Rennin-angiotensin System and Inflammation

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Contents

Lipid Accumulation and Endothelial Activation

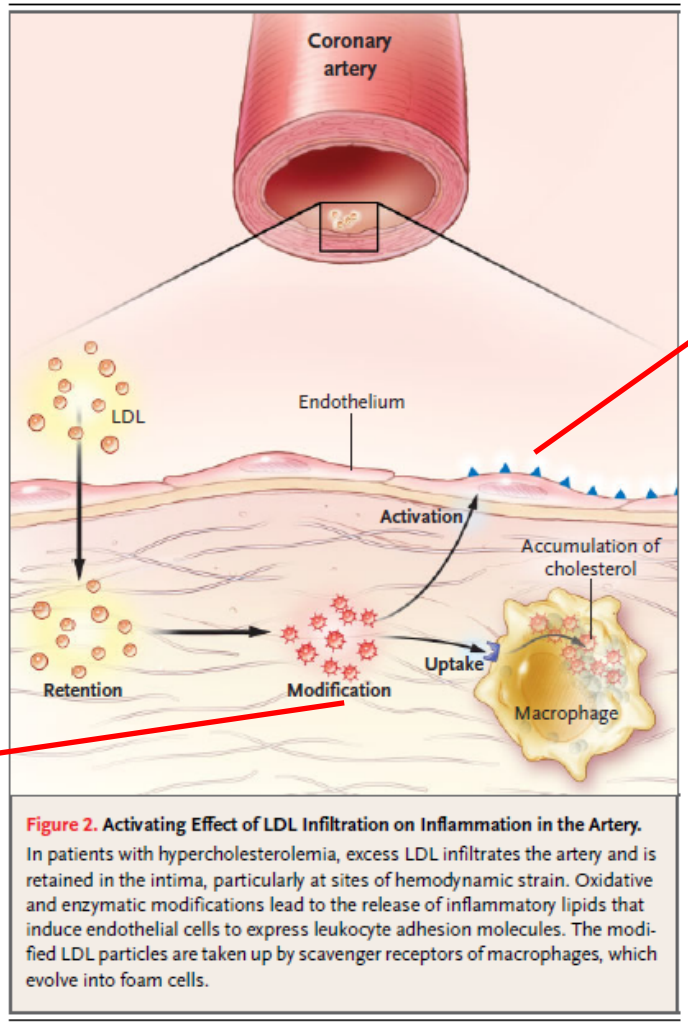


Figure 2. Activating Effect of LDL Infiltration on Inflammation in the Artery.
In patients with hypercholesterolemia, excess LDL infiltrates the artery and is retained in the intima, particularly at sites of hemodynamic strain. Oxidative and enzymatic modifications lead to the release of inflammatory lipids that induce endothelial cells to express leukocyte adhesion molecules. The modified LDL particles are taken up by scavenger receptors of macrophages, which evolve into foam cells.

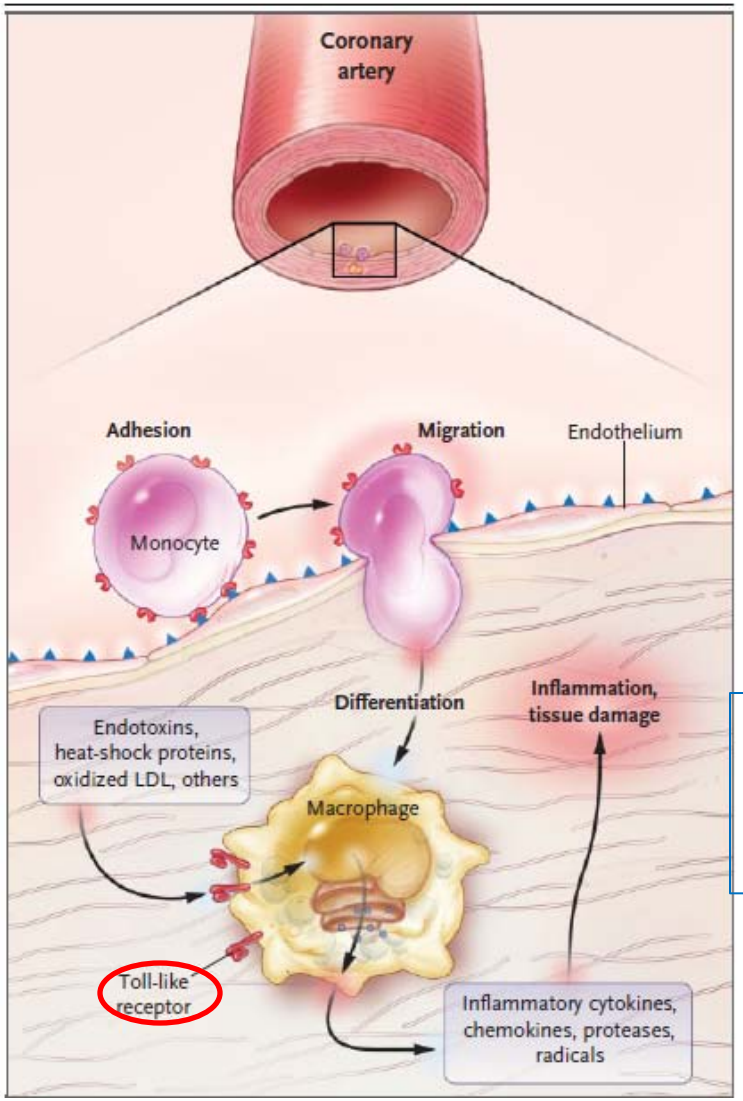
Adhesion molecule and inflammatory gene

Platelet is the firs t cell to come
Inhibition of platelet adhesion
Reduce leukocyte infiltration

oxidization

N Engl J Med 2005;352:1685-95.

Macrophage Infiltrate



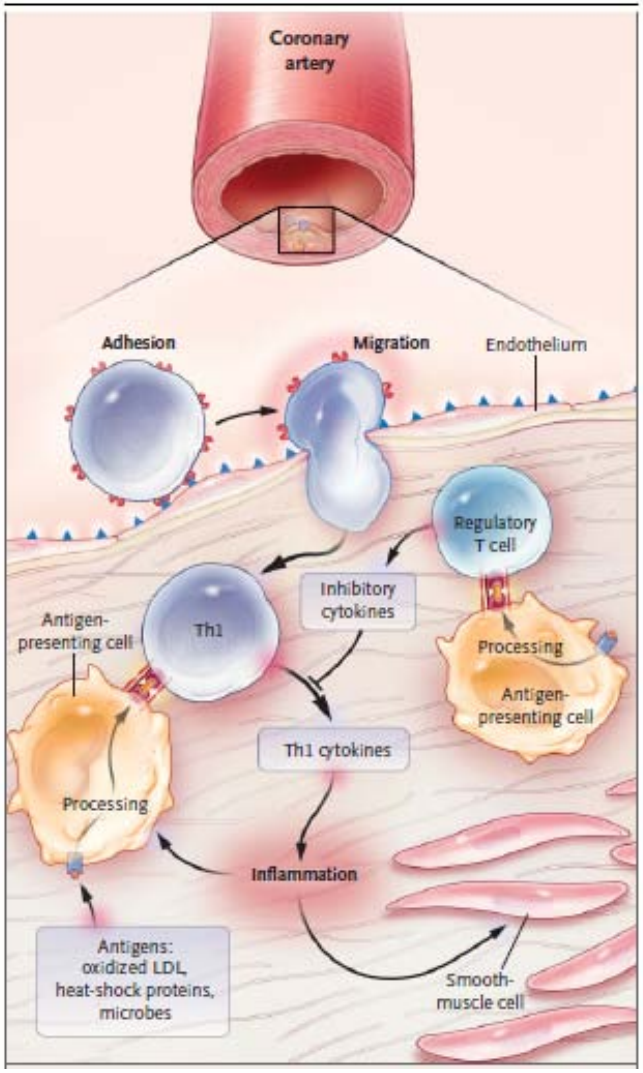
MCSF induce macrophage Differentiation including Pattern-recognition molecules Including scavenger receptor and Toll-like receptor

VCAM offer adhesion site

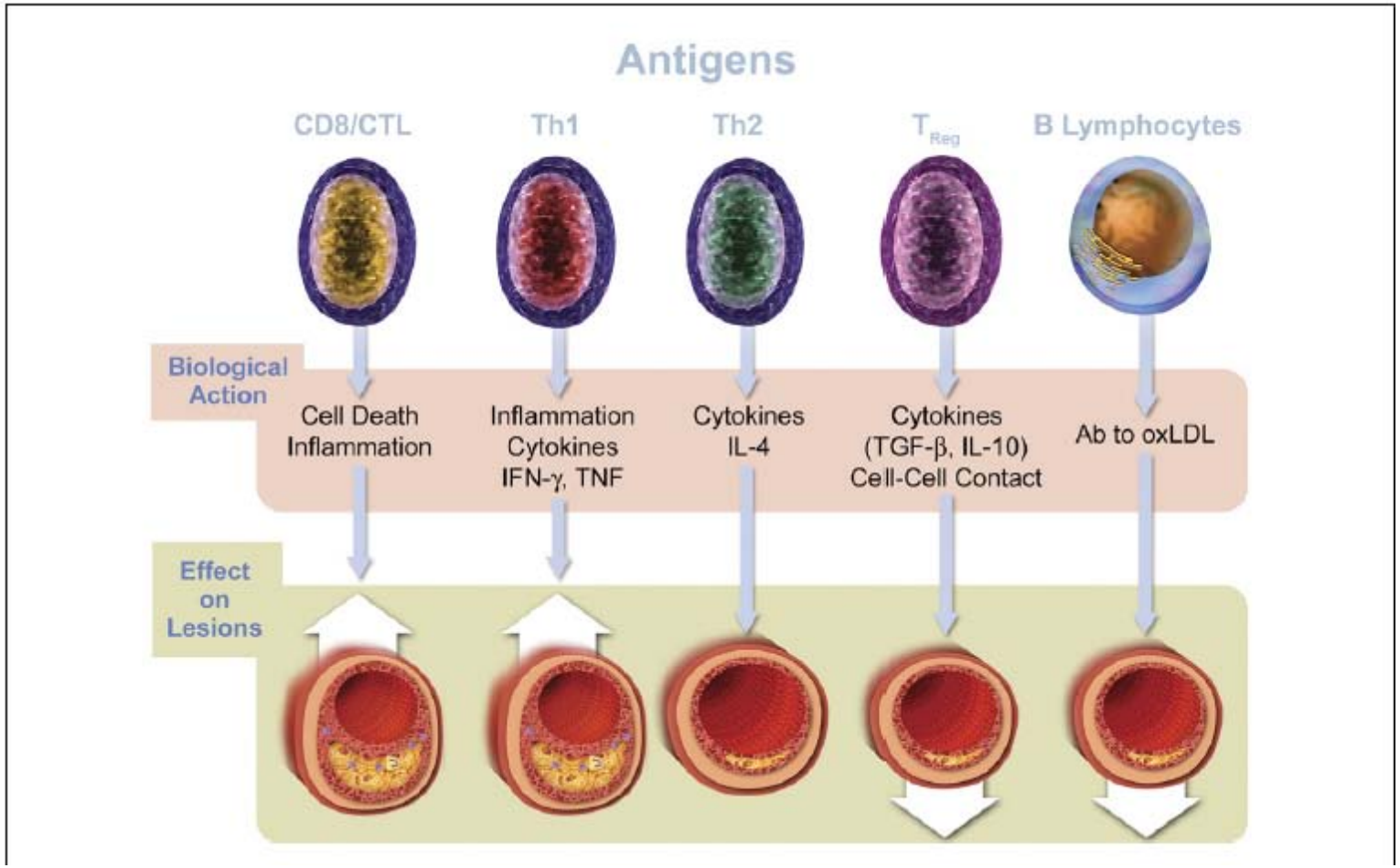
Scavenger receptor internalized ox LDL and change macrophage to foamy cell if lipid not mobilized adequately

N Engl J Med 2005;352:1685-95.

T-Cell Activation

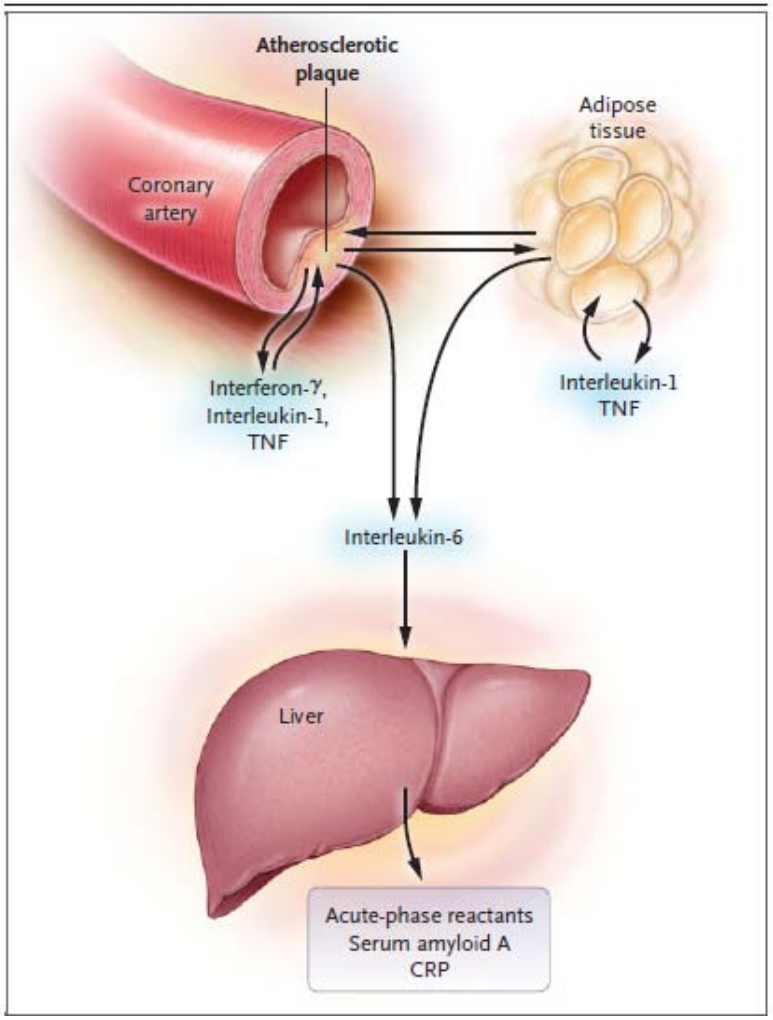


Different Lymphocyte on Atherosclerosis



(J Am Coll Cardiol 2009;54:2129–38)

Cytokine Cascade



N Engl J Med 2005;352:1685-95.

C-reactive protein (CRP)[2] was discovered in 1930 by William Tillett and Thomas Francis from the Rockefeller University. They described a third serologic fraction, or "fraction C," that could be isolated from patients infected with pneumococcus that was distinct from previously known capsular polysaccharide and nucleoprotein fractions detectable by specific antibody response *(1)*. A decade later, Oswald Avery and Maclyn McCarty—the research team who originally described the "transforming principle" and the concept that genes are made of DNA—also described CRP as an "acute-phase reactant" that was increased in serum of patients suffering from a spectrum of inflammatory stimuli, including myocarditis and the inflammation associated with rheumatic fever *(2–4)*.

Clinical Chemistry 55:2
209–215 (2009)

identified CRP as a hepatically derived, nonglycosylated, circulating pentraxin composed of 5 identical subunits arranged with pentameric symmetry that had characteristic calcium-dependent binding to specific ligands, including binding to LDL cholesterol *(7–13)*. They and other investigators further demonstrated that the bulk of circulating CRP is produced by hepatocytes largely under regulatory control of inflammatory cytokines including interleukin-6 (IL-6) and tumor necrosis factor-α; that the plasma half-life of CRP is approximately 19 h under basal and stress conditions; and thus that the plasma concentration is largely determined by synthetic rate

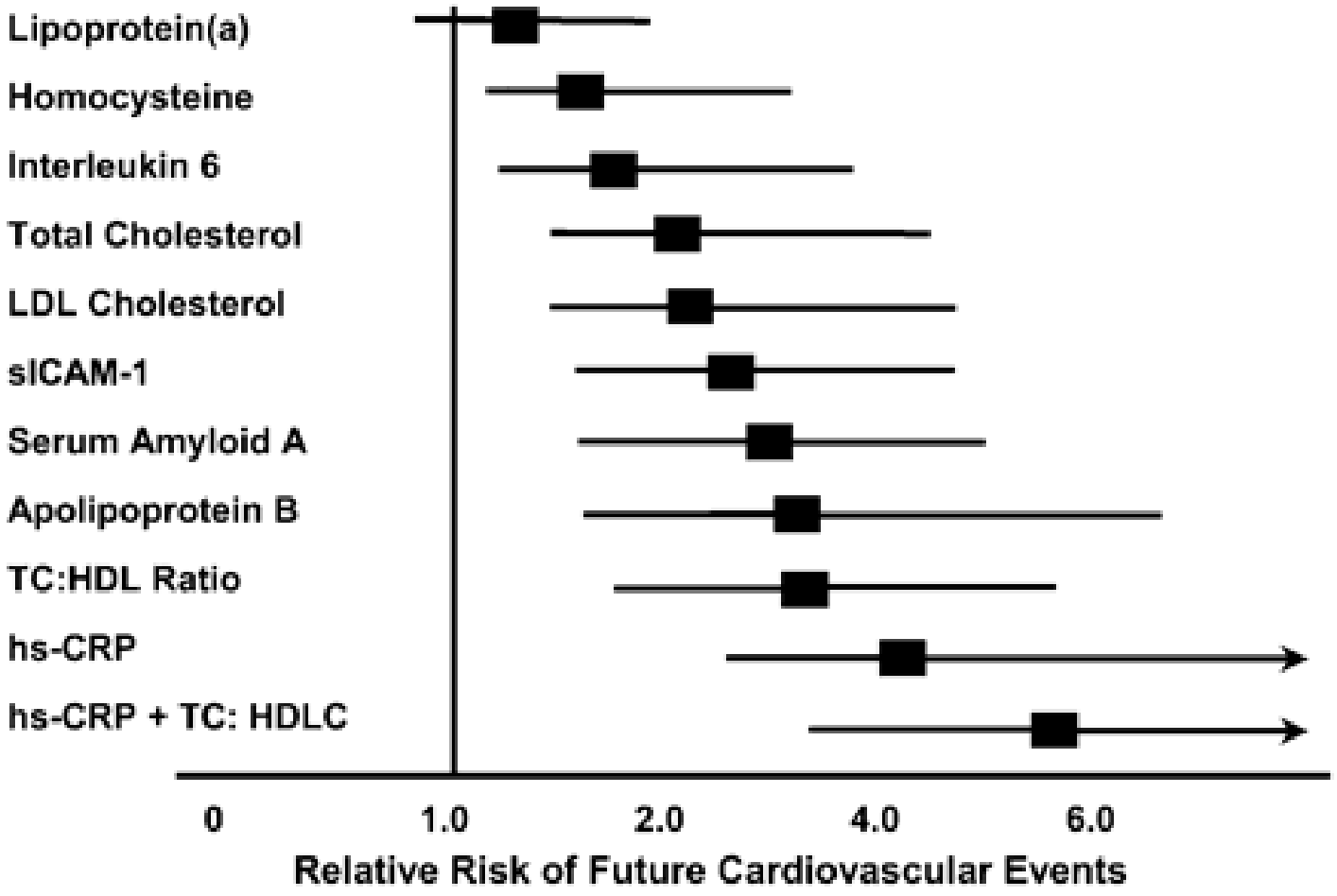
Clinical Chemistry 55:2
209–215 (2009)

hs-CRP

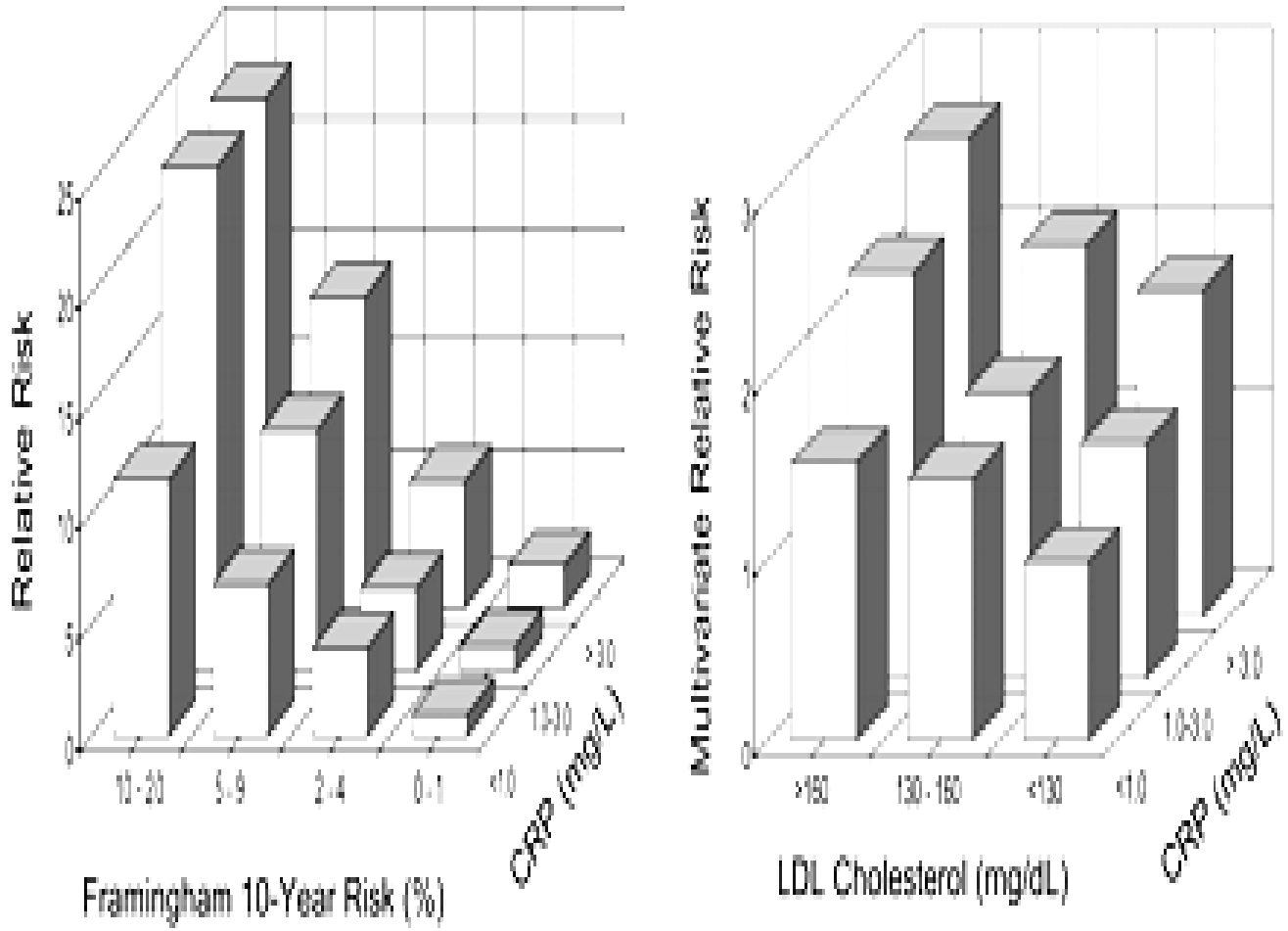
- Relative stable over time
- Relative chemical stable
- Long half life
- No diurnal change

(J Am Coll Cardiol 2009;54:2129–38)

Hs CRP is an Independent Risk Indicator

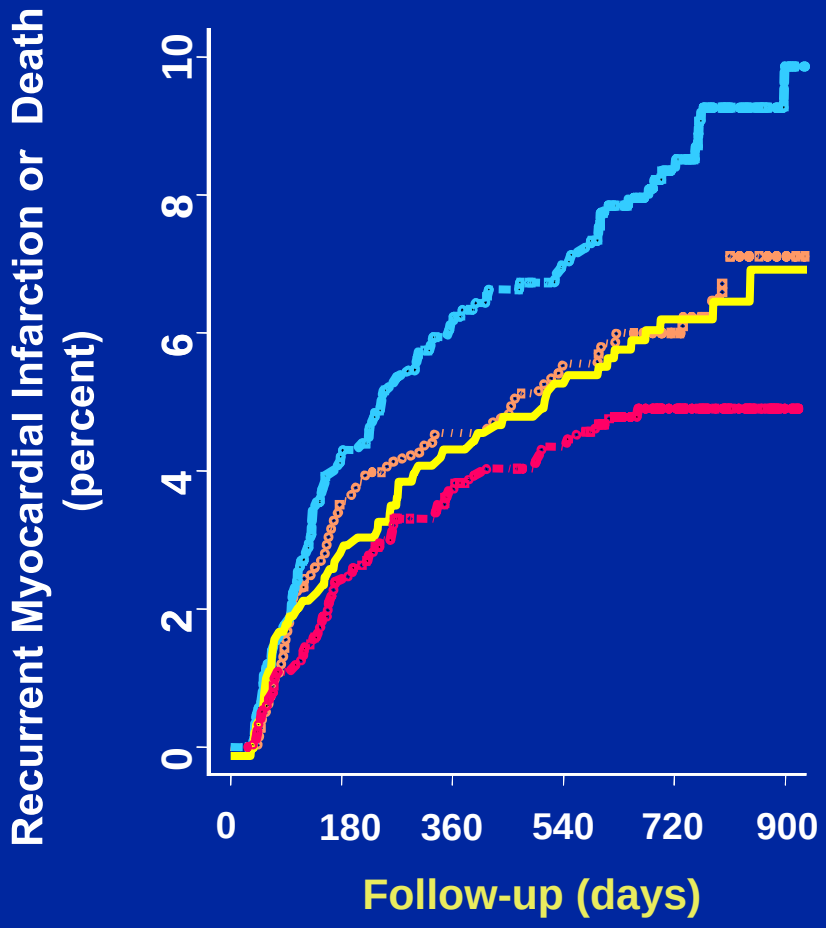


Hs-CRP Further Classify Risk Group in Addition to Other Risk Factors

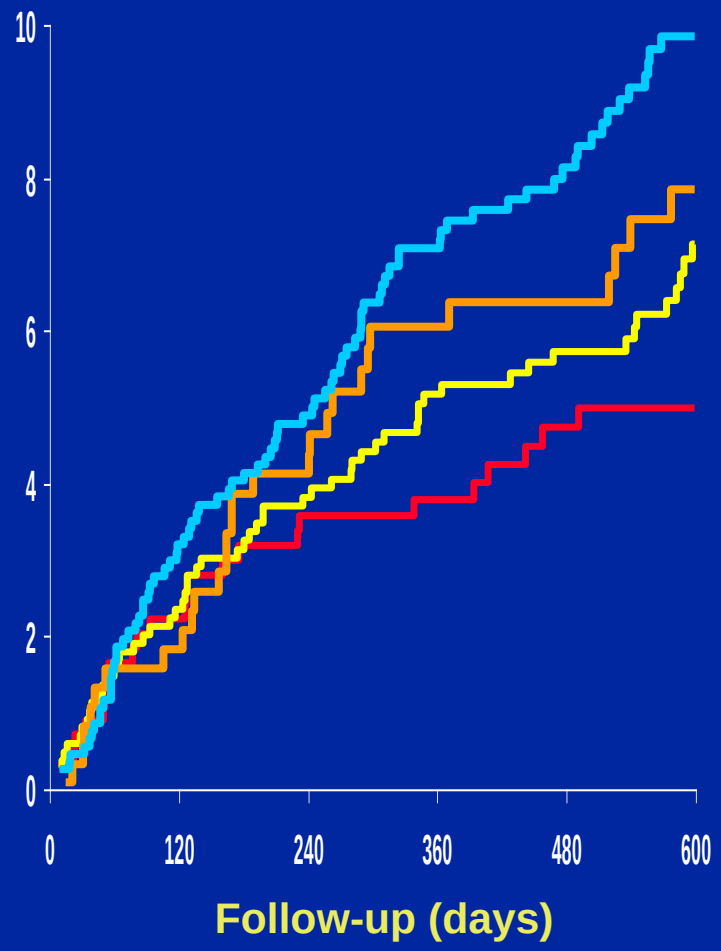


Clinical Relevance of Achieving LDL-C < 70 mg/dL and hsCRP < 2 mg/L Following Initiation of Statin Therapy

LDL>70, hsCRP>2 LDL<70, hsCRP>2 LDL>70, hsCRP<2 LDL<70, hsCRP<2



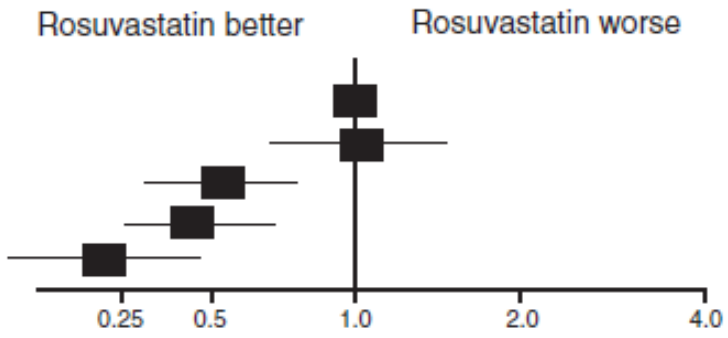
PROVE IT – TIMI 22
NEJM 2005;352:20-28.



A to Z
Circulation 2006;114:281-8

Hs-CRP Reduction Further Reduce the Clinical Events

	N	Rate
Placebo	7832	1.11
LDL≥70mg/dL,hsCRP≥2 mg/L	1384	1.11
LDL<70mg/dL,hsCRP≥2 mg/L	2921	0.62
LDL≥70mg/dL,hsCRP<2 mg/L	726	0.54
LDL<70mg/dL,hsCRP<2 mg/L	2685	0.38



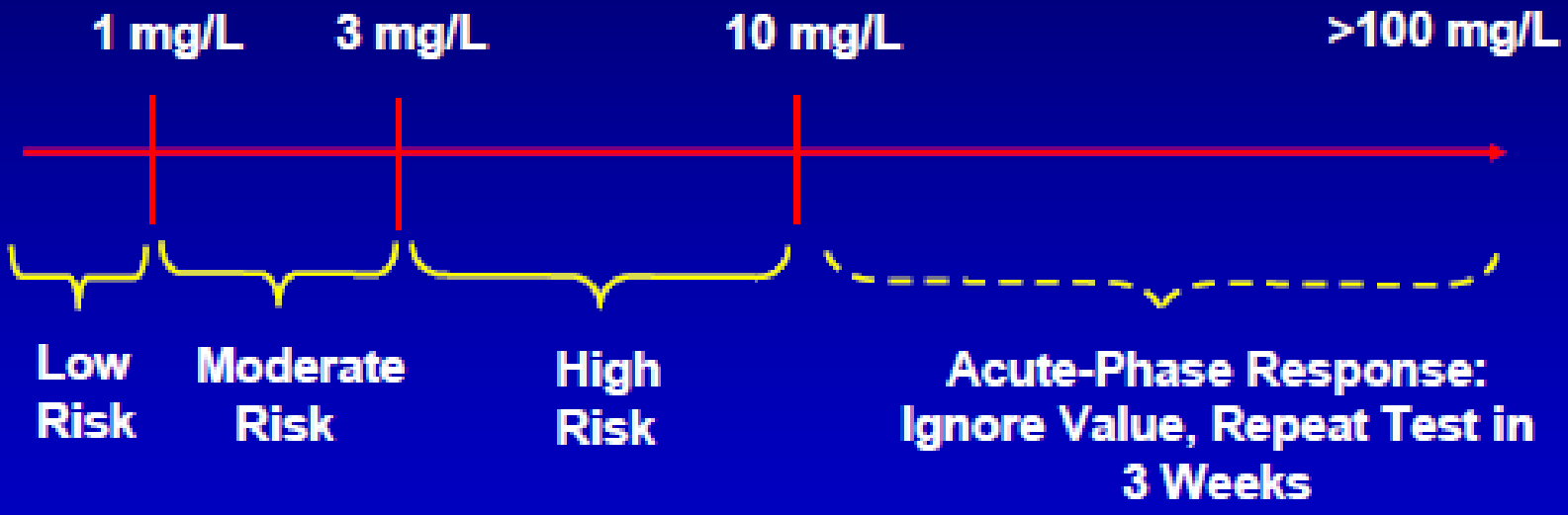
JUPITER
LDL reduction, hsCRP reduction, or both?

Minimal Correlation between change in LDL and change in hsCRP

	r value
Achieved LDLC, Achieved hsCRP	0.10
Percent change in LDLC, Percent change in hsCRP	0.15

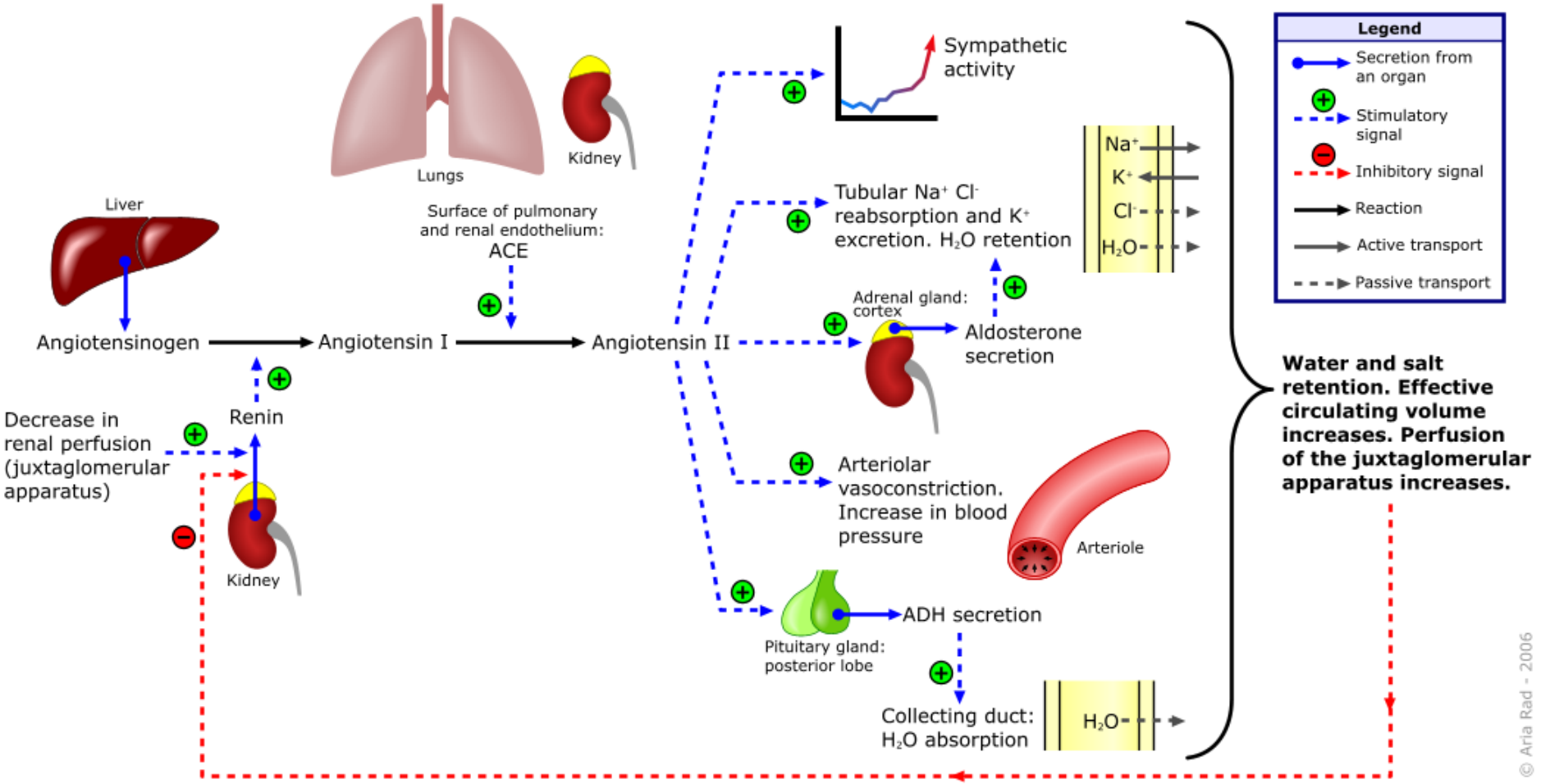
Less than 2 percent of the variance in achieved hsCRP was explained by the variance in achieved LDLC

Clinical Application of hs-CRP for Cardiovascular Risk Prediction



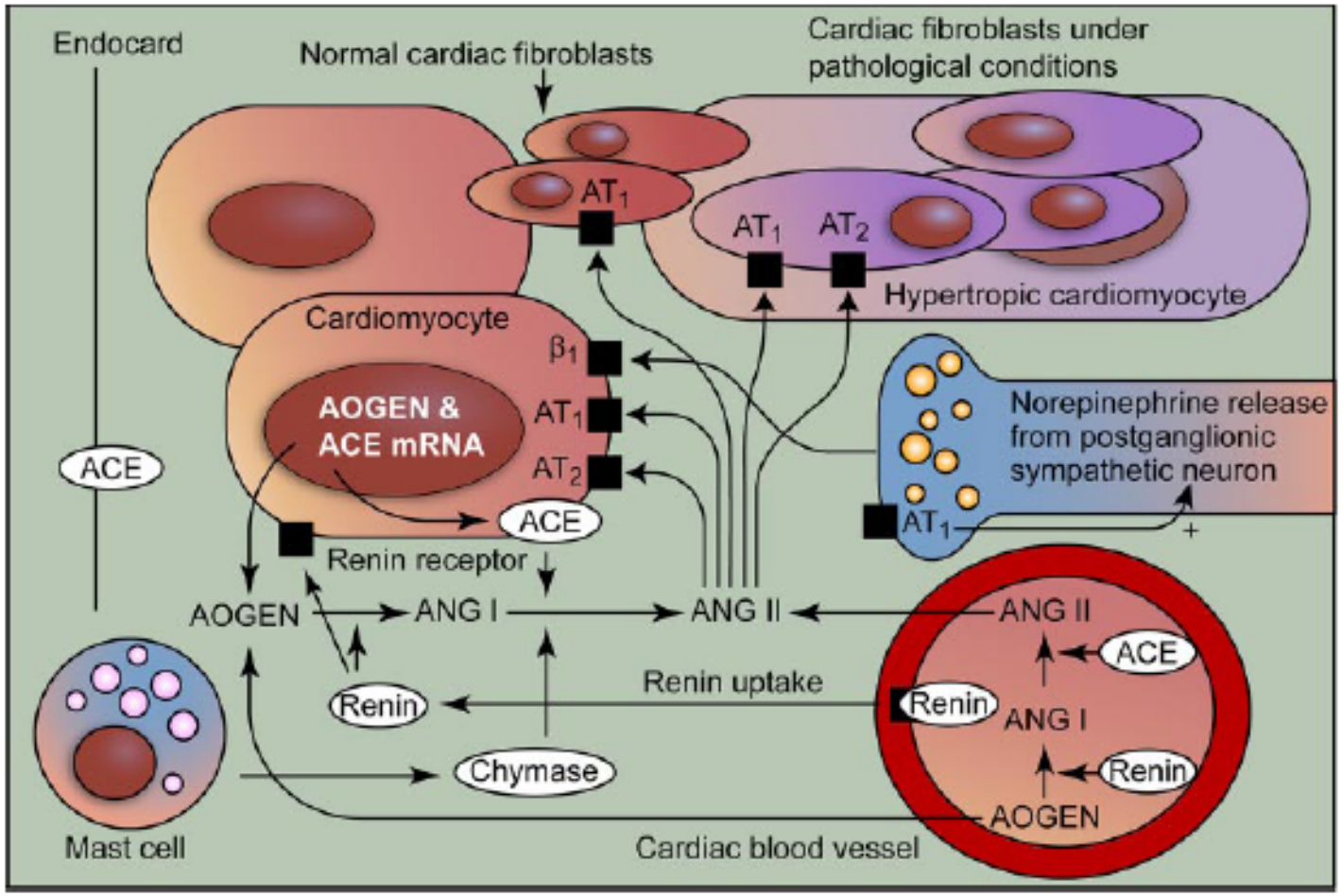
AHA/CDC Statement. *Circulation* 2003; 107:499–511

Renin-angiotensin-aldosterone system

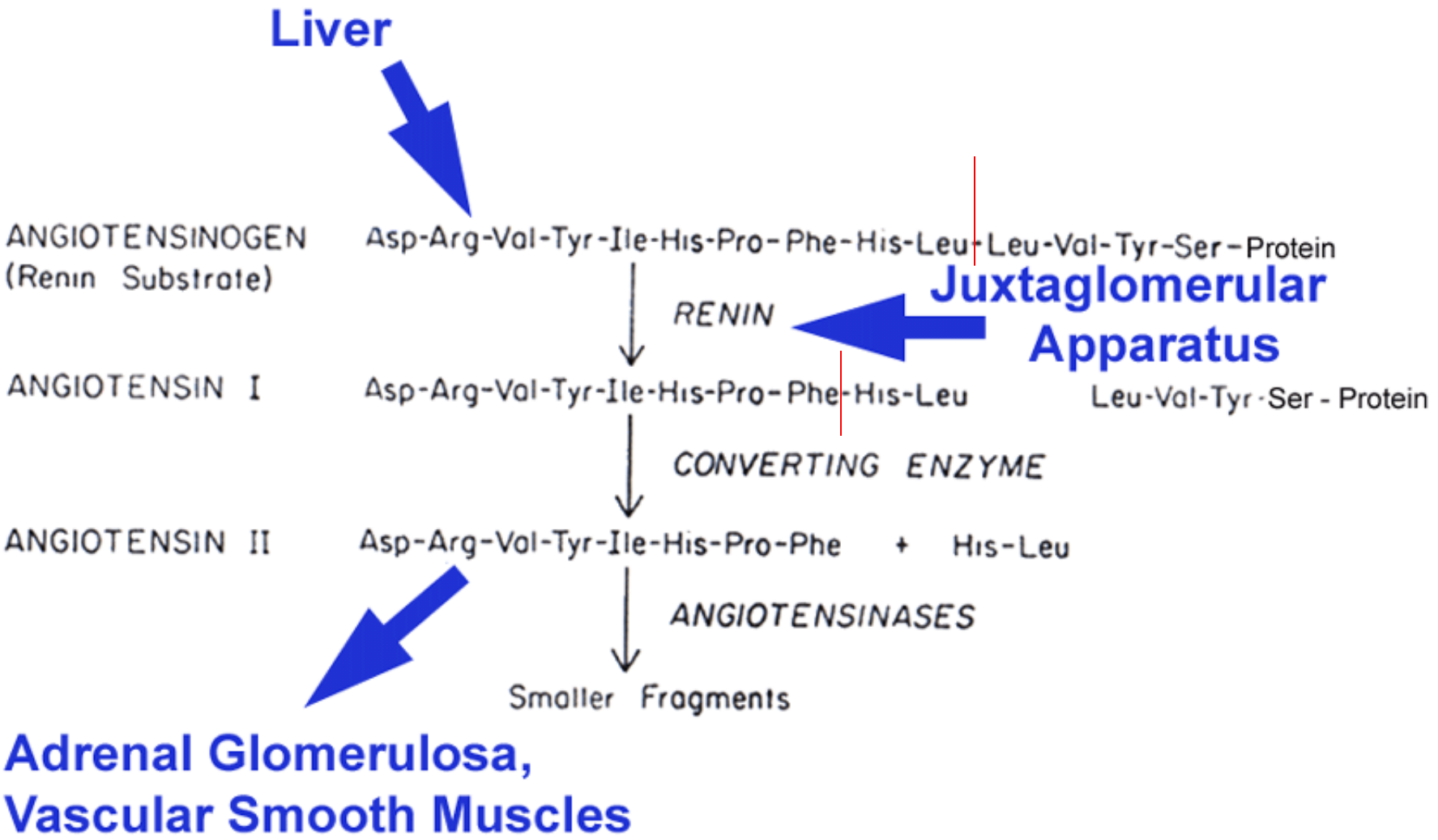


In heart, Ang II is mainly converted by chymase(Circ Res 80: 219–227, 1997.)

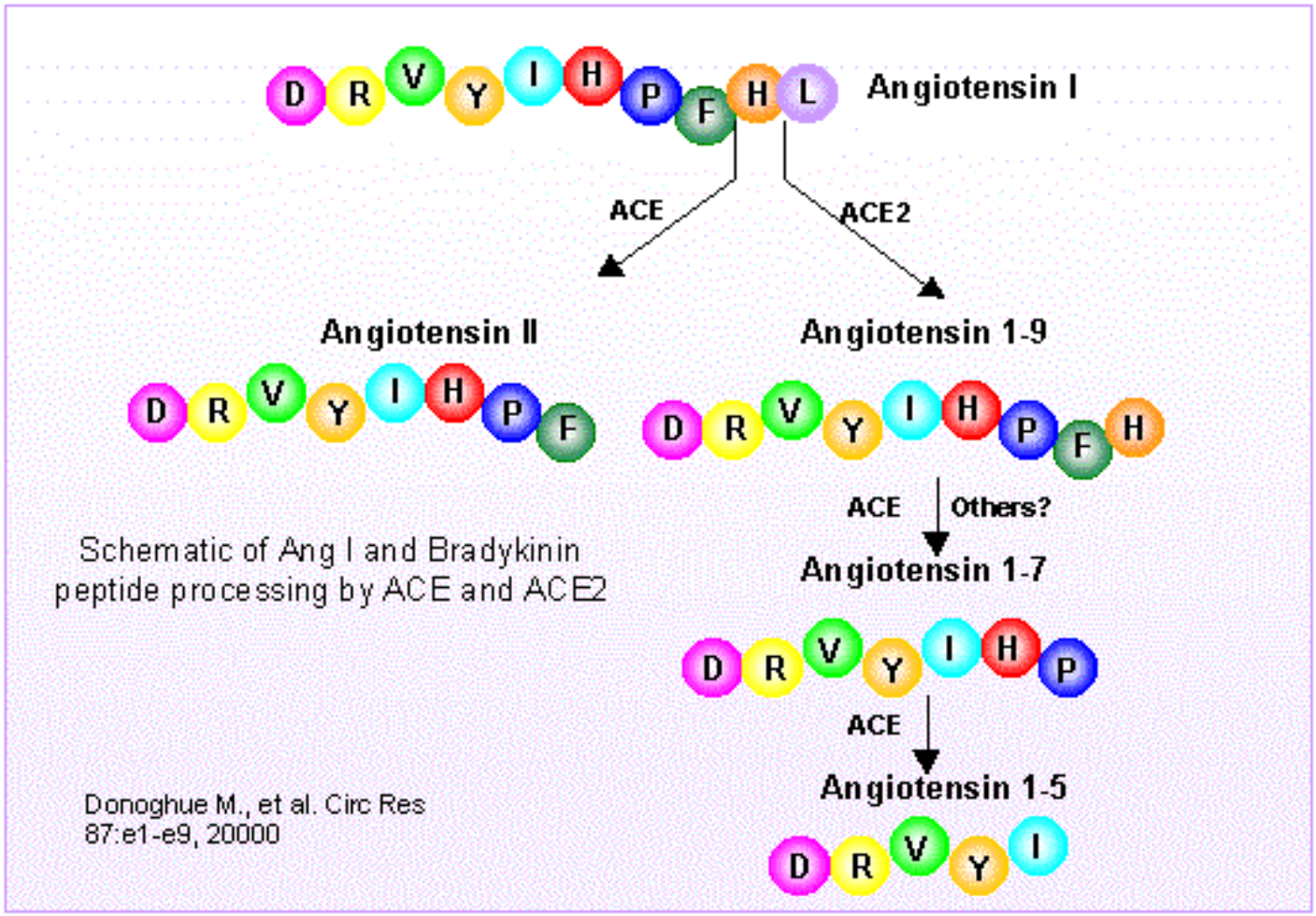
The Renin-Angiotensin System in the Heart



Angiotensin Metabolism

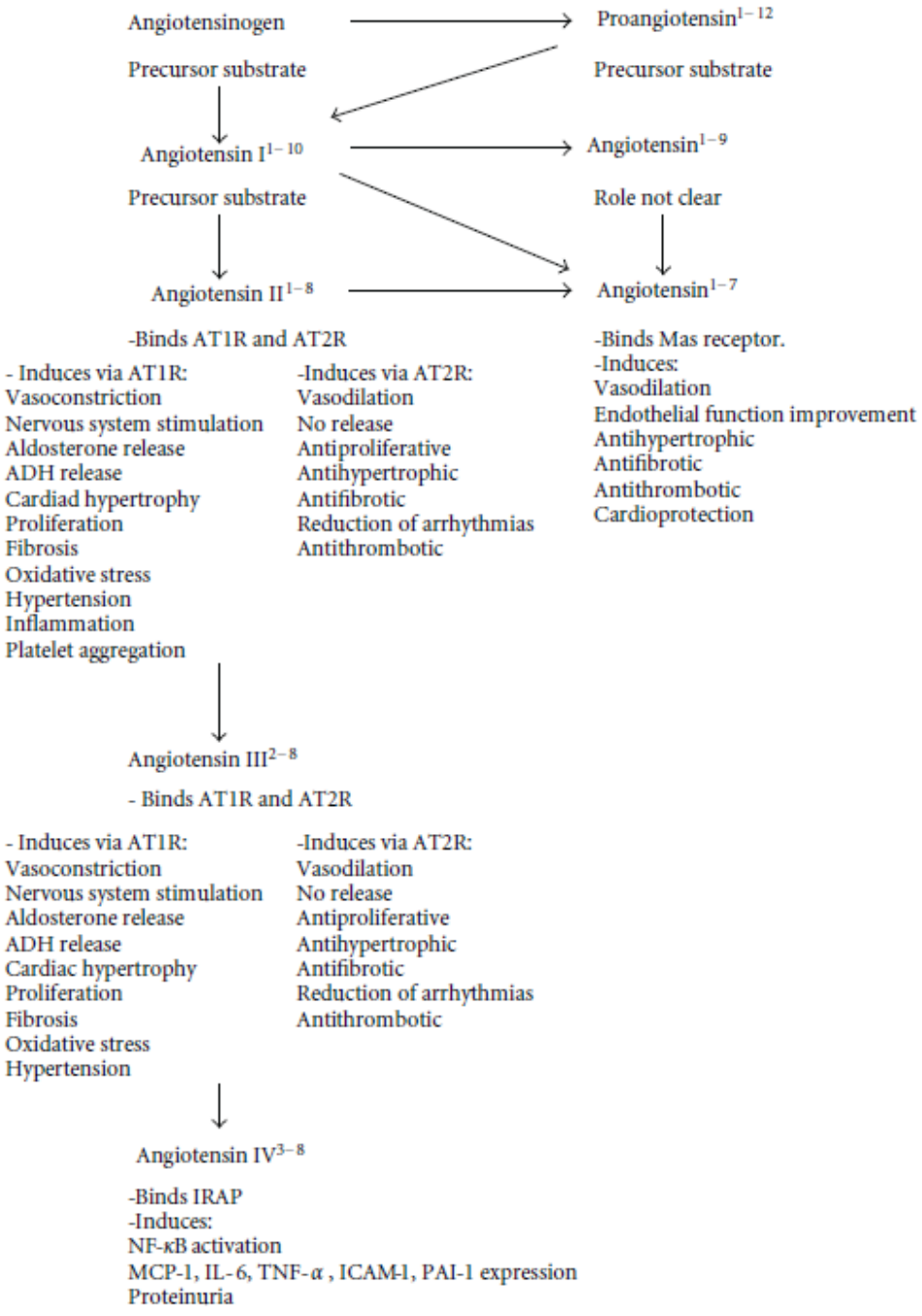


ACE and ACE 2


D R V Y I H P F H L
Angiotensin I
ACE
ACE2
Angiotensin II
D R V Y I H P F
Angiotensin 1-9
D R V Y I H P F H
ACE
Others?
Angiotensin 1-7
D R V Y I H P
ACE
Angiotensin 1-5
D R V Y I
Schematic of Ang I and Bradykinin peptide processing by ACE and ACE2
Donoghue M., et al. Circ Res 87:e1-e9, 20000

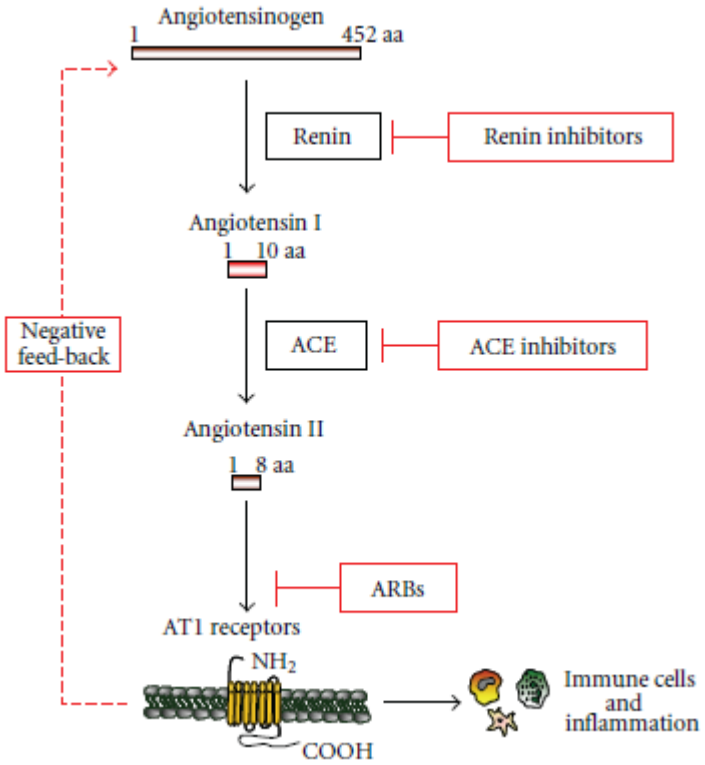
Angiotensin II Receptors

- The **angiotensin receptors** belong to the seven-membrane super family of G protein-coupled receptors with angiotensins as ligand.
- Angiotensin II interacts with 2 pharmacologically distinct subtypes of cell surface receptors, types 1 and 2 .
- Type 1 receptors seem to mediate the major cardiovascular effects of angiotensin II .
- Ang II also binds to AT2 receptors, inducing a counter-regulatory vasodilatation that is largely mediated by bradykinin and NO.



Mediators of Inflammation
Volume 2009, Article ID 752406, 13 pages

Inflammation Effect of Renin Angiotensin System



Angiotensin II could up-regulate

(1) adhesion molecules

(2) cytokines

(3)complement system

(4) growth factors

Recruited inflammatory cell could produce Ang II.

Table 1: Clinical studies evaluating effects of RAS blockade on circulating inflammatory markers. When two active drugs are administered, the effects demonstrated are with respect to basal values; when an active deug and placebo are used, the comparisons are between the two arms. CABG: coronary artery bypass grafting; ACEI: ACE inhibitors.

Studies	Patients	Clinical conditions	Drugs	Main effects	
Sheth et al. [93]	107	Chronic heart failure	Lisinopril versus Omapatrilat	↑ IL-10 (Omapatrilat) = IL-6	
Jilma et al. [94]	32	Essential hypertension	Enalapril versus Losartan	↓ E-selectin ↓ ICAM-1 ↓ VCAM-1 ↓ MCP-1	Enalapril
Koh et al. [95]	45	Essential hypertension	Candesartan versus Placebo	↓ MCP-1 ↓ TNF-α = CRP	
Di Napoli and Papa [96]	507	Ischemic stroke	ACEI versus Other hypotensive drugs	↓ CRP (ACEI)	
Tsikouris et al. [97]	30	Acute myocardial infarction	Quinapril versus Enalapril	↓ CRP (Quinapril)	
Schieffer et al. [98]	48	Coronary artery disease Essential hypertension	Enalapril versus Irbesartan	↑ IL-10 ↓ MMP-9 ↓ IL-6 ↓ CRP	Both Irbesartan
Fliser et al. [99]	199	Essential hypertension and/or Vascular disease Diabetes mellitus LDL-C > 150 mg/dL	Olmesartan versus Placebo	↓ CRP ↓ TNF-α ↓ IL-6 ↓ MCP-1	
Trevelyan et al. [100]	45	Angina pectoris awaiting CABG	Enalapril or Losartan versus Control	↓ IL-1ra ↓ IL-6 = IL-10 = IL-8 n.d.	
Tikiz et al. [101]	45	Rheumatoid arthritis	Quinapril versus Placebo	= CRP = TNF-α = IL-1β = IL-6	
Krysiak and Okopień [102]	90	Coronary artery disease	Perindopril or Enalapril versus Placebo	↓ MCP-1 ↑ IL-10 ↓ CRP	Both (Perindopril)

Comparison of Low-Dose Versus High-Dose Losartan Treatment on Morbidity and Mortality in Angiotensin-Converting-Enzyme-Inhibitor-Intolerant Patients with Heart Failure and Reduced Left Ventricular Ejection Fraction: Results of the HEAAL* Study

Marvin A. Konstam, James D. Neaton, Kenneth Dickstein, Helmut Drexler, Michel Komajda, Felipe A. Martinez, Gunter A.J. Riegger, Ronald D. Smith, William Malbecq, Soneil Guptha, Philip A. Poole-Wilson for the HEAAL investigators

* Heart failure Endpoint evaluation with the Angiotensin II Antagonist Losartan

Lancet 2009; **374:** 1840–48

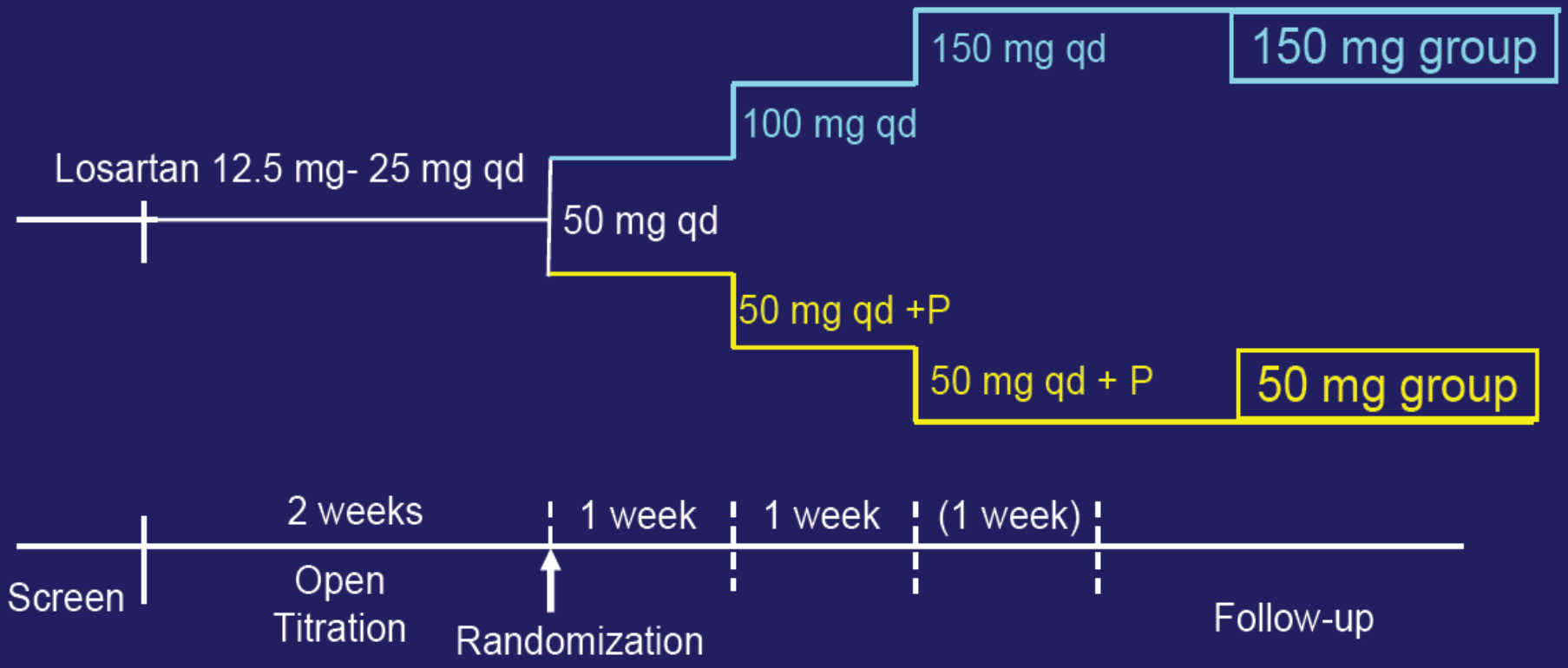
Inclusion Criteria

- Inclusion
  - NYHA II-IV Heart Failure
  - LVEF ≤40%
  - Intolerance to ACEI

- Exclusion
  - Known intolerance to ARBs
  - Systolic BP < 90 mm Hg
  - Myocarditis, pericarditis, or stenotic valvular disease
  - MI, unstable angina, PTCA, or CABG within prior 12 wks
  - CVA or TIA within prior 12 weeks

Konstam MA et al, Lancet 2009; **374:** 1840–48

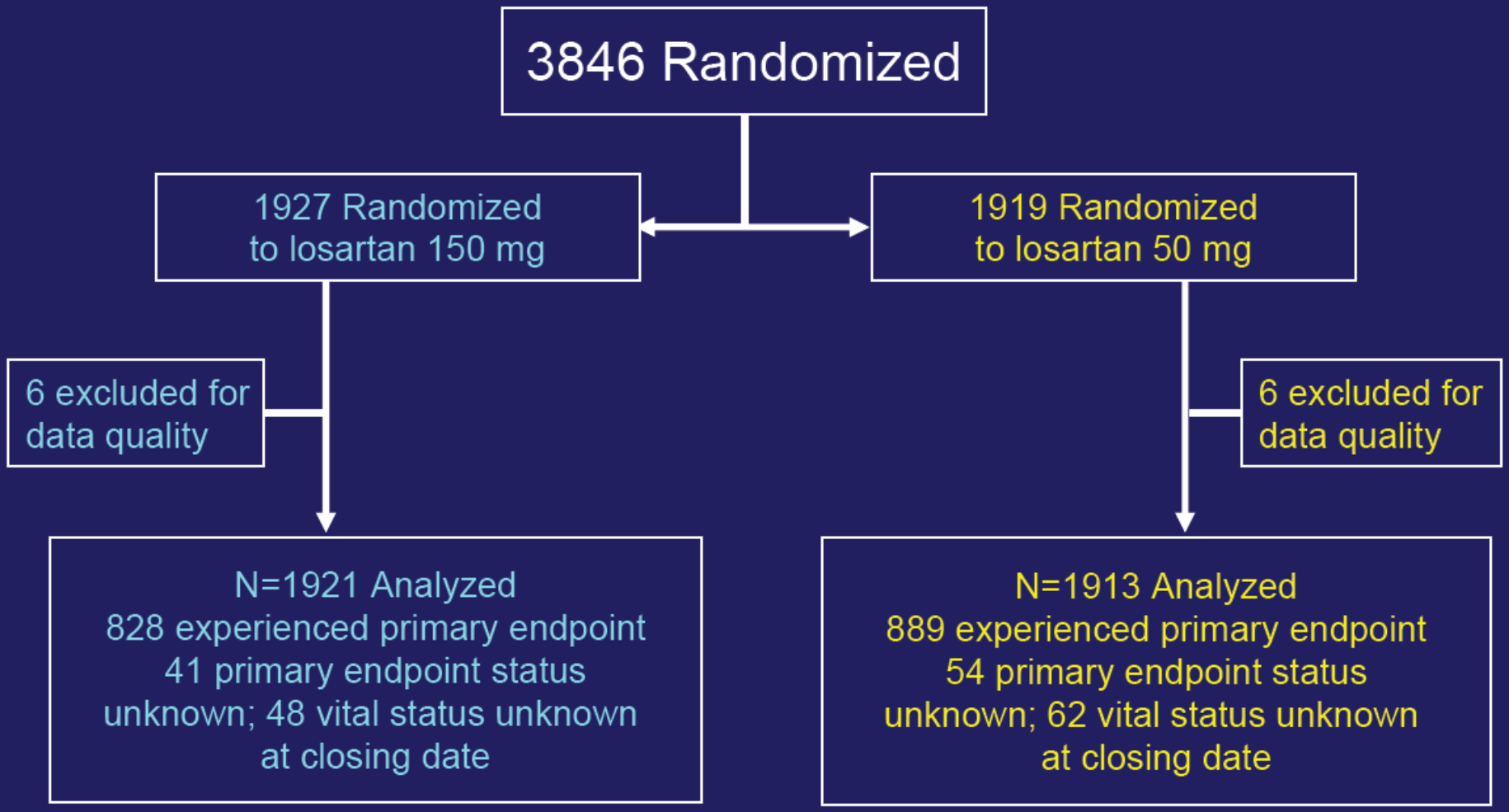
Study Design and Sample Size



- Primary endpoint: death or hospitalization for HF
- 1710 patients with primary endpoint events provided 95% power for HR = 0.837 for superiority with 2-sided α = 0.043

Konstam MA et al, Lancet 2009; **374:** 1840–48

Disposition of Patients



Konstam MA et al, Lancet 2009; **374:** 1840–48

HEAAL

Patient Follow-up and Dosing

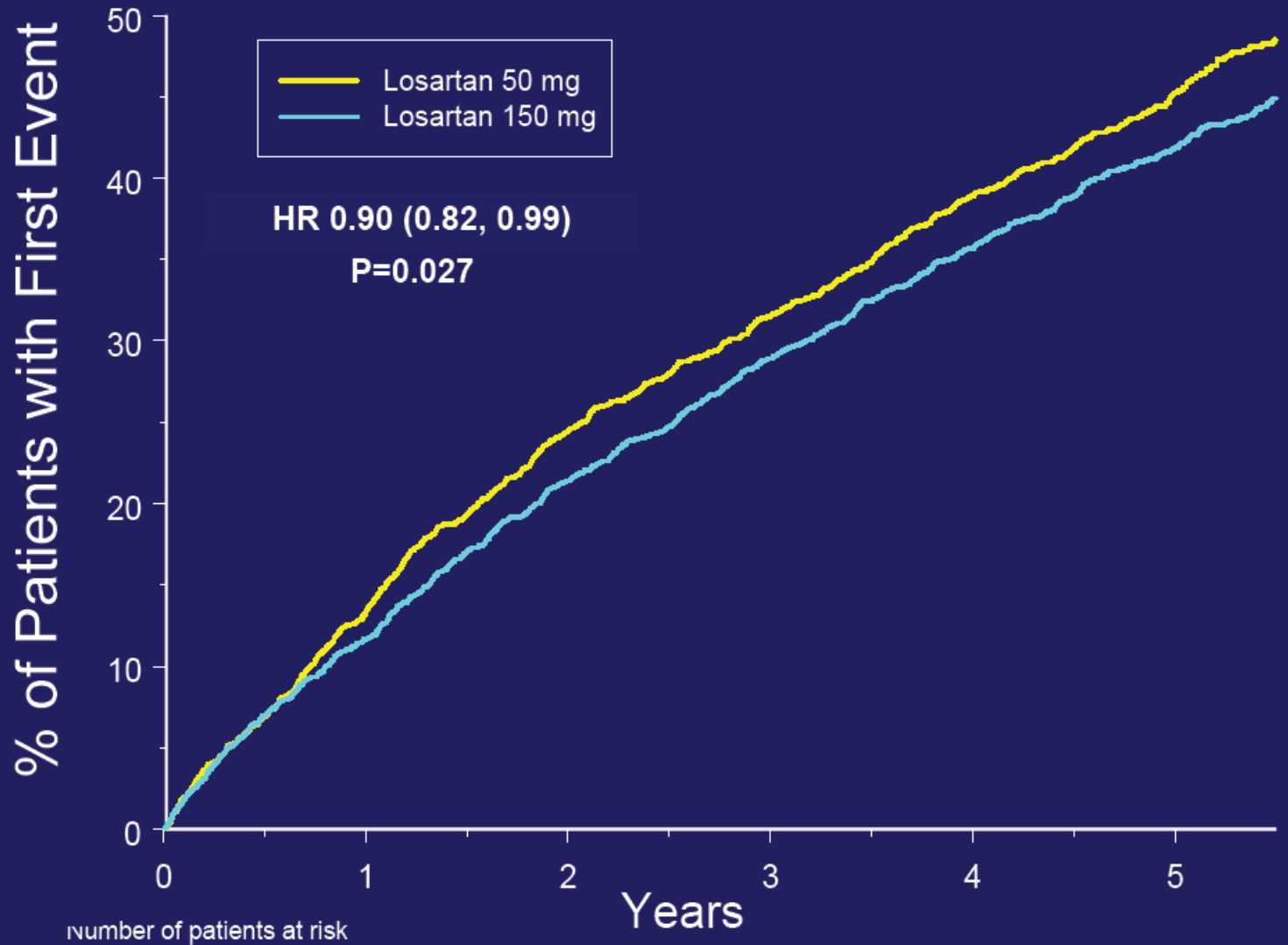
	Losartan 150 mg	Losartan 50 mg
Median follow-up time (yrs)*	4.7	4.7
Discontinuations (%)	28.3	27.3
Discontinuations for AE (%)	7.7	7.0
Mean dose (mg/day)**	128.9	45.6

*Follow up = time from randomization to study end or primary endpoint

**Including time off drug

Konstam MA et al, Lancet 2009; **374:** 1840–48

Primary Endpoint
Death or Hospitalization for HF



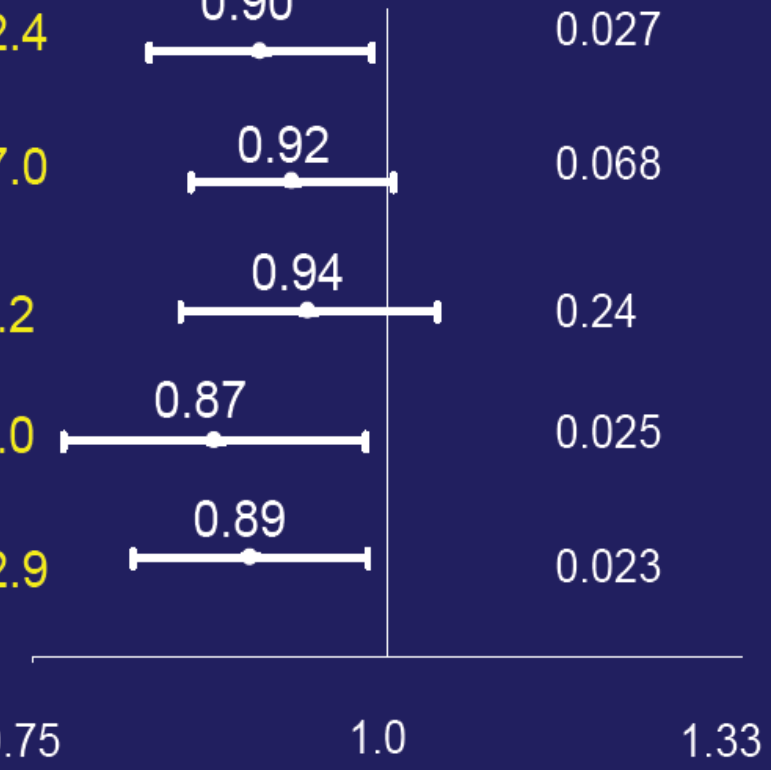
Number of patients at risk

Losartan 50 mg	1646	1422	1277	1126	644
Losartan 150 mg	1684	1493	1344	1205	711

Konstam MA et al, Lancet 2009; **374:** 1840–48

Primary and Major Secondary Endpoints and Components

	Losartan 150mg		Losartan 50mg		Hazard Ratio (95%CI)	P-value
	No.	Rate*	No.	Rate*		
Death or HF hospitalization	828	11.1	889	12.4	0.90	0.027
Death or CV hospitalization	1037	15.6	1085	17.0	0.92	0.068
Death	635	7.6	665	8.2	0.94	0.24
HF hospitalization	450	6.0	503	7.0	0.87	0.025
CV hospitalization	762	11.5	826	12.9	0.89	0.023



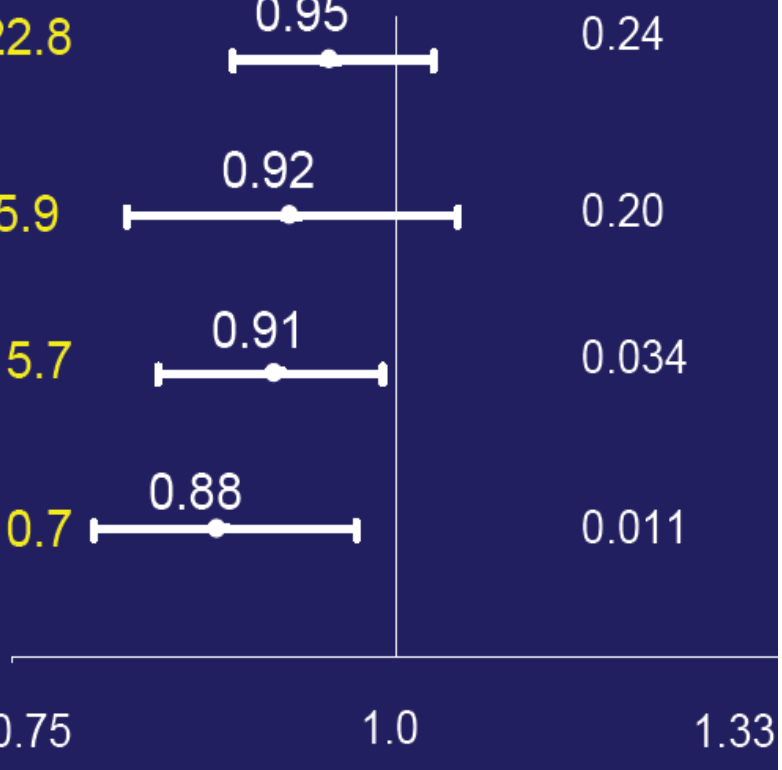
*Rate per 100 person years

Konstam MA et al, Lancet 2009; **374:** 1840–48

HEAAL

Other Outcomes

	Losartan 150mg		Losartan 50mg		Hazard Ratio (95%CI)	P-value
	No.	Rate*	No.	Rate*		
Death or all cause hospitalization	1237	21.6	1269	22.8	0.95	0.24
CV death	448	5.4	478	5.9	0.92	0.20
CV death or CV hospitalization	942	14.2	1003	15.7	0.91	0.034
CV death or HF hospitalization	698	9.3	771	10.7	0.88	0.011

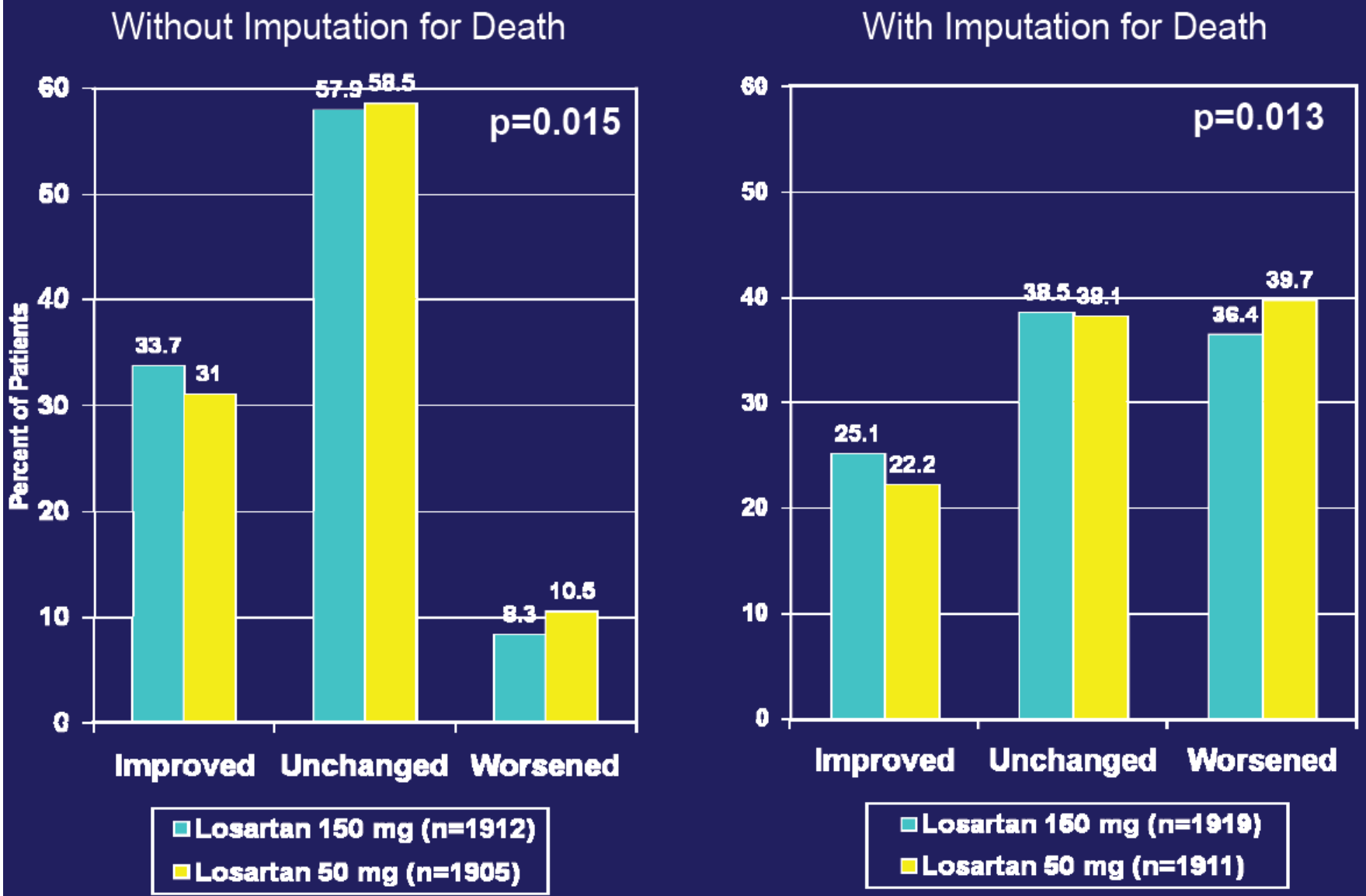


*Rate per 100 person years

Konstam MA et al, Lancet 2009; **374:** 1840–48

Change in NYHA Class*

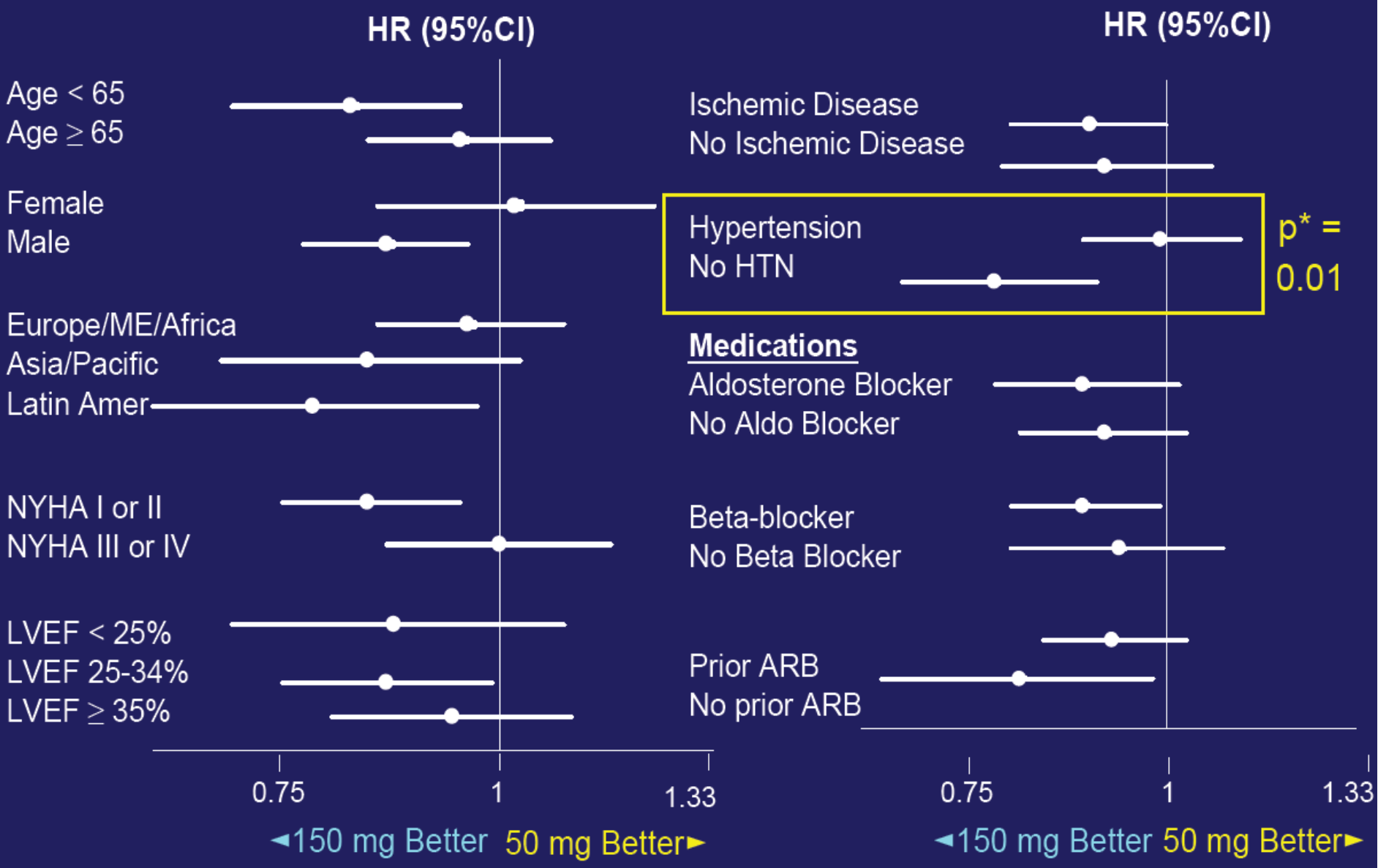
Percent of Patients



*From baseline to last available data

Konstam MA et al, Lancet 2009; **374:** 1840–48

Primary Endpoint: Selected Subgroups

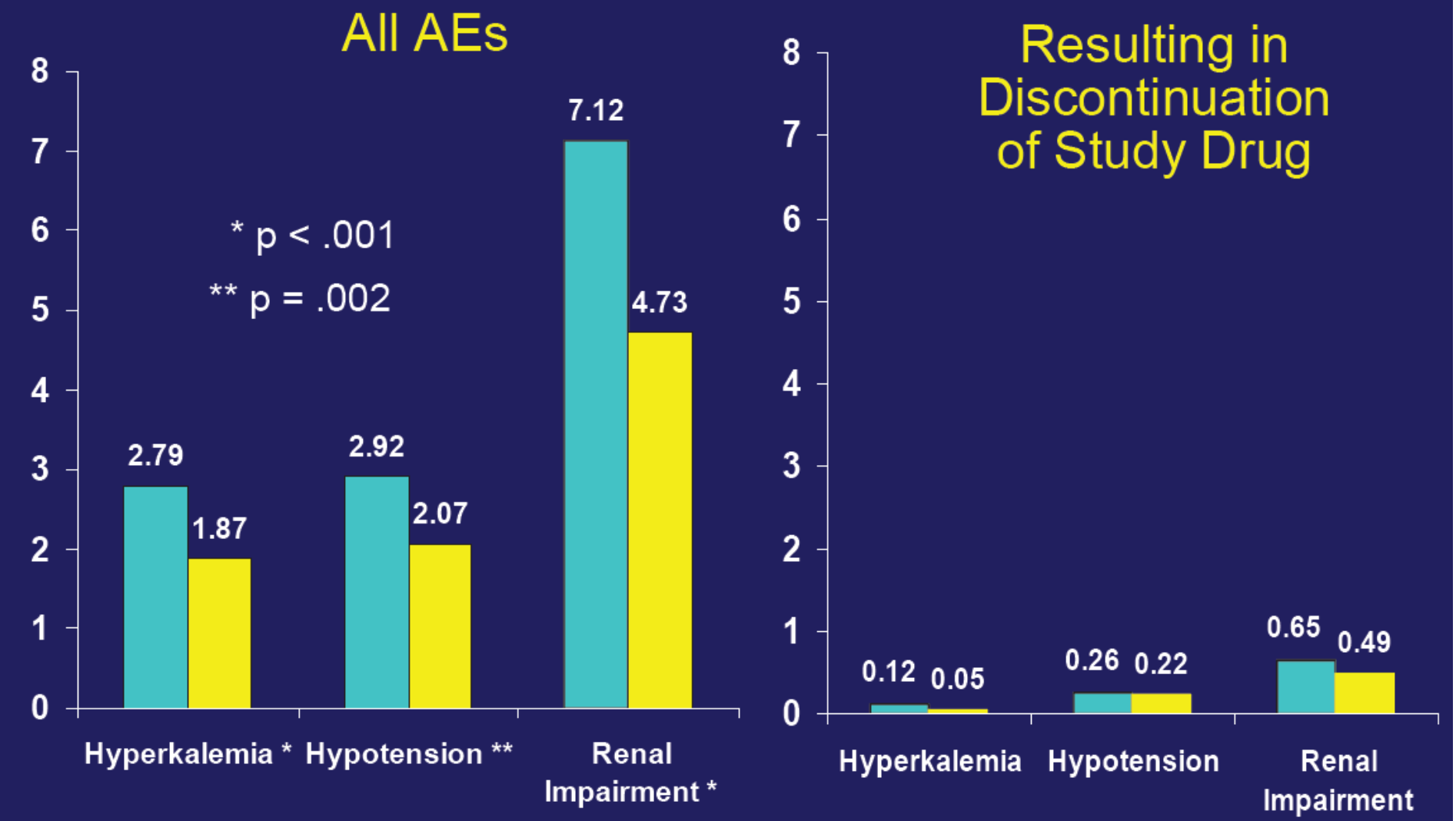


Konstam MA et al. Lancet 2009; **374:** 1840–48

* p for interaction

Selected Adverse Events

Rate / 100 person-years



Konstam MA et al, Lancet 2009; **374:** 1840–48

ELITE Study

(Evaluation of Losartan in the Elderly Study)

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

Authors: Pitt B, Segal R, Martinez F, Meurers G, Cowley A, Thomas I, Deedwania P, et al.
Source: Lancet. 349:747-52. March 15, 1997.

ELITE Study

Subjects

- Patients 65 years or older, with an ejection fraction less than 40% and NYHA class II, III or IV congestive heart failure. Patients were recruited at 125 centers in the Americas, Europe and South Africa.
- Multiple exclusion criteria. Primarily:
  - Prior treatment with an ACE inhibitor or losartan.
  - Chronic cough or history of angio-edema.
  - Recent unstable cardiac condition (mainly ischemic).
  - Significant valvular or arrhythmic heart disease.
  - Systolic BP under 90 mmHg or uncontrolled hypertension.
  - Significant other medical conditions (renal or hepatic failure, uncontrolled diabetes, anemia).

Lancet. 349:747-52. March 15, 1997.

ELITE Study

Intervention

- Patients were randomized to 48 weeks of therapy with either captopril or losartan.
- Captopril was started at 6.25 mg three times daily, titrated up to 50 mg three times daily. Losartan was started at 12.5 mg, titrated up to 50 mg daily.
- Patients were assessed weekly during the titration phase, then every 3 months.

Lancet. 349:747-52. March 15, 1997.

Results

Primary endpoint

- There was *no significant difference* in the incidence of the primary endpoint (persistent increase in serum creatinine), which was 10.5% in each group. However, because of the lower than expected event rate in the captopril group, the study was underpowered to look at this issue.
- Effect on mortality and CHF
  - *Total mortality was 4.8% in the losartan group*, vs. 8.7% in the captopril group (p=0.035).
  - Taking into account age stratification, the risk reduction was 0.46 (95% CI 0.05-0.69). This reduction was seen in all subgroups, except among women.
  - *Hospital admissions for CHF* were 5.7% in both groups. *Improvement in NYHA functional class* was similar in the two groups; the number of patients in class I or II increased from 66% to 80% in the losartan group, and from 64% to 81% in the captopril group.

Lancet. 349:747-52. March 15, 1997.

Drug discontinuations

- *There were 111 discontinuations of the study drug in the captopril group, vs. 65 in the losartan group*.
- Reasons for discontinuation included classic ACEI side-effects (cough, hyperkalemia, perturbance of taste, rash and angio-edema), which occurred in 33 captopril patients vs. 2 losartan patients. Other reasons for discontinuation were fairly evenly distributed between the two groups. Of note, death was listed as a reason for discontinuation in 5 patients in the captopril group, vs. 1 patient in the losartan group (see comments below).

Lancet. 349:747-52. March 15, 1997.

ELITE - II

Study Design

≥ 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
Baseline Characteristics

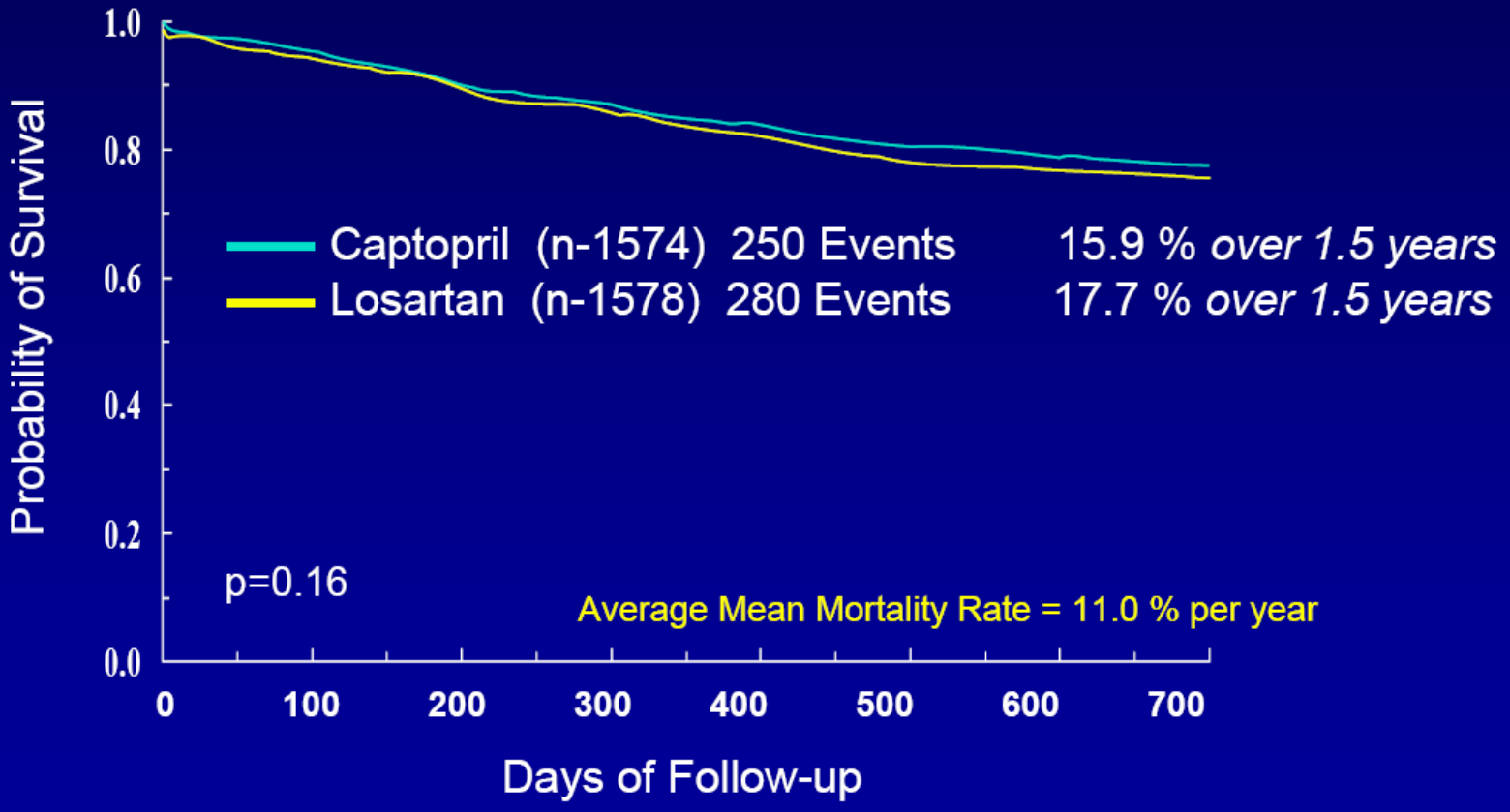
	Losartan *n = 1578*	Captopril *n = 1574*
Age (mean, yrs.)	71.4	71.5
Gender (male / female %)	70 / 30	69 / 31
Ejection Fraction (mean %)	31	31
NYHA Functional Class II / III / IV (%)	49 / 45 / 6	49 / 45 / 6
Ischemic History (%)	80	79
Prior ACE – I (%)	23	24
Beta Blocker (%) → *Limited to 25% by design but not reached*	24	23
Diuretic (%)	77	78
Cardiac Glycoside (%)	49	50
Aspirin / Salicylates (%)	59	59

P = NS losartan vs captopril

Lancet 2000; 355:1582-87

ELITE II

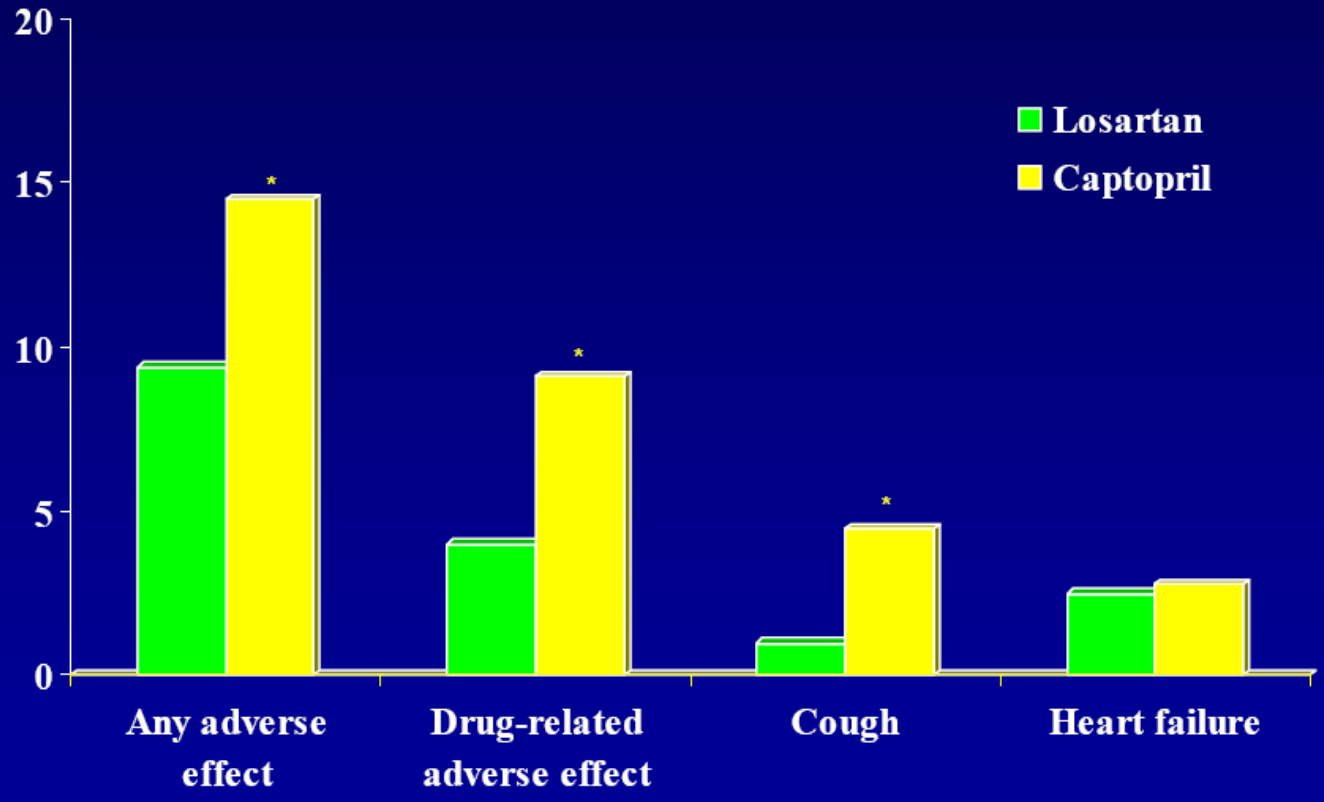
- Primary Endpoint: All-Cause Mortality -



Lancet 2000; 355:1582-87

ELITE II

Withdrawal for Adverse Experience (Excluding Death)



* p = 0.001 between groups
Patients who died were excluded from any adverse effect and drug-related adverse effects.

Lancet 2000; 355:1582-87

ELITE II
Study Endpoint Summary

	Losartan *n = 1578* number (%)	Captopril *n = 1574* number (%)	Hazards Ratio (95% CI)*	P Value
All-cause mortality (primary endpoint)	280 (17.7)	250 (15.9)	1.13 (0.95-1.35)	P = 0.16 NS
Sudden death or/ resuscitated cardiac arrest	142 (9.0)	115 (7.3)	1.25 (0.98, 1.60)	P = 0.08 NS
Combined total mortality or hospitalizations for any reason	752 (47.7)	707 (44.9)	1.07 (0.97, 1.19)	P = 0.18 NS
Withdrawal for Adverse Experiences	149 (9.4)	228 (14.5)		P = < 0.001

Lancet 2000; 355:1582-87

Summary

- HEAAL represents the first study to investigate the dose-response of an ARB on clinical outcomes in patients with HF.
- Compared with losartan 50 mg daily, losartan 150 mg daily reduced the rate of the combined endpoint of all-cause mortality or HF hospitalization
- The 150 mg dose was associated with higher rates of hypotension, hyperkalemia, and renal impairment, although the overall rates of clinically relevant adverse events were small.

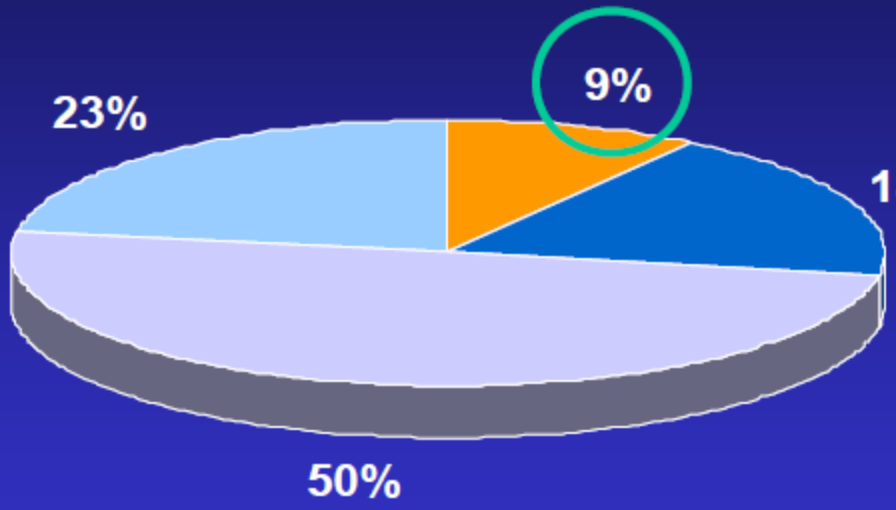
Conclusions

- In patients with HF, reduced LVEF, and ACE inhibitor intolerance, incremental value is derived from up-titrating ARB doses to levels demonstrated to confer benefit on clinical outcomes.
- Our findings confirm the view that incremental inhibition of the renin-angiotensin system, within the range explored in HF trials to date, achieves a progressively favorable impact on clinical outcomes.

LIFE: Distribution of Therapy fo the Two Treatment Groups *

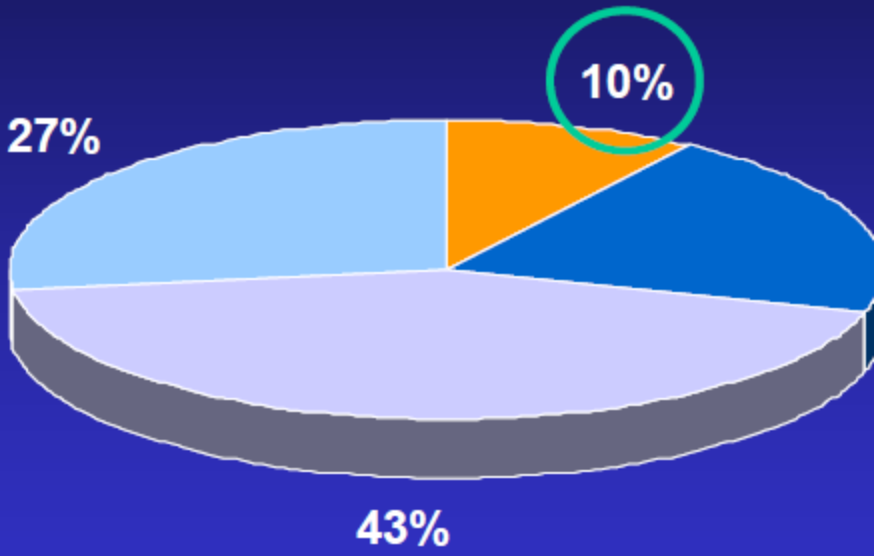
Losartan

Mean dosage mg 82



Atenolol

Mean dosage mg 79



- 50 mg only
- 50 mg plus additional therapy including HCTZ
- 100 mg with or without additional therapy including HCTZ
- Off study therapy

* At endpoint or end of follow

B Dahlof et al. Lancet 2002;359:995-1003