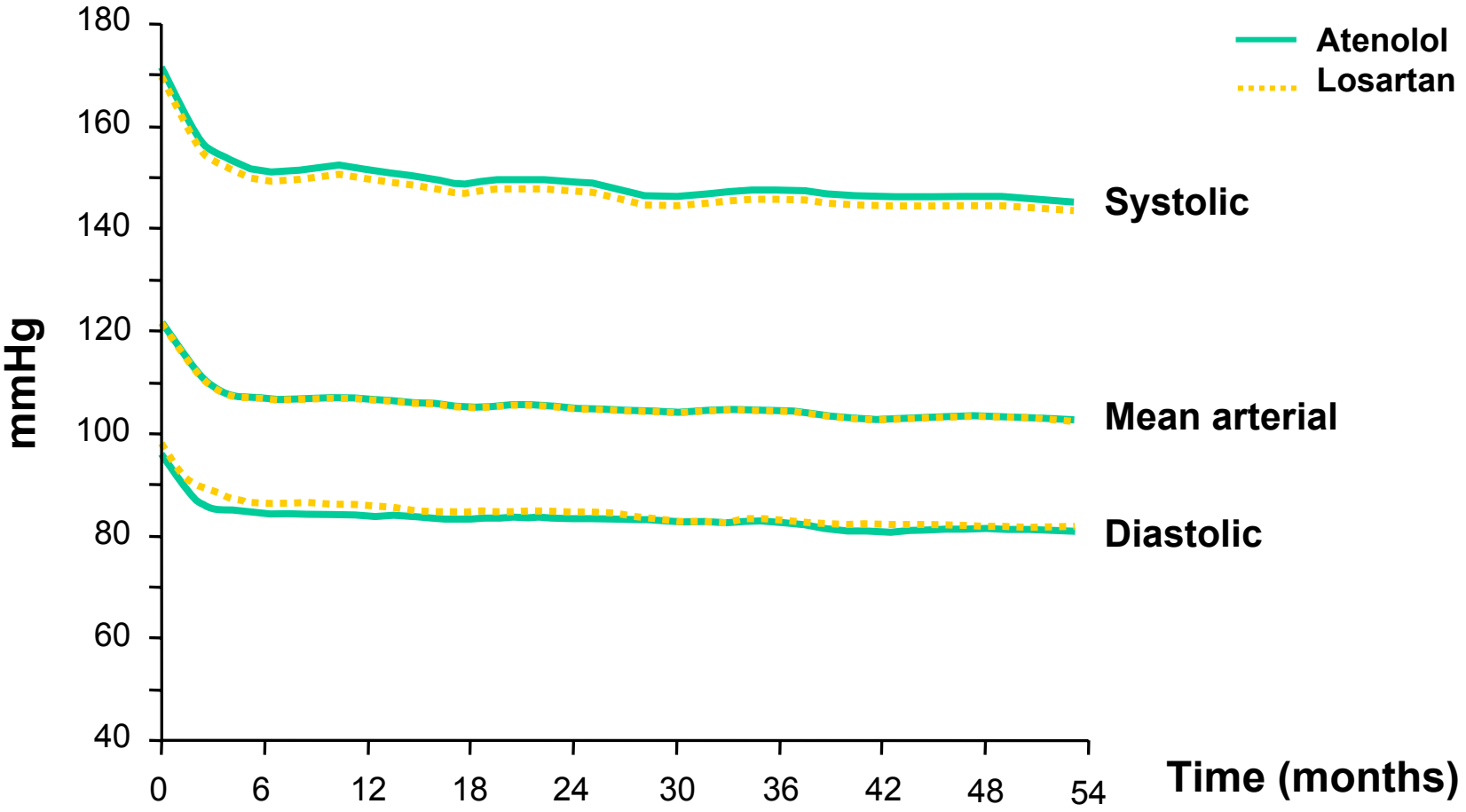


* Titration encouraged if SiDBP ≥90 mmHg or SiSBP ≥140 mmHg but was mandatory if SiBP ≥160 / 95 mmHg

**Other antihypertensives excluding ACEIs, A II antagonists, beta blockers

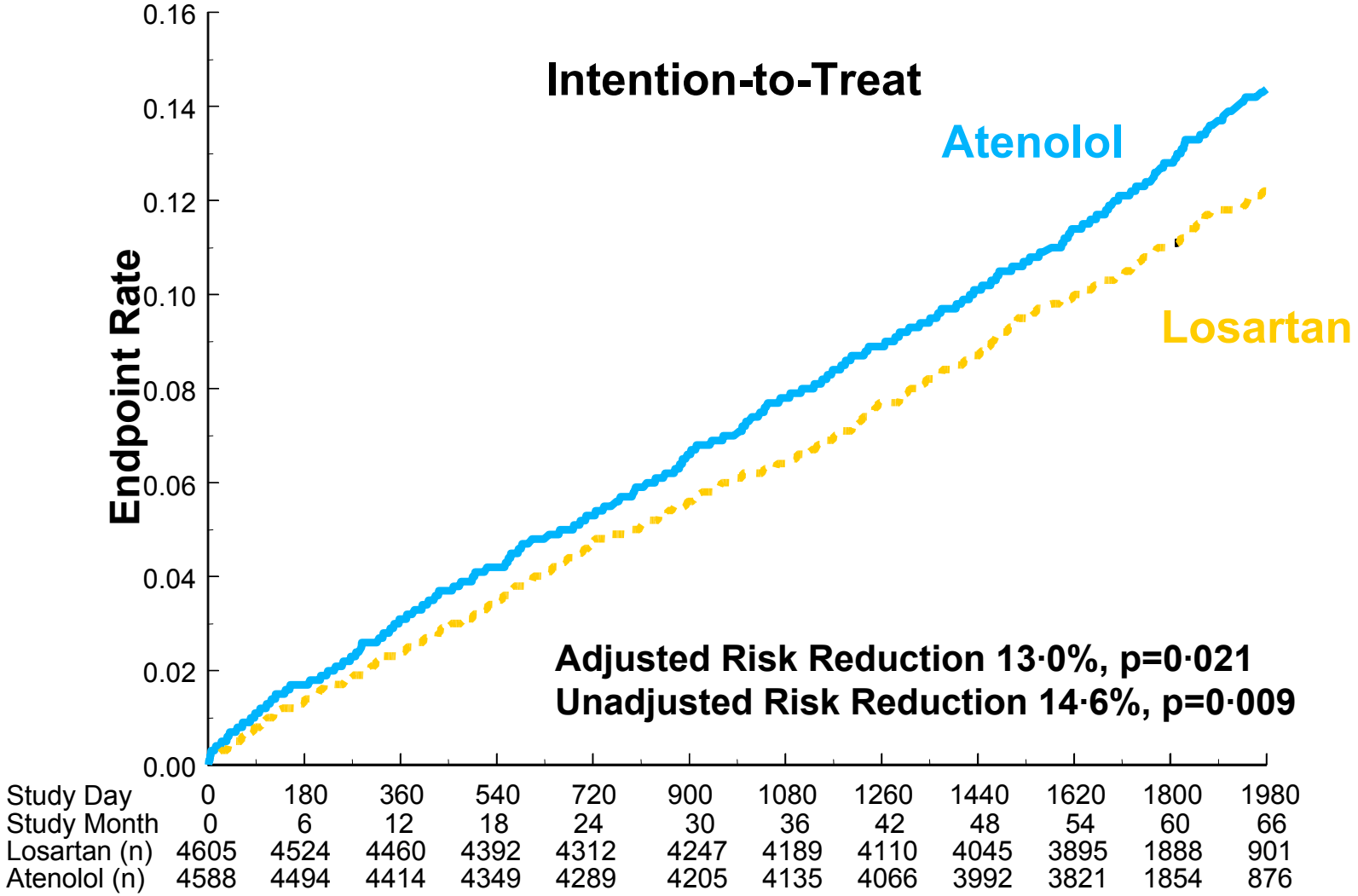
Lancet 2002;359;995-1003-1010

LIFE : **BP reductions**



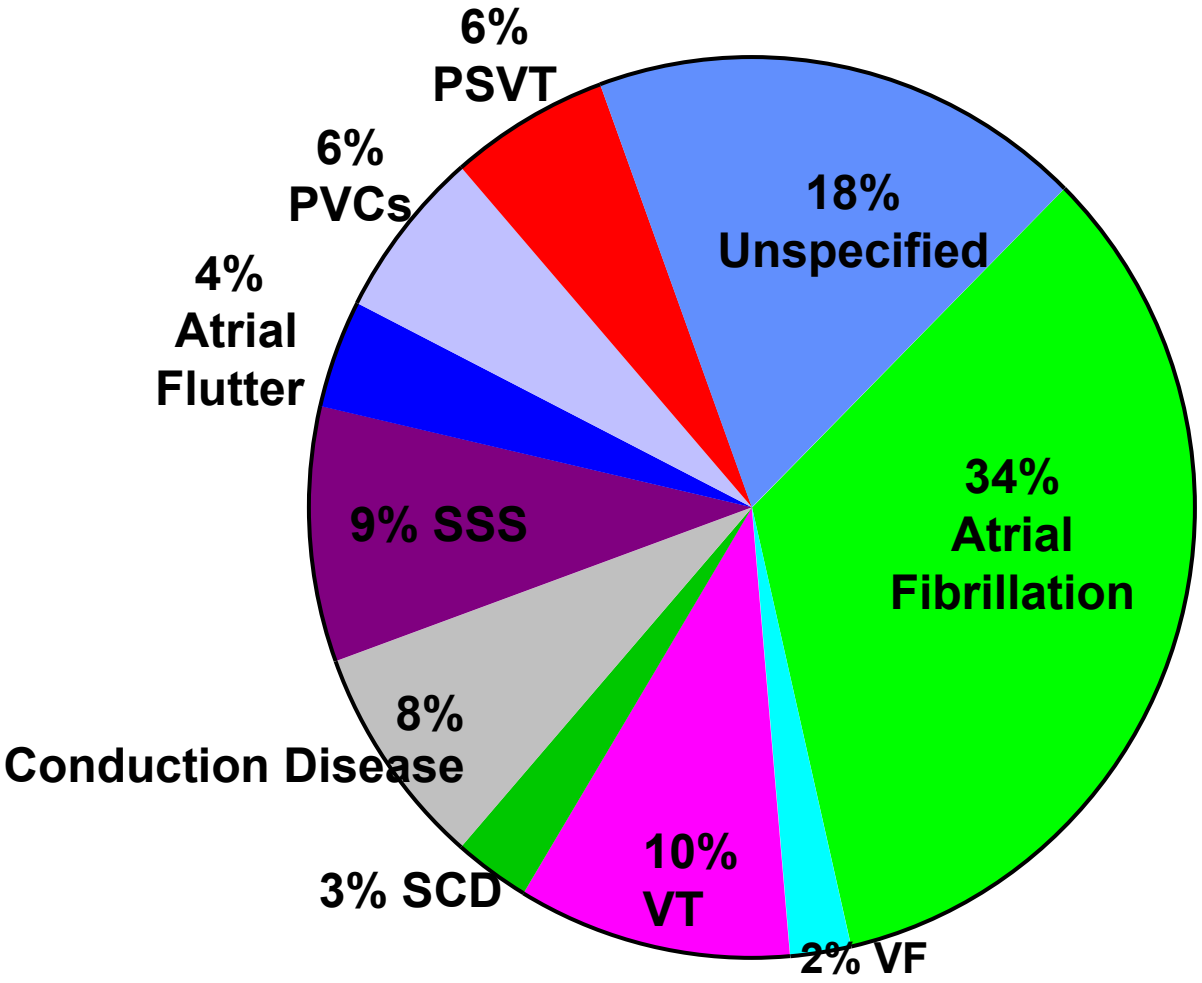
Lancet 2002;359;995-1003-1010

LIFE : Primary Composite Endpoint



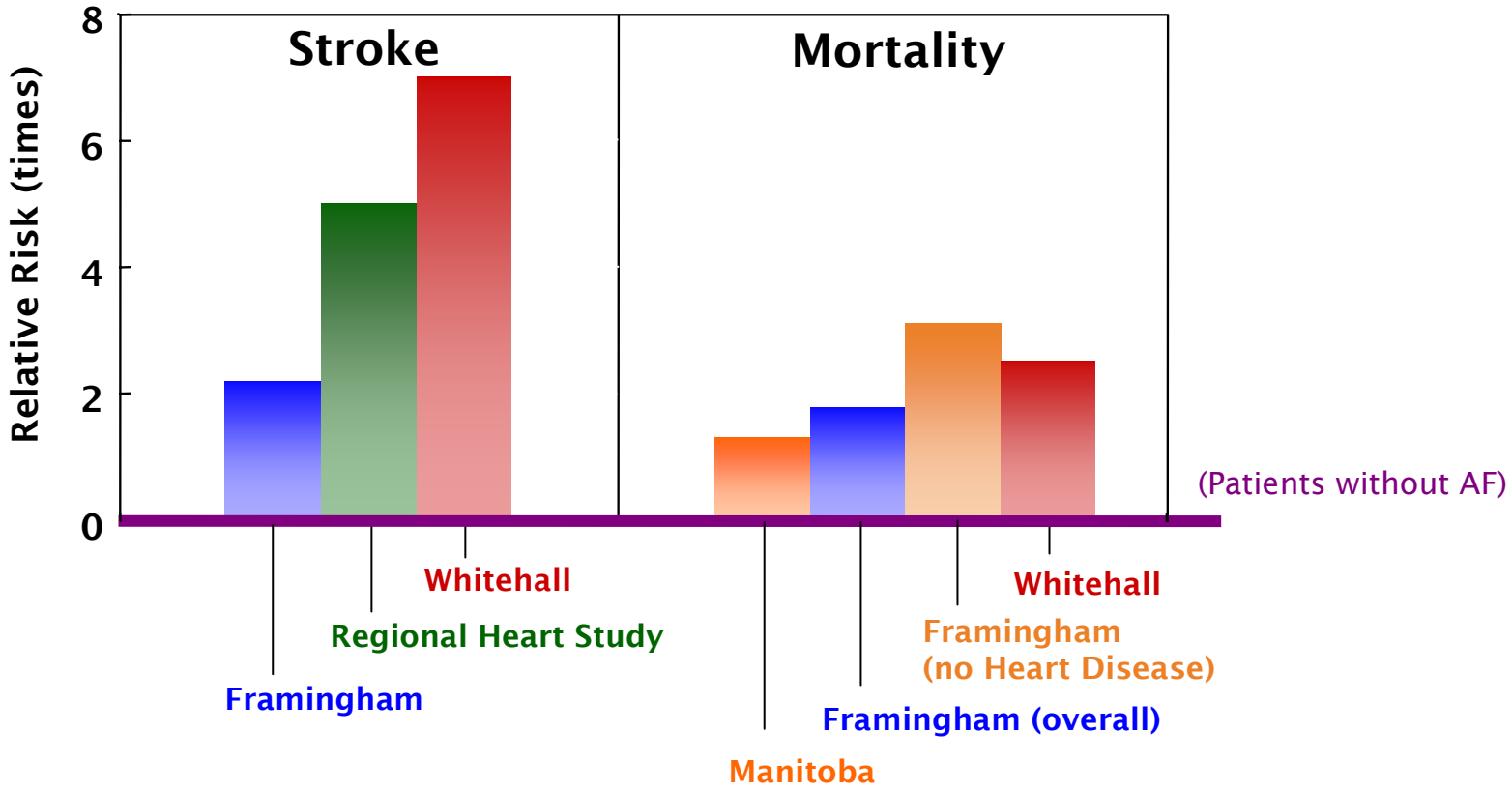
Lancet 2002;359;995-1003-1010

Atrial fibrillation accounts for 1/3 of all patients discharges with arrhythmia as principal diagnosis



J Am Coll Cardiol. 1992;19(3):41A.

Relative Risk of Stroke and Mortality in Patients with AF vs. without AF

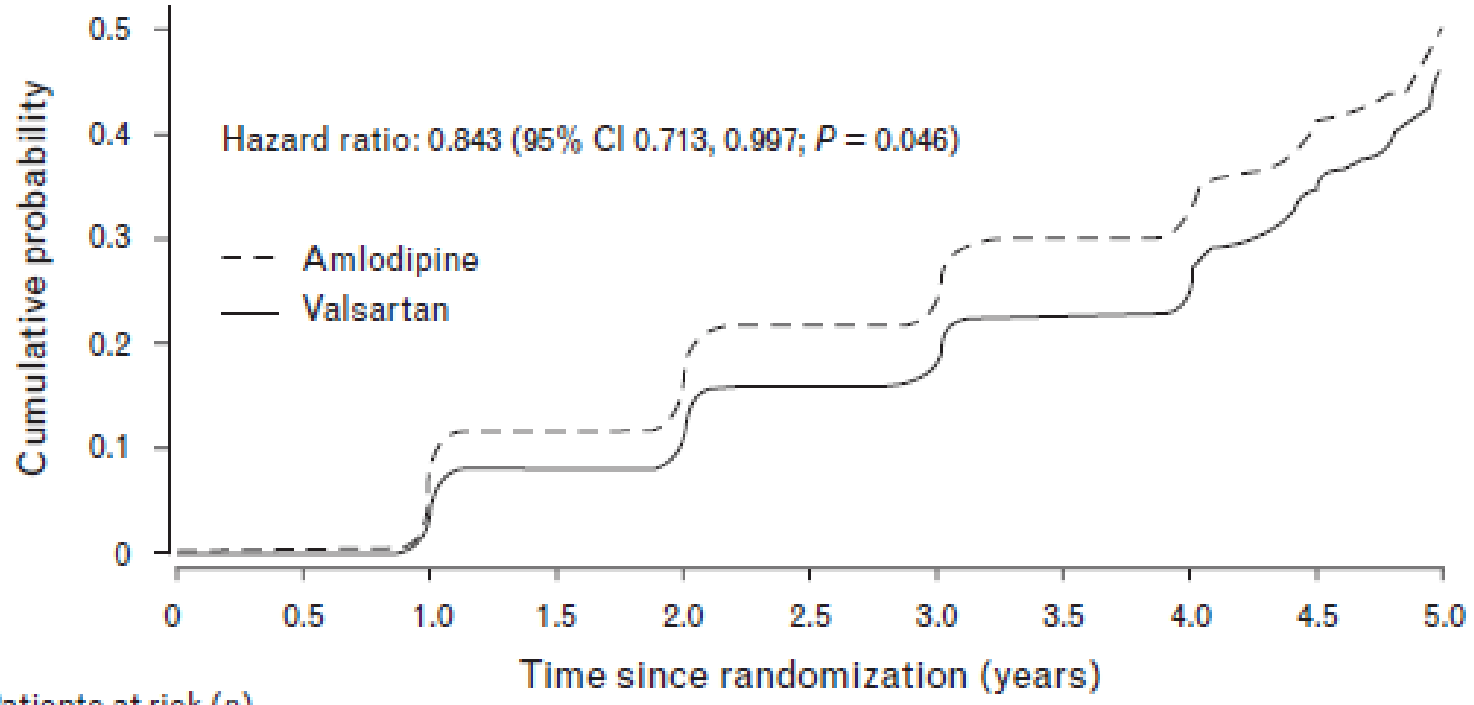


Stroke rate in Non-Rheumatic HD with AF : ↑5% / year

Lancet 1987;1:526
Am Heart J 1983;106:389
Am J Med 1995;98:476

VALUE - AF :

Reduces the risk of new onset AF by 16%



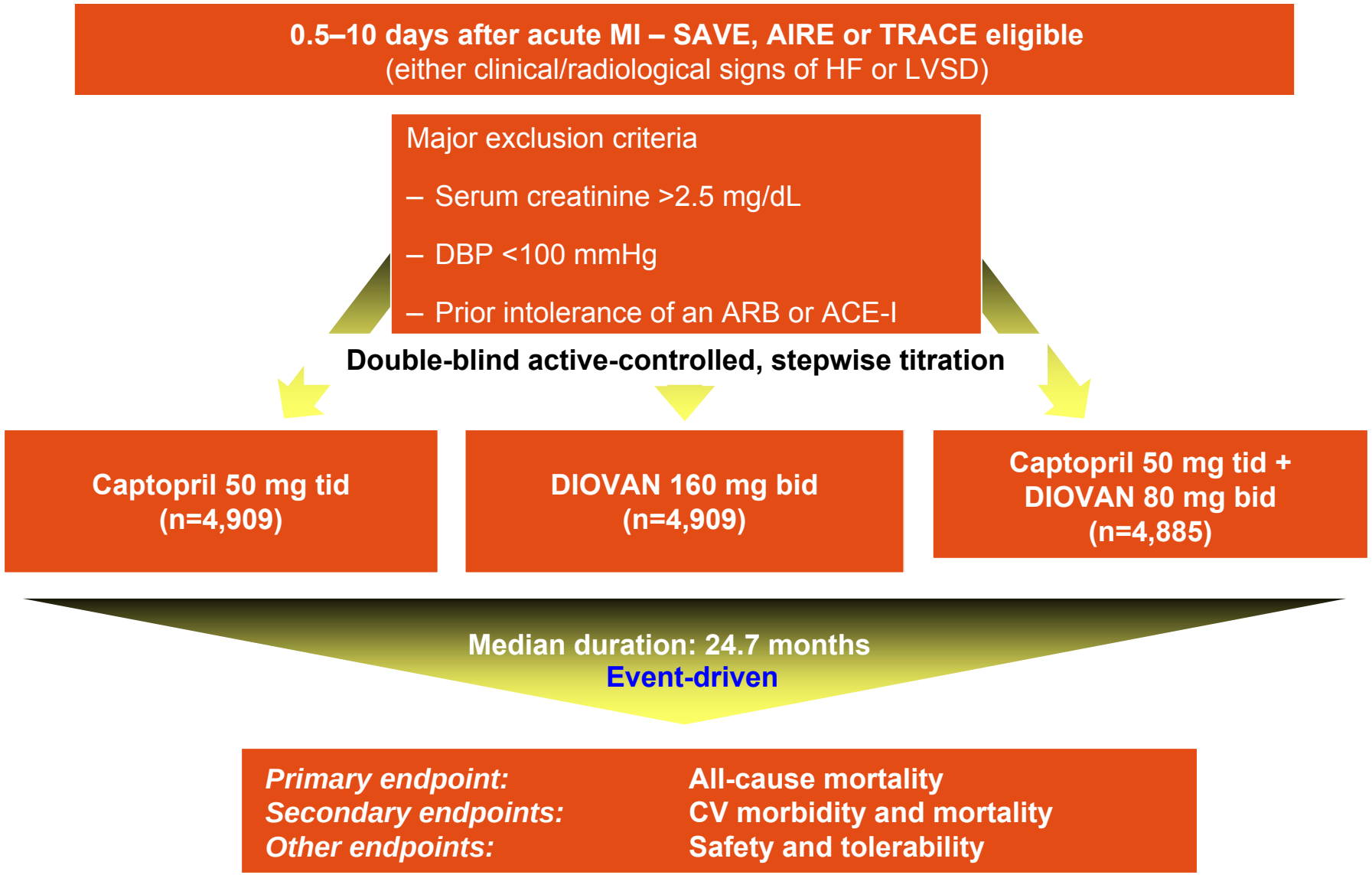
Patients at risk (*n*)

Year	0	1	2	3	4	5
Amlodipine	6888	6882	6610	6266	5789	1673
Valsartan	6872	6862	6618	6274	5818	1664

- DIOVAN significantly reduces the risk of new-onset AF by 16% compared with amlodipine
- DIOVAN significantly reduces the risk of persistent AF by 32% compared with amlodipine

J Hypertens 2008, 26:403–411

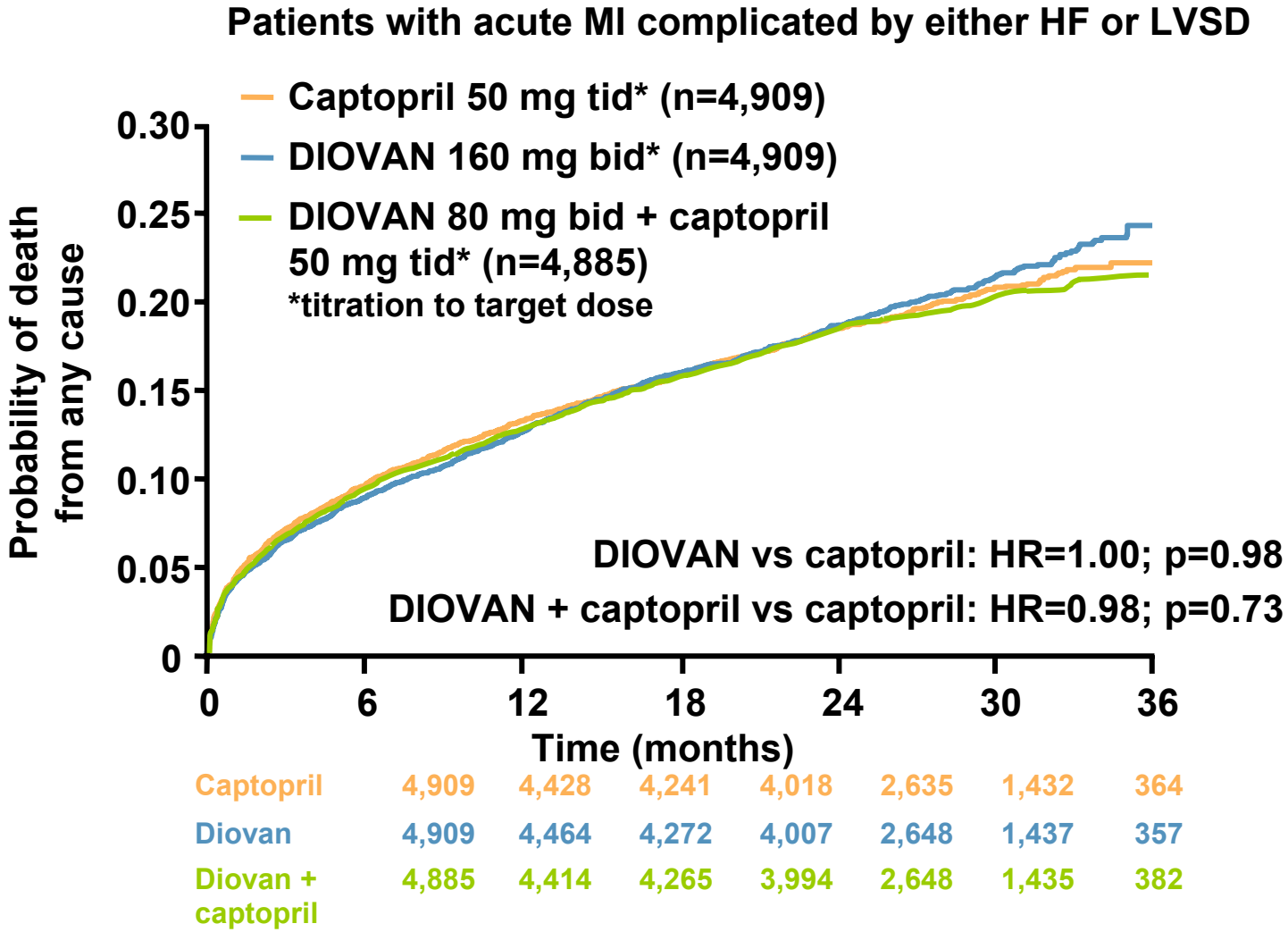
VALIANT: Study Design and Inclusion Criteria



Am Heart J 2000;140:727–50
N Engl J Med 2003;349:1893–906

VALIANT:

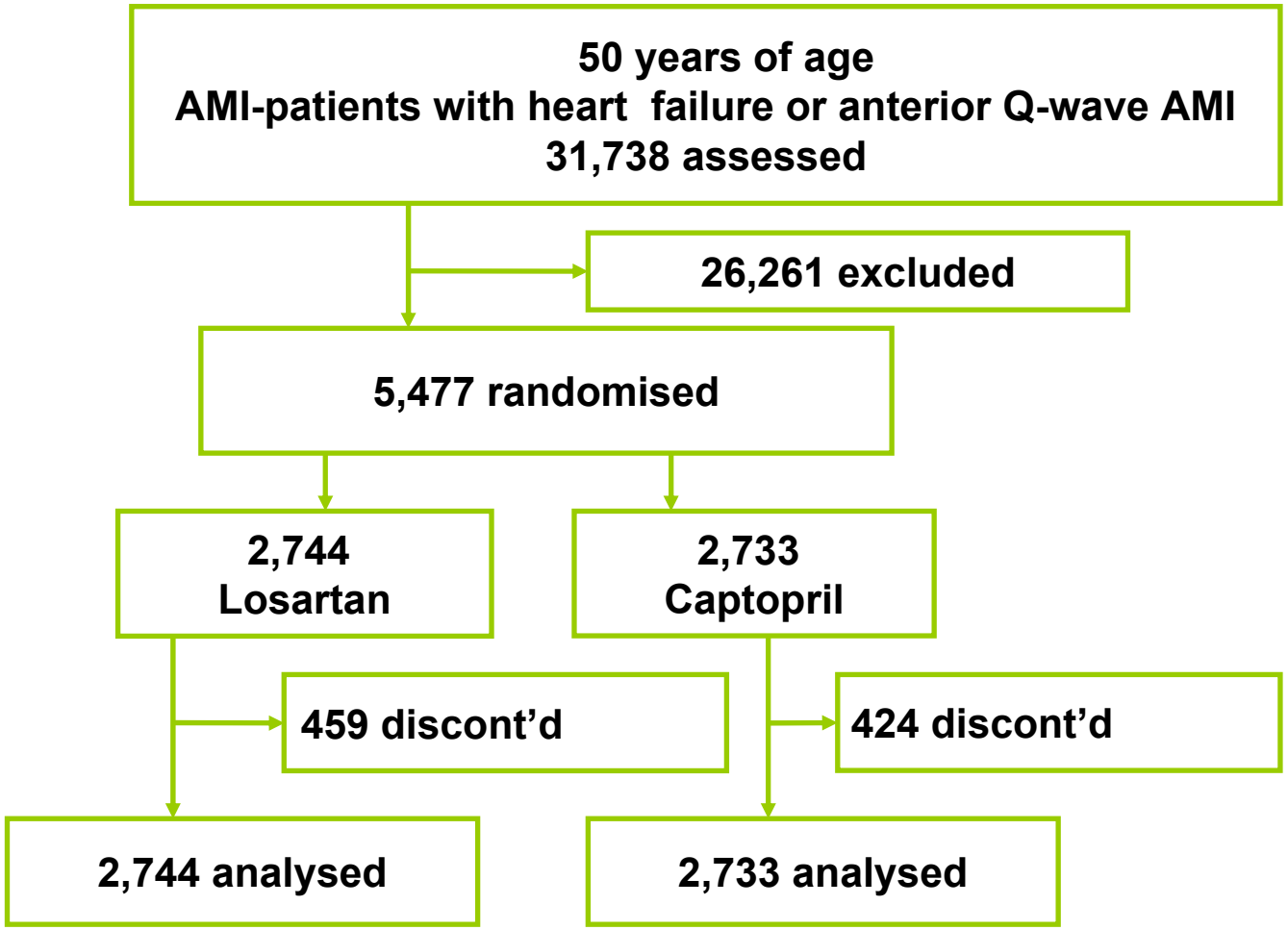
Risk of Mortality is Similarly Reduced with Valsartan and Captopril



LVSD = left ventricular systolic dysfunction
HF = heart failure

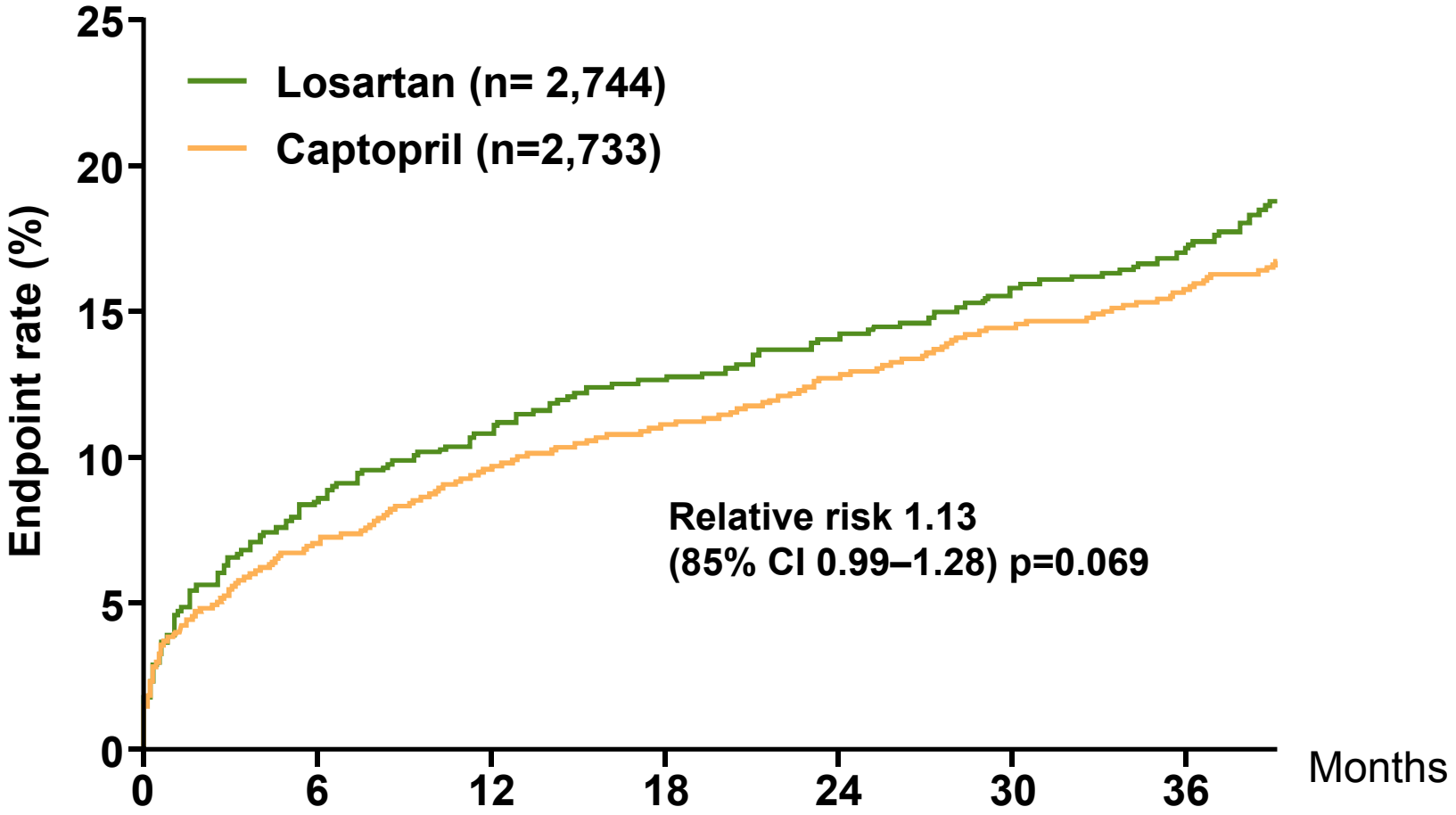
N Engl J Med 2003;349:1893–906

OPTIMAAL(Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan)



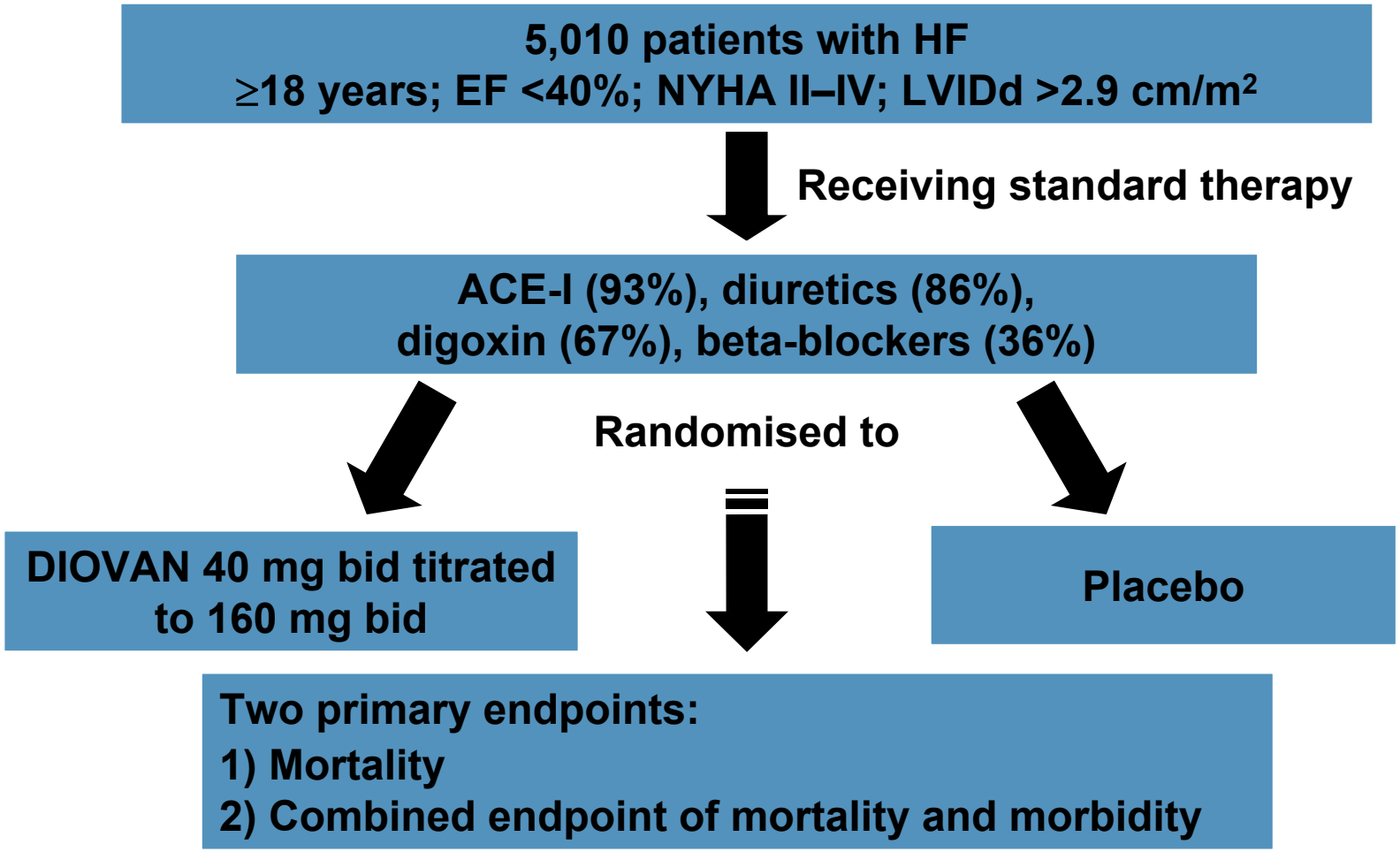
Lancet 2002;360:752–60

OPTIMAAL: No Difference in Mortality Risk Between Losartan and Captopril



Lancet 2002;360:752–60

Val-HeFT (The Valsartan in Heart Failure Trial)

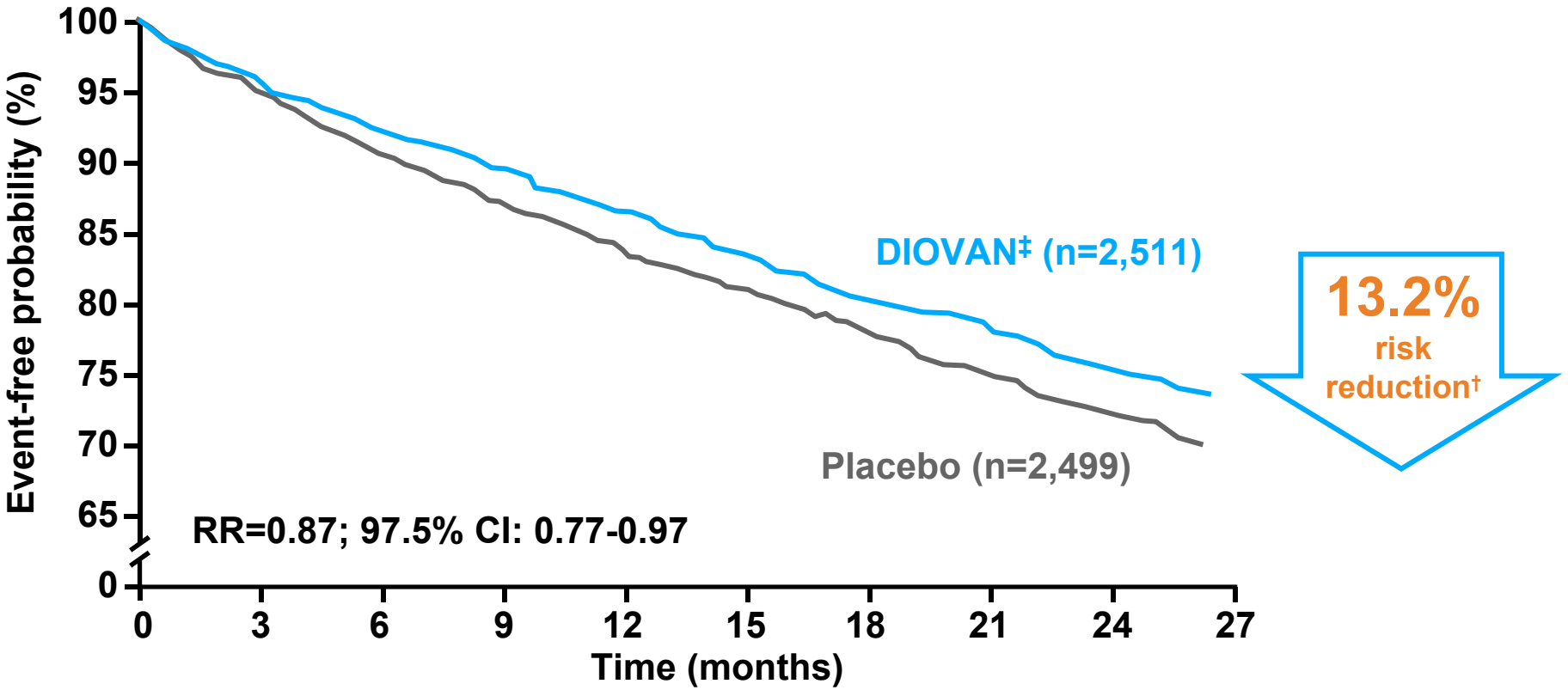


EF = ejection fraction
NYHA = New York Heart Association
LVIDd = left-ventricular internal diastolic diameter

N Engl J Med 2001;345:1667–75

Val-HeFT: Improves CV Outcomes* in CHF

Results from a 23-month mean follow-up study in 5,010 patients with CHF on standard therapy (Val-HeFT study)



*__Combined 1° endpoint__: all-cause mortality, cardiac arrest with resuscitation, hospitalization for worsening HF, or therapy with intravenous inotropes or vasodilators; †p=0.009 vs. placebo; **1° endpoint of mortality was not** significantly different between valsartan and placebo; ‡DIOVAN regimen started at 40 mg bid after placebo run-in, doubled every 2 weeks to target 160 mg bid

Cohn et al. *N Engl J Med* 2001;345:1667-1675

ELITE II :Evaluation of Losartan in the Elderly Study

Randomised trial of losartan versus captopril in patients over 65 with heart failure

≥ 60 yrs; NYHA II - IV; EF ≤ 40 %
ACEI naive or < 7 days in 3 months prior to entry
Standard Rx (± Dig / Diuretics), ß - blocker stratification

Captopril
50 mg 3 times daily
n = 1574

Event Driven
Targeting 510 deaths
estimate 2 yrs
median follow-up 555 days

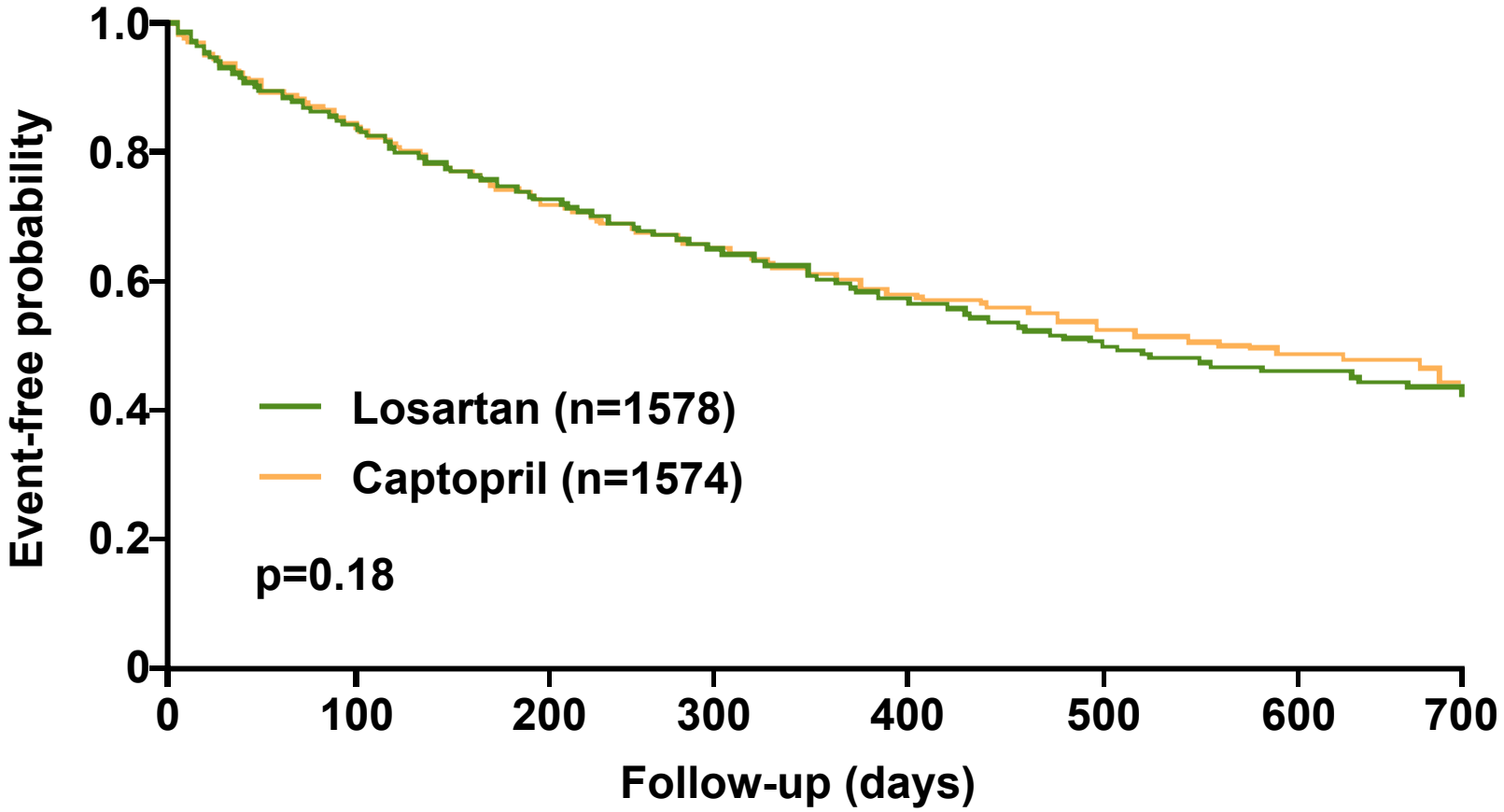
Losartan
50 mg daily
n = 1578

Primary Endpoint : ***All-cause Mortality***
Secondary Endpoint : ***Sudden cardiac death and/or Resuscitated Arrest***
Other : ***All-cause Mortality / Hospitalizations***
Safety and Tolerability

Lancet 2000;355:1582–87

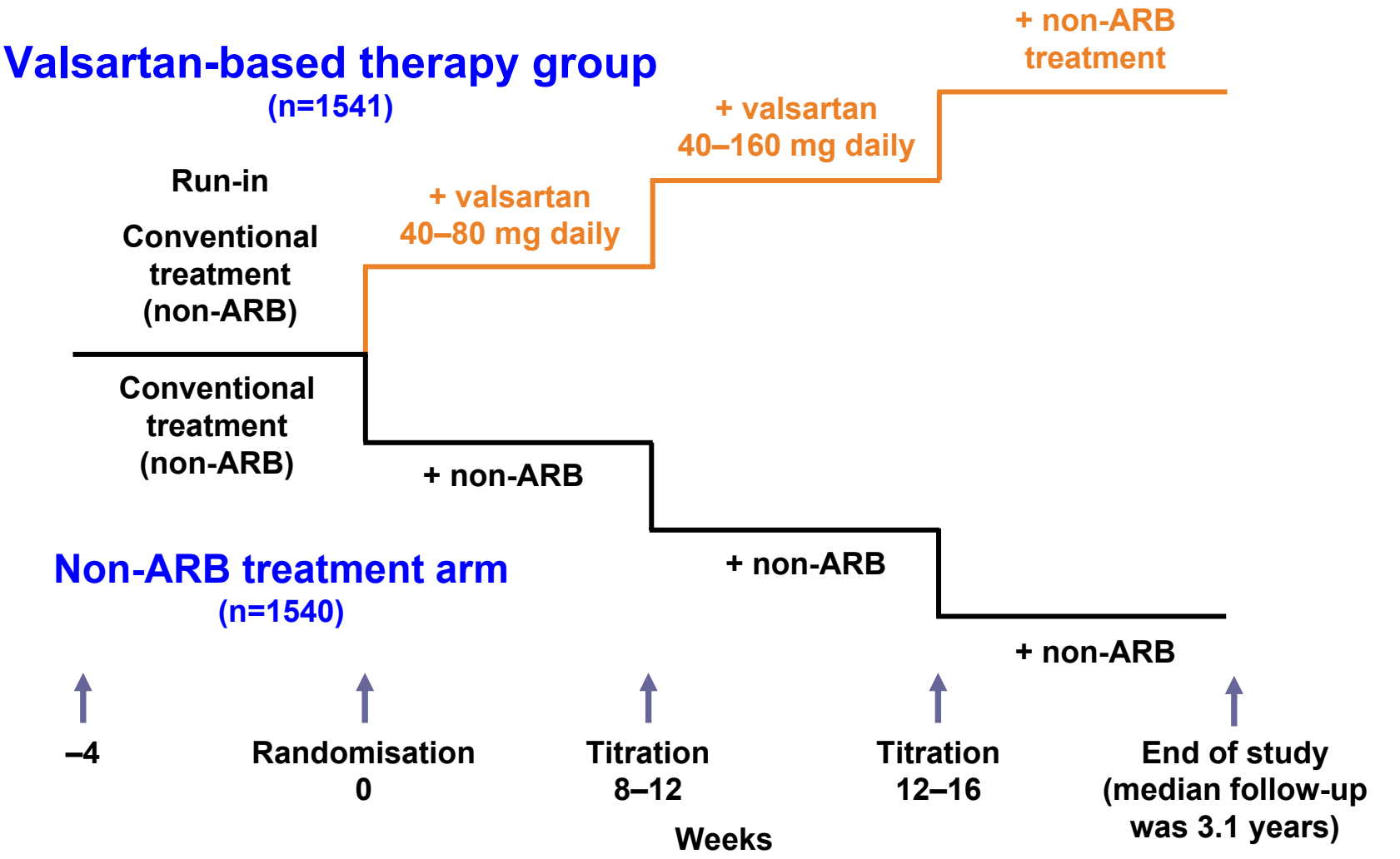
ELITE II:

Risk of All-cause Mortality or Hospital Admission is Similarly Reduced with Losartan and Captopril



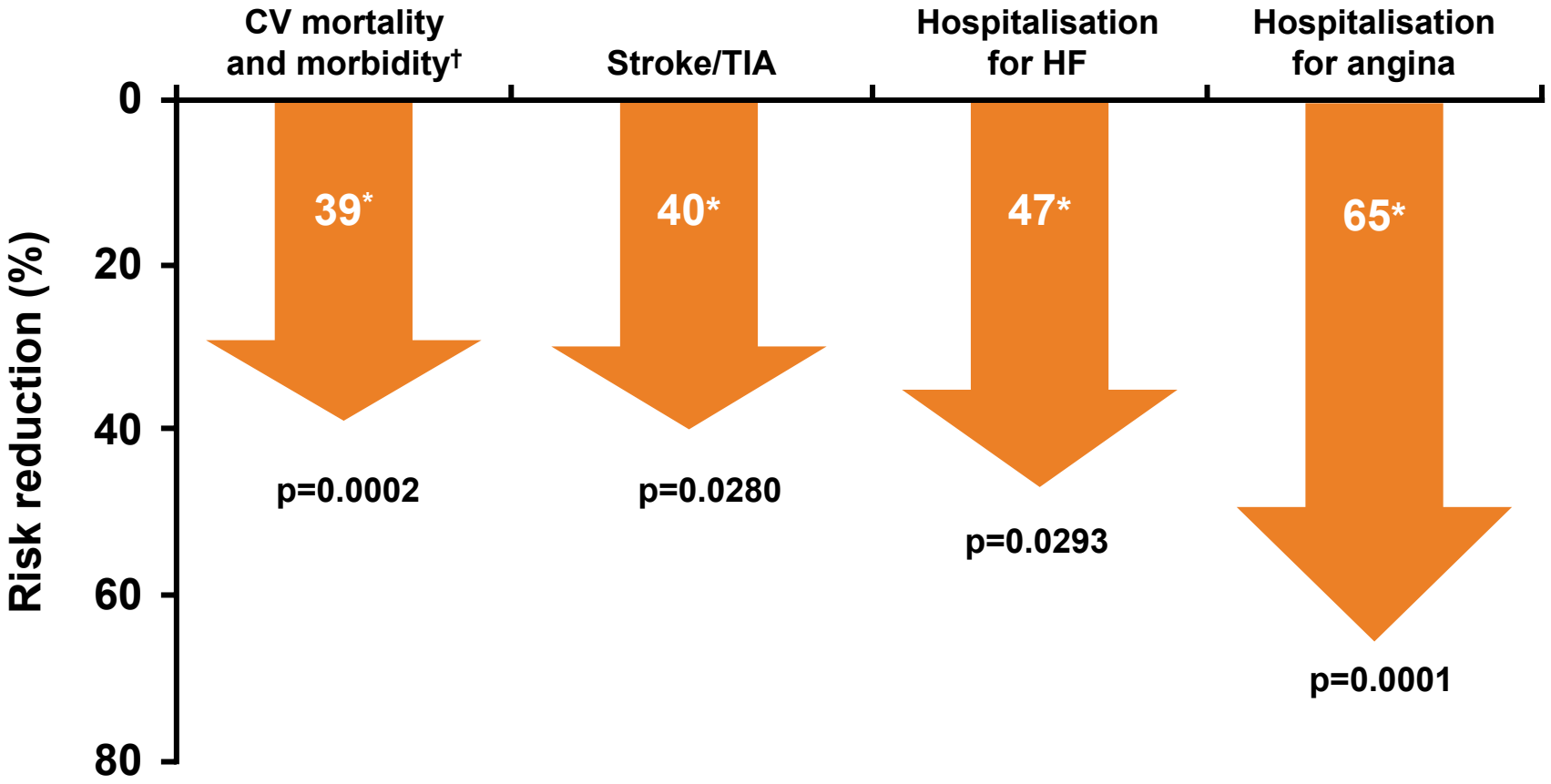
Lancet 2000;355:1582–87

JIKEI HEART : Valsartan-based Therapy Improved Outcomes in Japanese Patients with HT and/or Coronary Heart Disease and/or HF



Mochizuki et al. Lancet 2007;369:1431–9

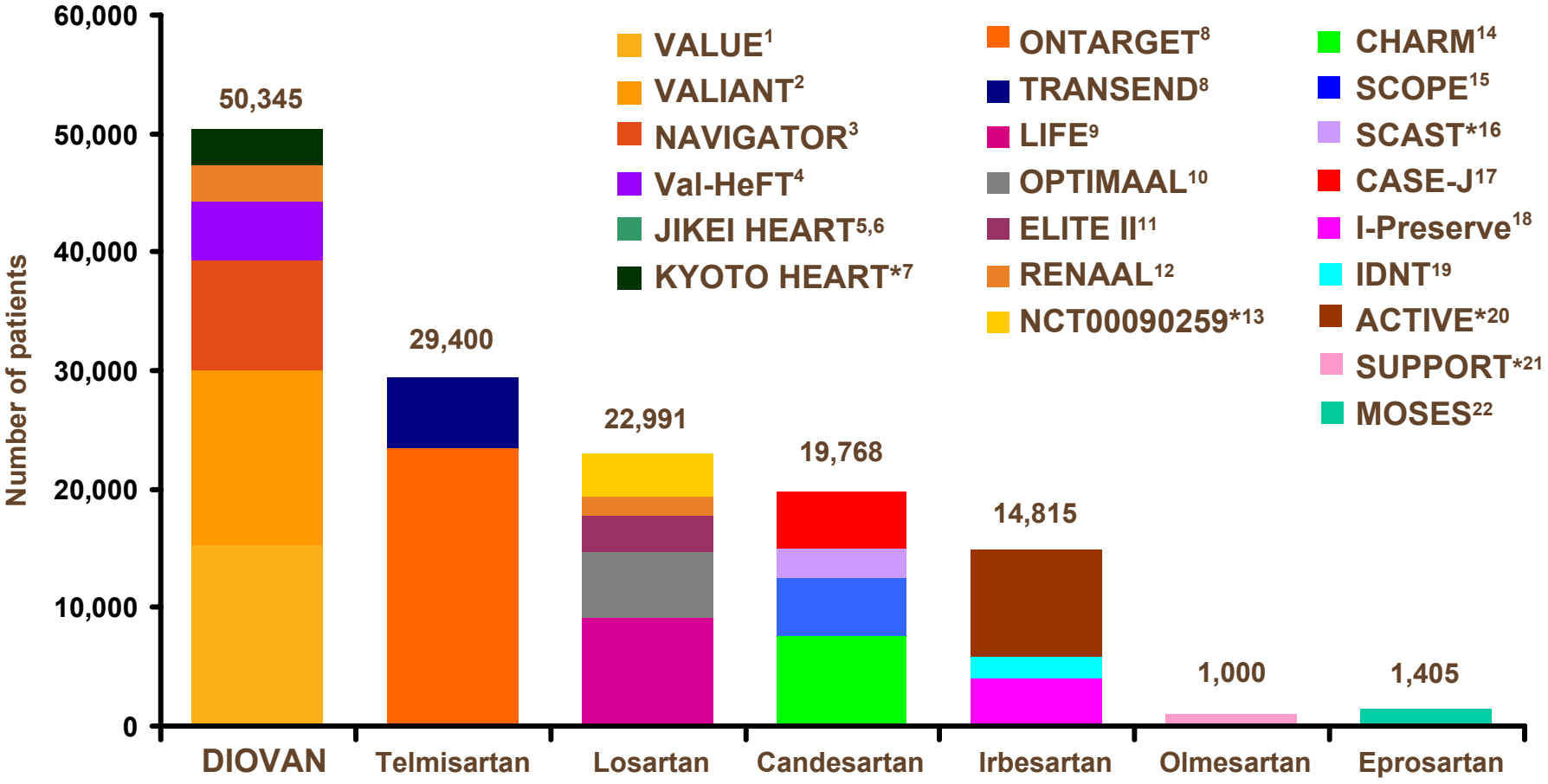
JIKEI HEART



TIA = transient ischemic attack
*With DIOVAN-based therapy compared with non-ARB therapy; †primary endpoint

Lancet 2007;369:1431–9

Mortality and Morbidity Endpoint Trials with ARB



[1]Julius et al. Lancet 2004;363:2022–31; [2]Pfeffer et al. NEJM 2003;349:1893–906; [3]www.novartis.com; [4]Cohn et al. NEJM 2001;345:1667–75; [5]Mochizuki et al. J Hypertens 2006;24(Suppl. 4):S31; [6]Mochizuki et al. Cardiovasc Drugs Ther 2004;18:305–9; [7]http://clinicaltrials.gov (NCT00149227) [8]www.ontarget-micardis.com; [9]Dahlof et al. Lancet 2002;359:955–1003; [10]Dickstein et al. Lancet 2002;360:752–60; [11]Pitt et al. Lancet 2000;355:1582–7; [12]Brenner et al. NEJM 2001;345:861–9; [13]http://clinicaltrials.gov (NCT00090259) [14]www.atacand.com; [15]Papademetriou et al. J Am Coll Cardiol 2004;44:1175–80; [16]http://clinicaltrials.gov (NCT00120003); [17]Ogihara J Hypertens 2006;24(Suppl. 4):S30; [18]Carson et al. J Card Fail 2005;11:576–85; [19]Lewis et al. NEJM 2001;345:851–60; [20]http://clinicaltrials.gov (NCT00249795); [21]http://clinicaltrials.gov (NCT00417222); [22]Schrader et al. Stroke 2005;36:1218–26

*Expected enrolment

HYPERTENSION

Management of hypertension in adults in primary care: partial update

This is a partial update of *NICE Clinical Guideline 18* (published August 2004). The recommendations in this update replace the recommendations on pharmacological interventions for hypertension (section 1.4 of the original NICE guideline, pp103–139 of the original full guideline). No other recommendations are affected.

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British Hypertension Society

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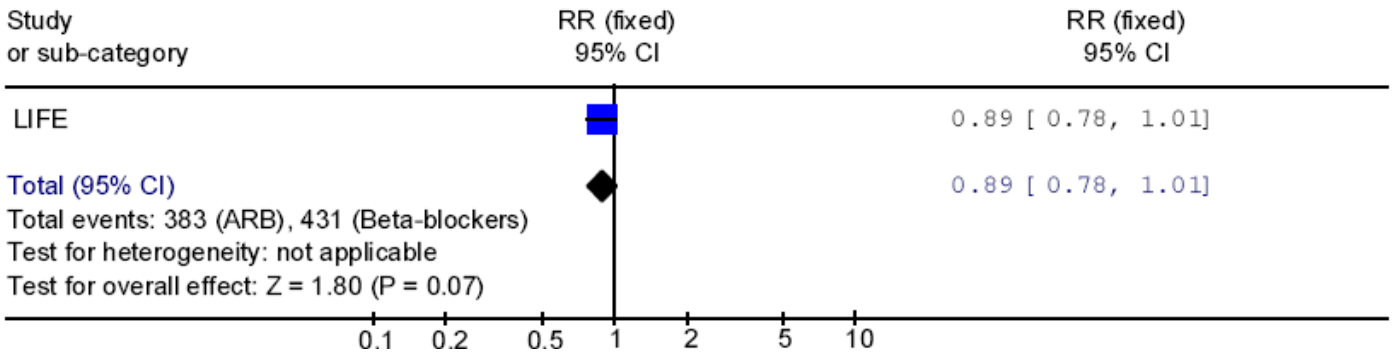
Setting higher medical standards

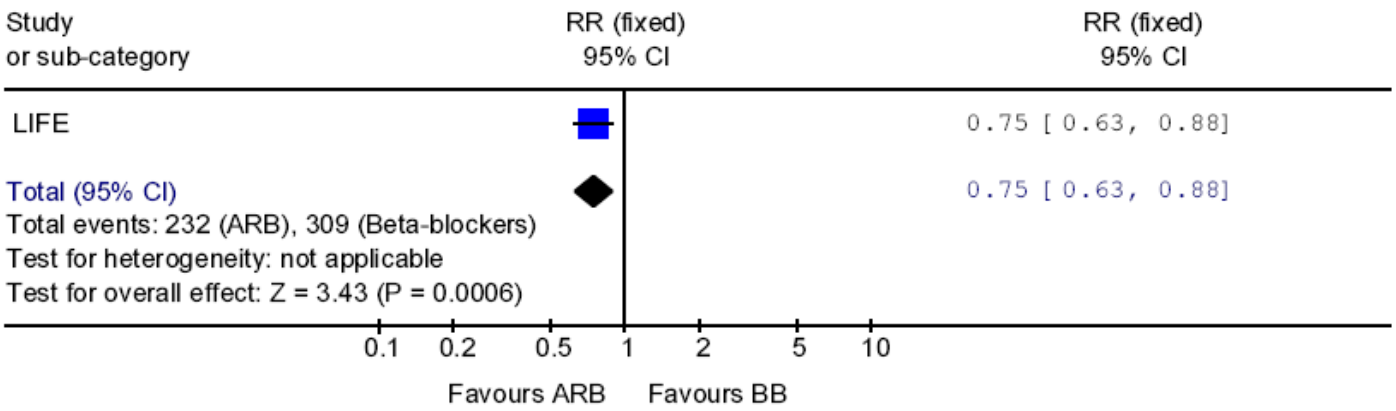
Table 1 Characteristics of included studies

Trial	Year published	I1 Drug	I2 Drug	Secondary drugs	I1 n	I2 n
ALLHAT[11–13]	2002	ACEi: lisinopril	CCB: amlodipine	BB/CAA	8778	8790
ALLHAT[11–13]	2002	ACEi: lisinopril	TD: chlorthalidone	BB/CAA	8778	14836
ALLHAT[11–13]	2002	CCB: amlodipine	TD: chlorthalidone	BB/CAA	8790	14836
ANBP2[27]	2003	ACEi: enalapril	TD: hydrochlorothiazide	BB/CCB/ARB	3044	3037
ASCOT[22]	2005	BB: atenolol	CCB: amlodipine	TD/ACEi	9618	9639
ELSA[28]	2002	BB: atenolol	CCB: lacidipine	TD	114	1128
HAPPHY[29]	1987	BB: atenolol/ metoprolol	TD: bendrofluazide/ hydrochlorothiazide	LD+VD	3265	3240
INSIGHT[30,31]	2000	CCB: nifedipine	TD: co-amilozide (hydrochlorothiazide)	BB/ACEi	3223	3203
JMIC-B[23,24]	2004	ACEi: enalapril/ imidapril	CCB: nifedipine retard	AB	822	828
LIFE[14–18]	2002	ARB: losartan	BB: atenolol	TD	4557	4546
MIDAS[33]	1998	CCB: isradipine	TD: hydrochlorothiazide	ACEi	442	441
MRC[34]	1985	BB: propranolol	TD: bendroflumethiazide	CAA	3558	3519
MRC-o[35]	1992	BB: atenolol	TD: hydrochlorothiazide (+amiloride)	BB/TD/CCB**	1102	1081
NICS-EH[36]	1999	CCB: nicardipine hydrochloride	TD: triclormethiazide	Not reported	204	210
PHYLLIS[25]	2004	ACEi: fosinopril (+pravastatin)	TD: hydrochlorothiazide (+pravastatin)	CCB	254	253
SHEP-p[8–10]	1985	TD: chlorthalidone	Placebo	Reserpine,BB, hydralazine	443	108
SHEP[4–7]	1991	TD: chlorthalidone	Placebo	BB, reserpine	2365	2371
STOP-H2[37–40]	1999	ACEi: enalapril/ lisinopril	CCB: felodipine/isradipine	TD/BB	2205	2196
SYST-EUR[1–3]	2000	CCB: nitrendipine	Placebo	ACEi, TD	2398	2297
VALUE[26]	2004	CCB: amlodipine	ARB: valsartan	TD	7596	7649
VHAS[41,42]	1998	CCB: verapamil	TD: chlorthalidone	ACE	707	707

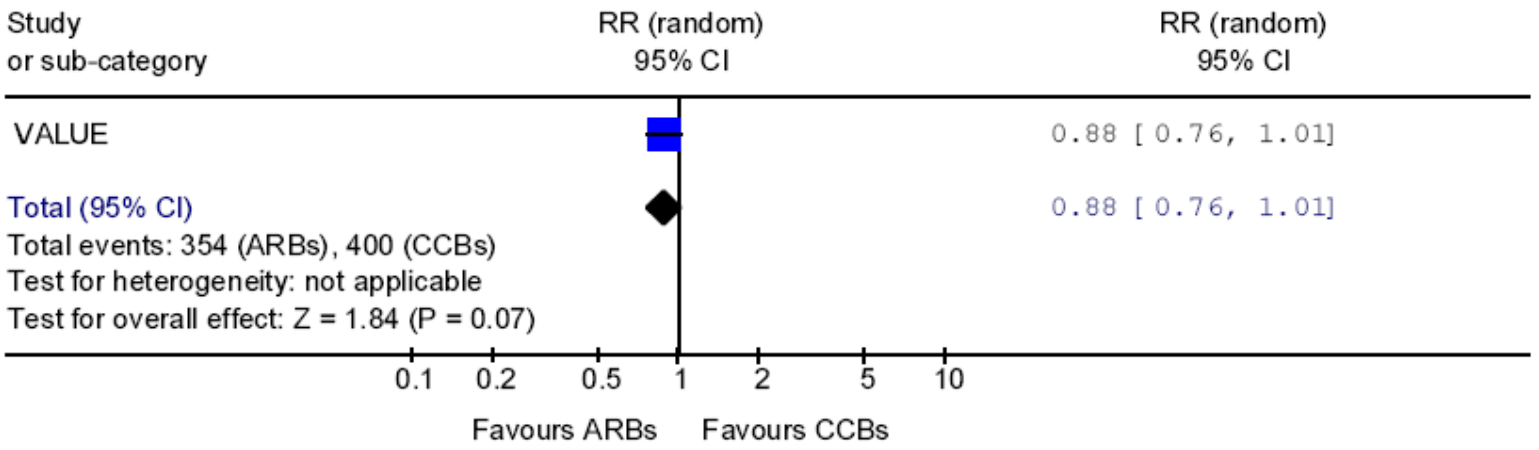
Comparison: 03 ARBs versus beta-blockers
Outcome: 01 Mortality



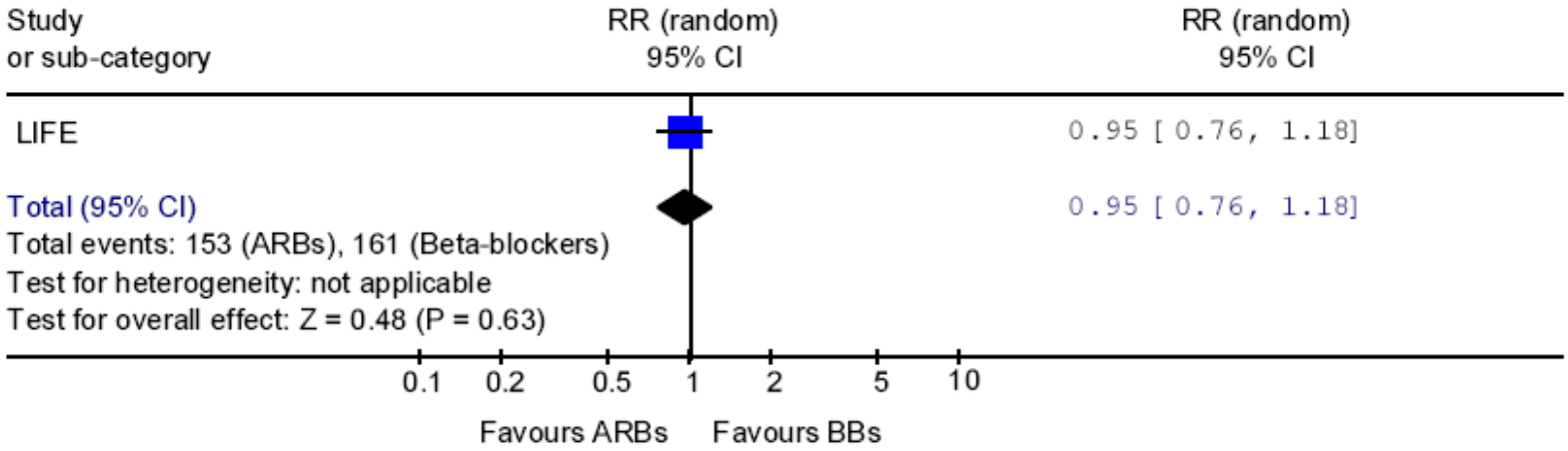
Comparison: 03 ARBs versus beta-blockers
Outcome: 03 Stroke



Comparison: 07 ARBs versus calcium-channel blockers
Outcome: 04 Heart failure



Comparison: 05 ARBs versus beta-blockers
Outcome: 05 Heart failure



Summary:

- **To protect and improve vascular and cardiac structure/function**
  - **understanding the effects of angiotensin II is an important issue in HT.**
- **Blocking the negative effects of angiotensin II at the AT_1 receptor**
  - **improves endothelial function,**
  - **improves inflammation,**
  - **reduces oxidative stress**
  - **improves left ventricular remodeling and function**
- **ARB has proven clinical benefits from HT to HF patients in the spectrum of CV continuum.**