بسم الله الرحمن الرحيم

Recent Concepts in ARBs

By

Essam Mahfouz,MD

Professor of Cardiology Mansoura university

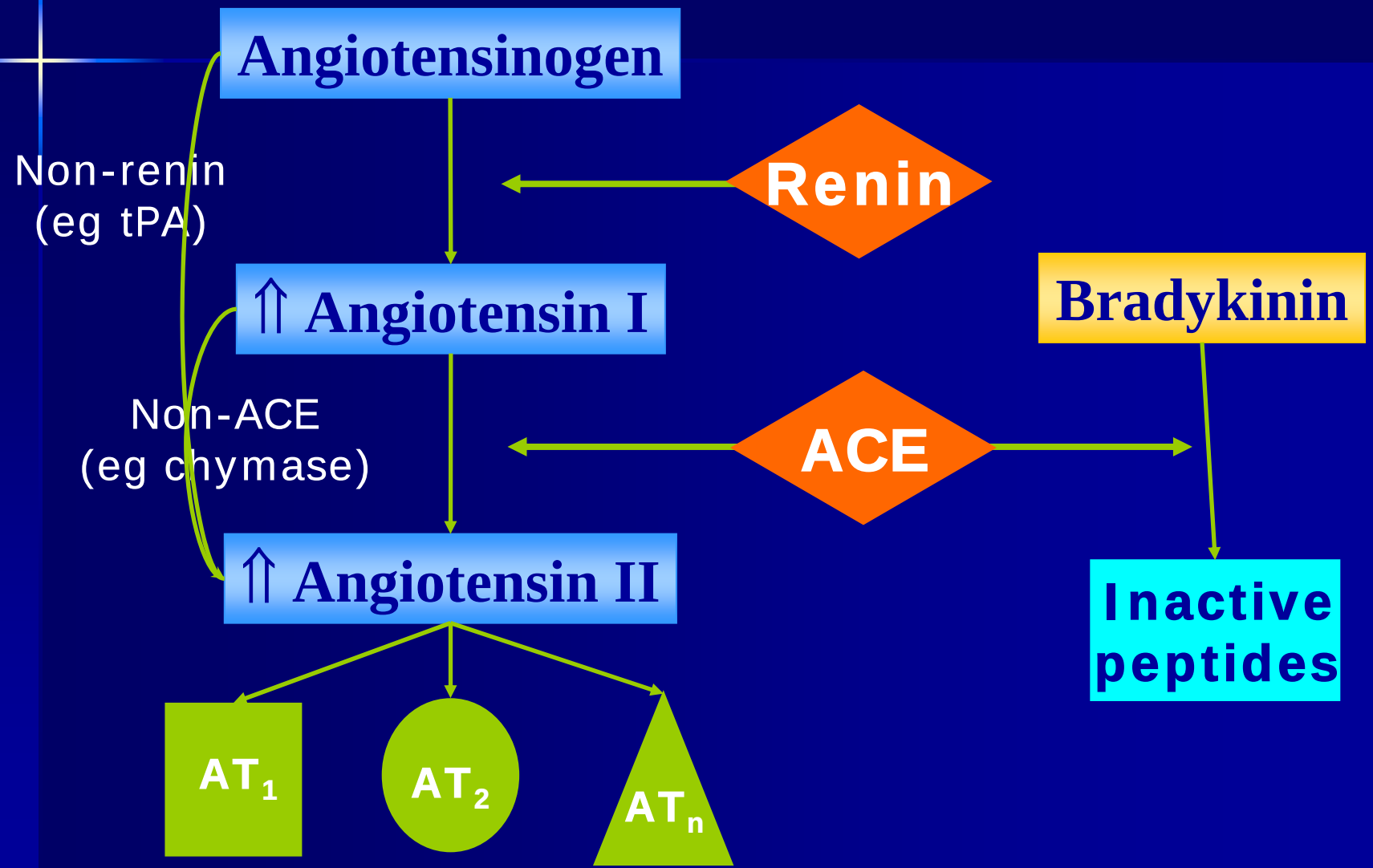
Recent Concepts in ARBs

- Introduction
- RAS and CV and renal disease
- Drugs that modify RAS
- Drug combinations is it beneficial?
- New benefits of ARBs
- Summary and conclusions

Introduction

- **RAS is known to play a key role in CV physio-pathology**
- **It has been proved that exaggeration of compensatory mechanisms involving RAS and sympathoadrenal system is responsible for mortality and morbidity in many CV and renal disorders**
- **Drugs that interfere with the activity of both system (ACEI, B-Blockers, ARBs& aldosterone antagonists) have been proved to be the most effective therapy in reducing mortality and morbidity in many large clinical trials**

Renin-Angiotensin Cascade



Differential effects AT II Receptors:

AT1 Receptors

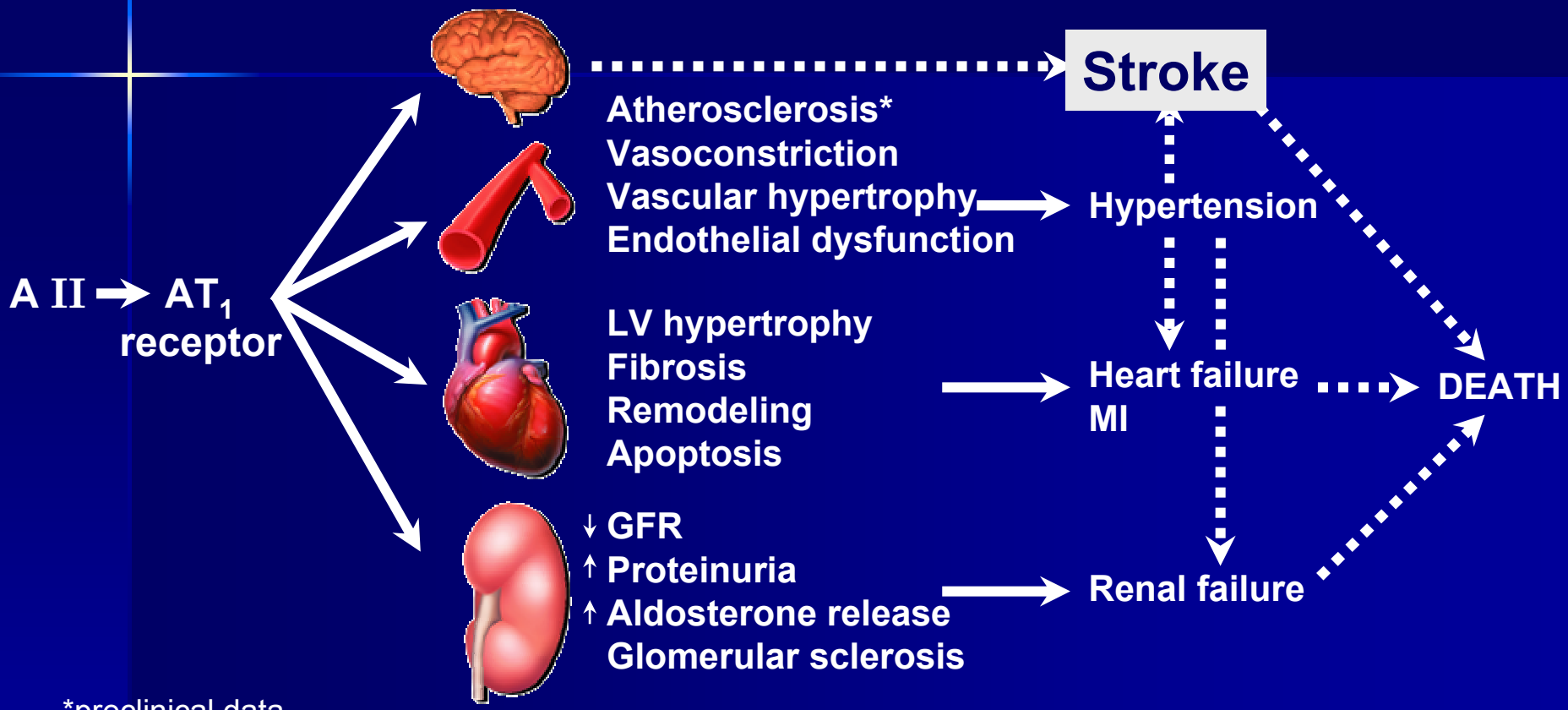
- VC
- Aldosterone secretion
- Renal tubular Na reabsorption
- Increased AVP
- Decreased RBF
- Cardiac hypertrophy
- Vascular SMC Proliferation
- + Peripheral NA activity
- + central sympathetic NS activity
- Central osmocontrol
- EC matrix formation

AT2 Receptors

- Fetal tissue development
- Inhibition of cell growth/proliferation
- ? VD
- Modulation of EC matrix
- Neuronal regeneration
- Cell differentiation
- apoptosis

Angiotensin II Plays a Central Rol

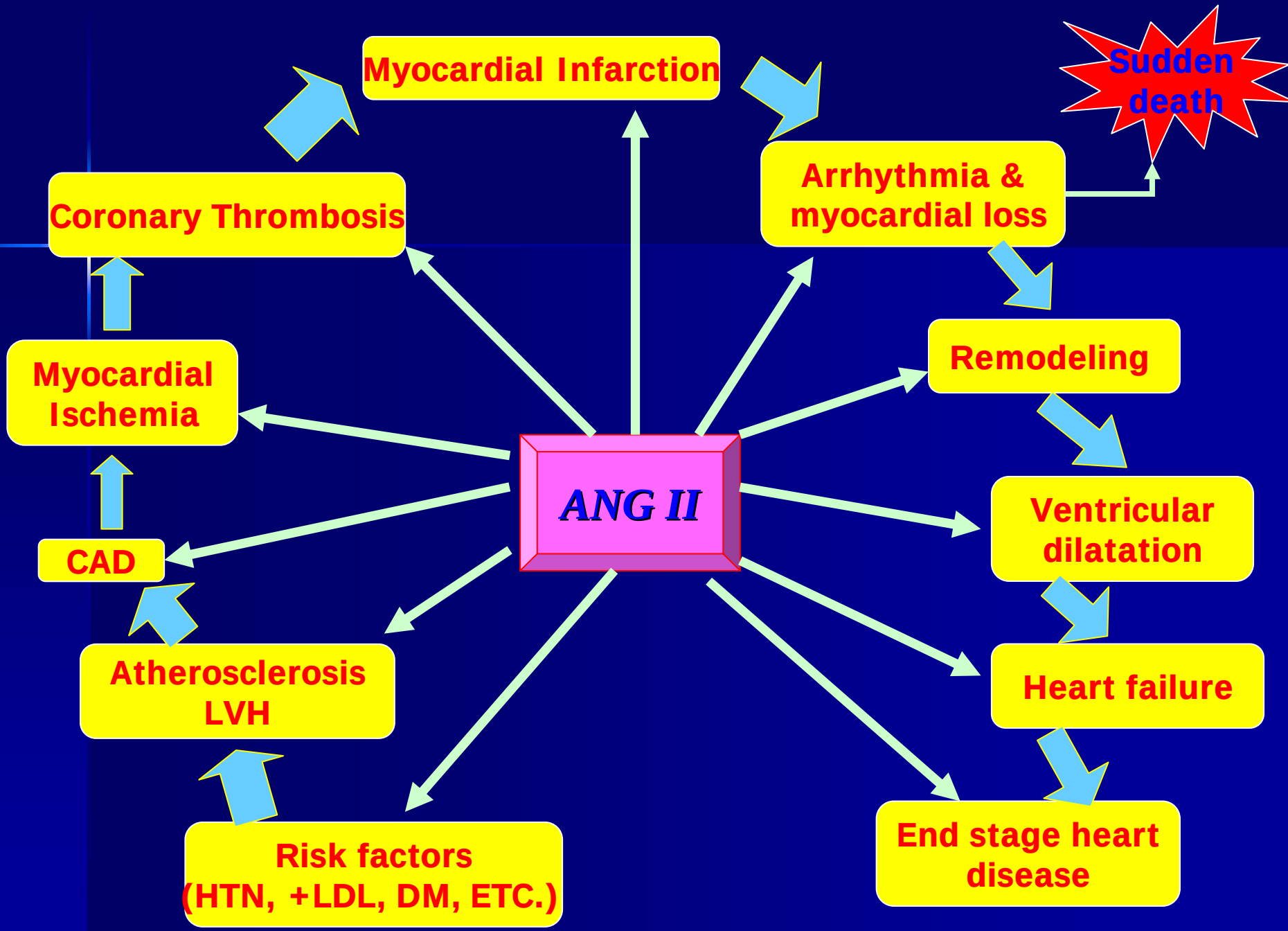
Organ Damage

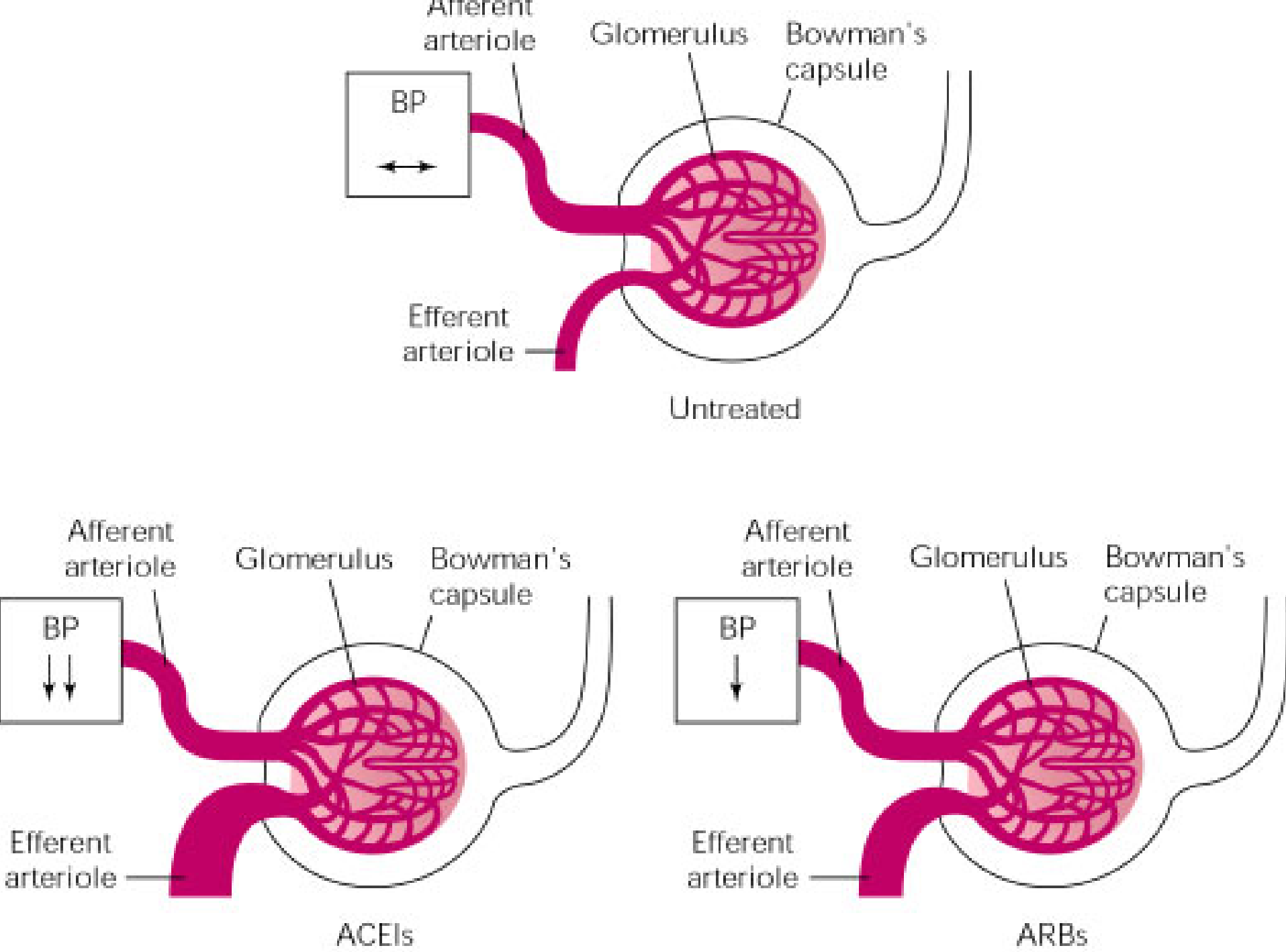


*preclinical data

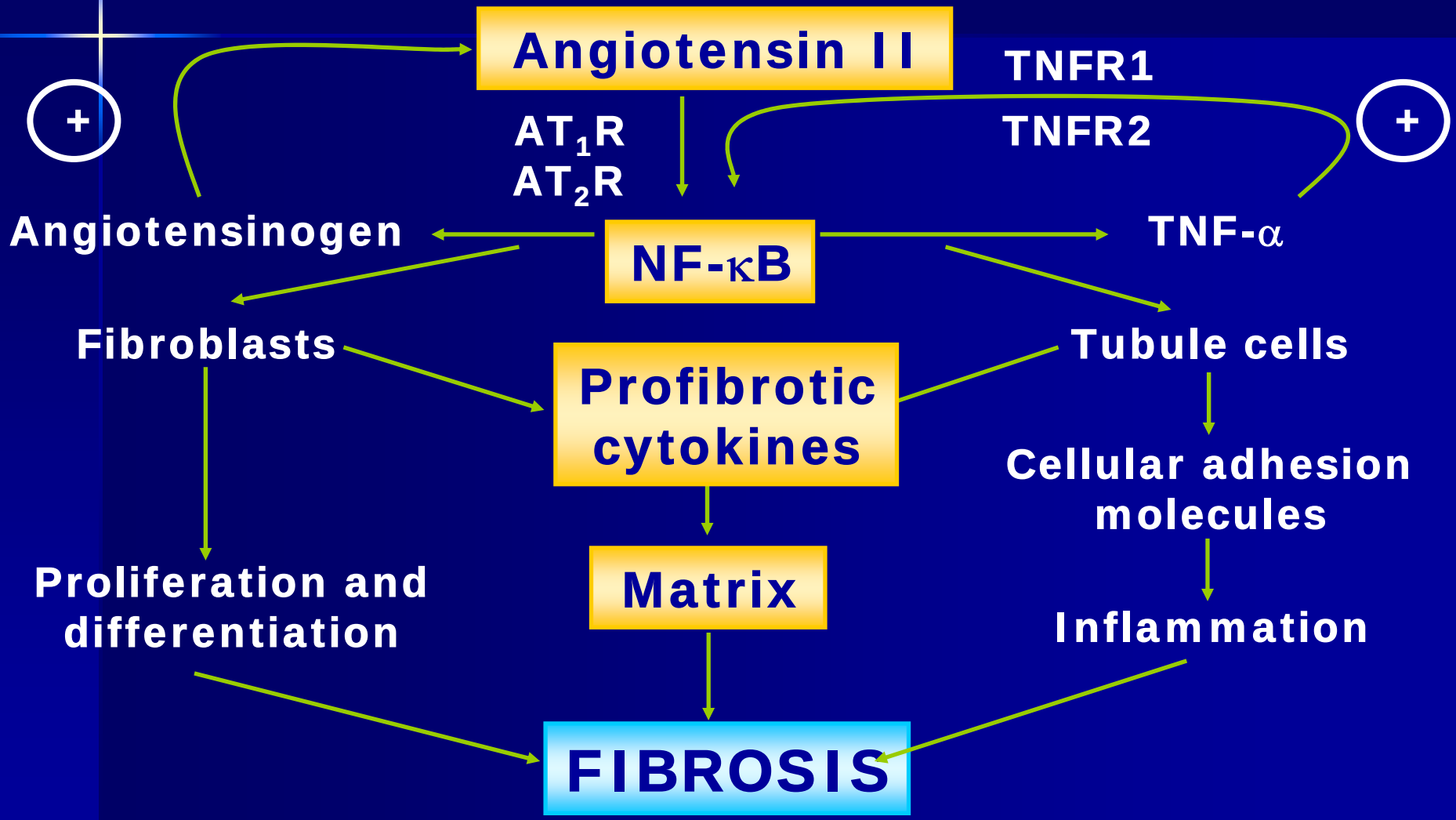
LV = left ventricular; MI = myocardial infarction; GFR = glomerular filtration rate

Adapted from Willenheimer R et al *Eur Heart J* 1999; 20(14): 997–1008, Dahlöf B *J Hum Hypertens* 1995; 9(suppl 5): S37–S44, Daugherty A et al *J Clin Invest* 2000; 105(11): 1605–1612, Fyhrquist F et al *J Hum Hypertens* 1995; 9(suppl 5): S19–S24, Booz GW, Baker KM *Heart Fail Rev* 1998; 3: 125–130, Beers MH, Berkow R, eds. *The Merck Manual of Diagnosis and Therapy*. 17th ed. Whitehouse Station, NJ: Merck Research Laboratories 1999: 1682–1704, Anderson S *Exp Nephrol* 1996; 4(suppl 1): 34–40, Fogo AB *Am J Kidney Dis* 2000; 35(2): 179–188

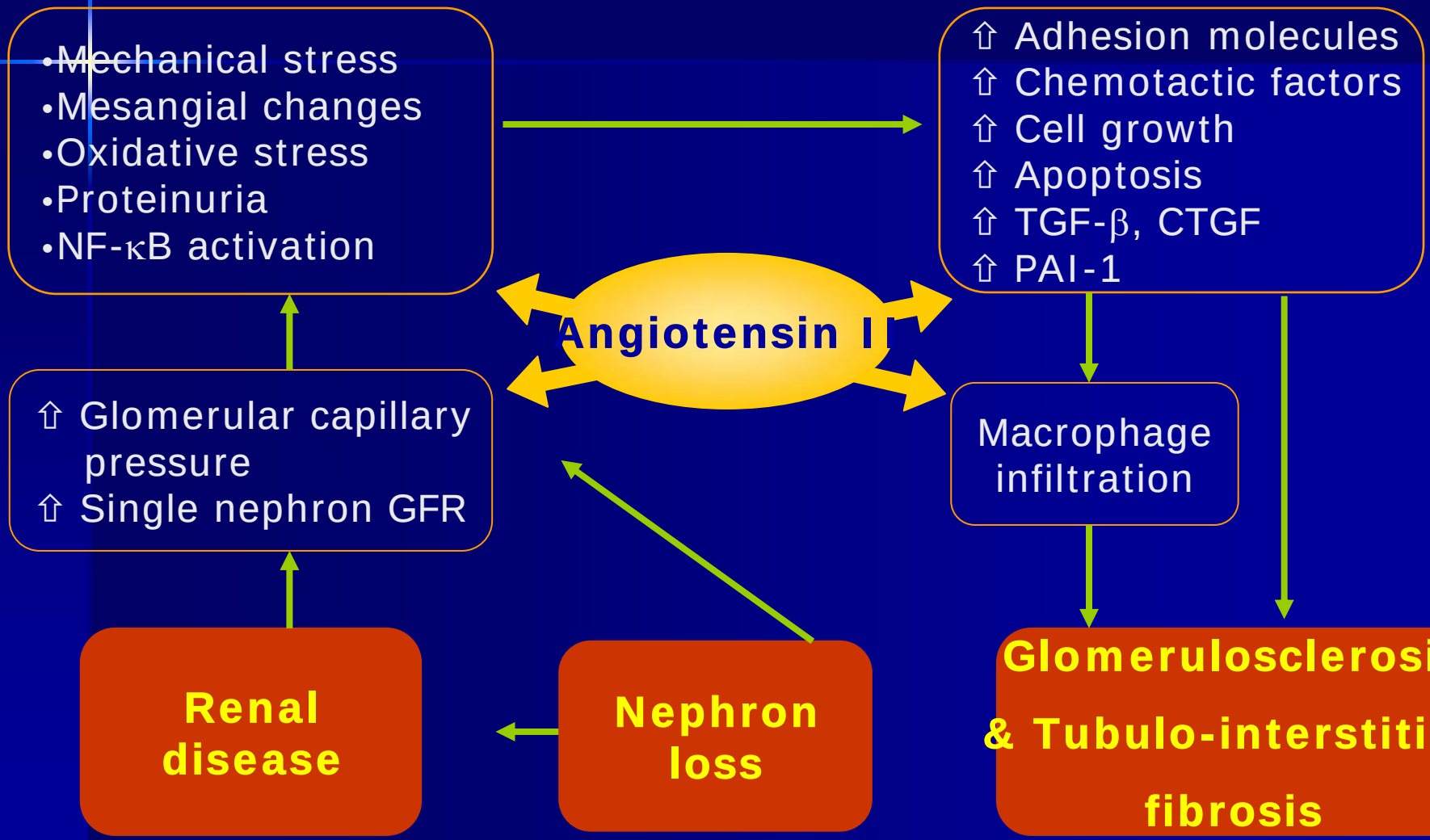

Myocardial Infarction
Sudden death
Arrhythmia & myocardial loss
Coronary Thrombosis
Remodeling
Myocardial Ischemia
ANG II
Ventricular dilatation
CAD
Heart failure
Atherosclerosis LVH
End stage heart disease
Risk factors (HTN, +LDL, DM, ETC.)


Afferent arteriole
Glomerulus
Bowman's capsule
BP
Efferent arteriole
Untreated
Afferent arteriole
Glomerulus
Bowman's capsule
BP
Efferent arteriole
ACEIs
Afferent arteriole
Glomerulus
Bowman's capsule
BP
Efferent arteriole
ARBs

Angiotensin II: Role in Renal Injury



Role of Angiotensin II in Chronic Renal Disease

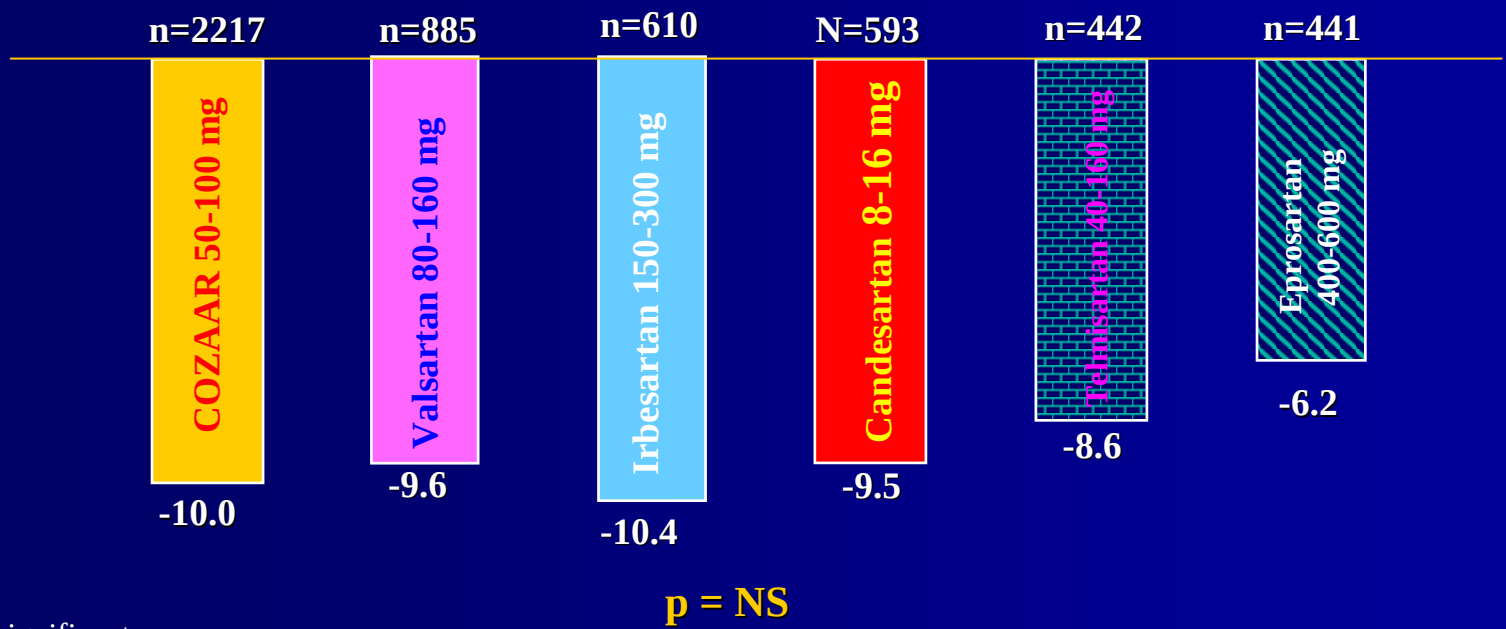


Adapted from Berk B. 2001.

Comparative Efficacy of A I I Antagonists

Absolute Weighted Average Change in DBP at Trough for AIIA Mono-therapies.

Meta-Analysis of 51 Published Double-blind, Randomized Controlled Trials, including > 5, 000 patients



NS = not significant

Conlin PR et al *J Clin Hyper*, 2000; 2 :253-257.

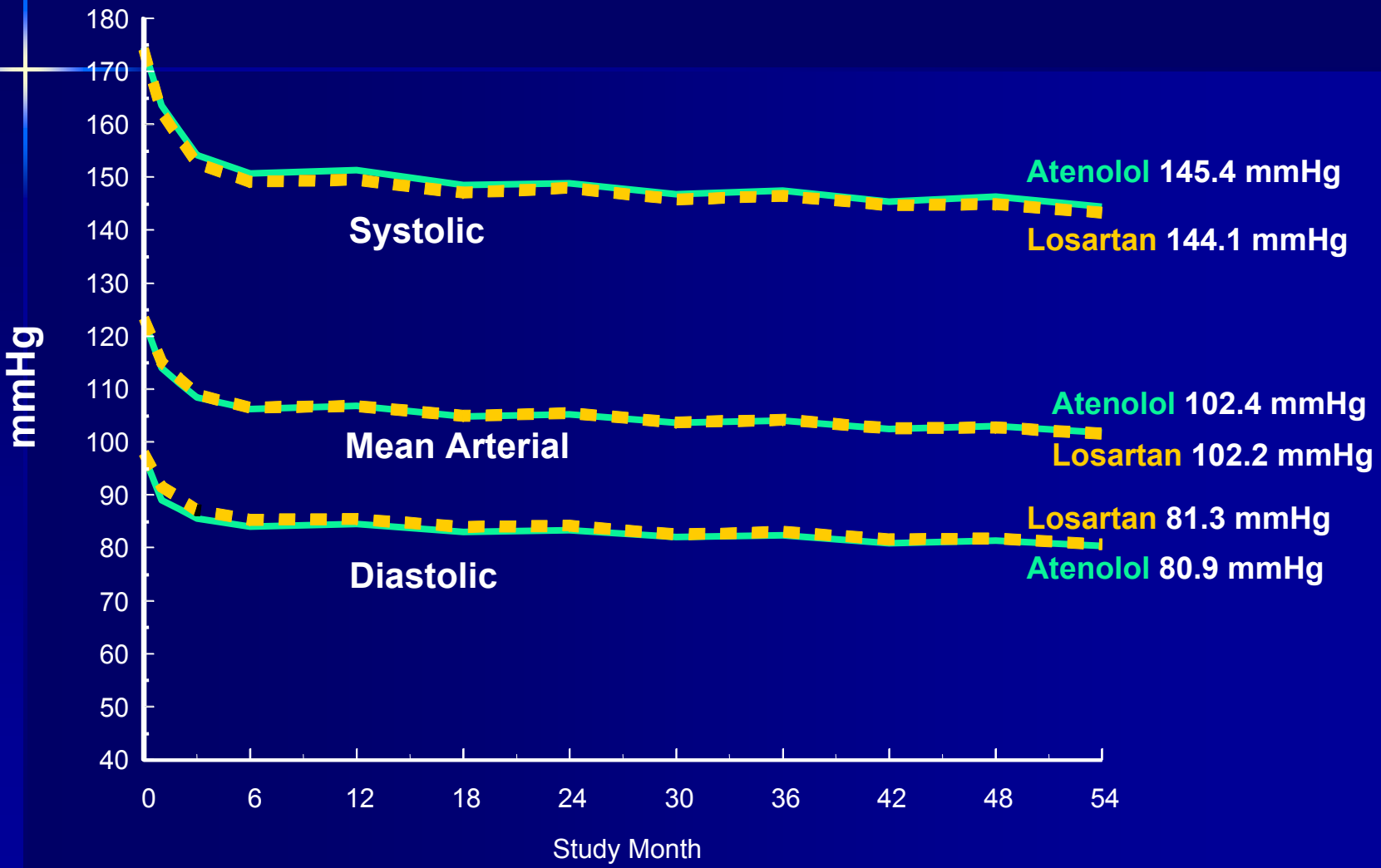
Pharmacology of clinically approved ARBs:

Generic name	Trade name	Dose mg/day	Active metabolite	½ life	Protein binding	T/P Ratio
Losartan	Cozaar	50-100	EXP-3174	2h	99%	~70%
Valsartan	Tareg	80-320	_	6h	92%	N/A%
Candesartan	Atacand	16-32	Candesartan	9h	99%	~ 100%
Telmisartan	Micardis	40-80	_	12-14	92%	~ 90%
Irbesartan	avapro	150-300	_	12-20h	90%	> 50%

Uses of ARBs:

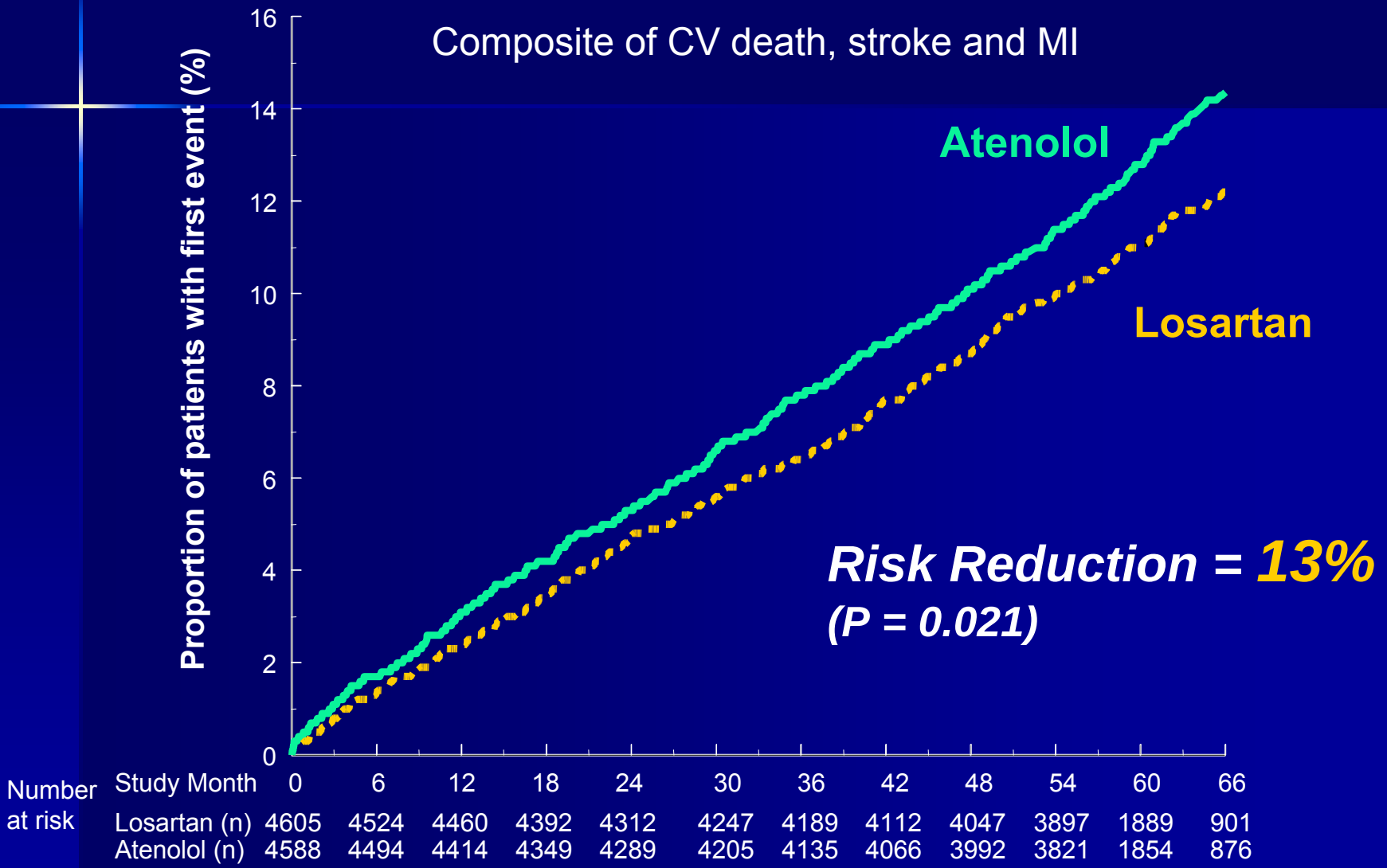
- Hypertension with LVH:
  1. LIFE study (losartan Vs atenolol)
  2. VALUE study (valsartan Vs amlodopine)
- Heart Failure (ELLITE II, VAL-HeFT, CHARM)
- DM
- Post MI (OPTIMAL , VALIANT)
- Restenosis (Val- Rest)
- Prevention of atherosclerosis in high risk patients (ONTARGET & TRANSCEND program telmisartan vs & in combination with ramipril)

LIFE: Comparable Blood Pressure Reductions



Dahlöf B et al *Lancet* 2002;359:995–1003.

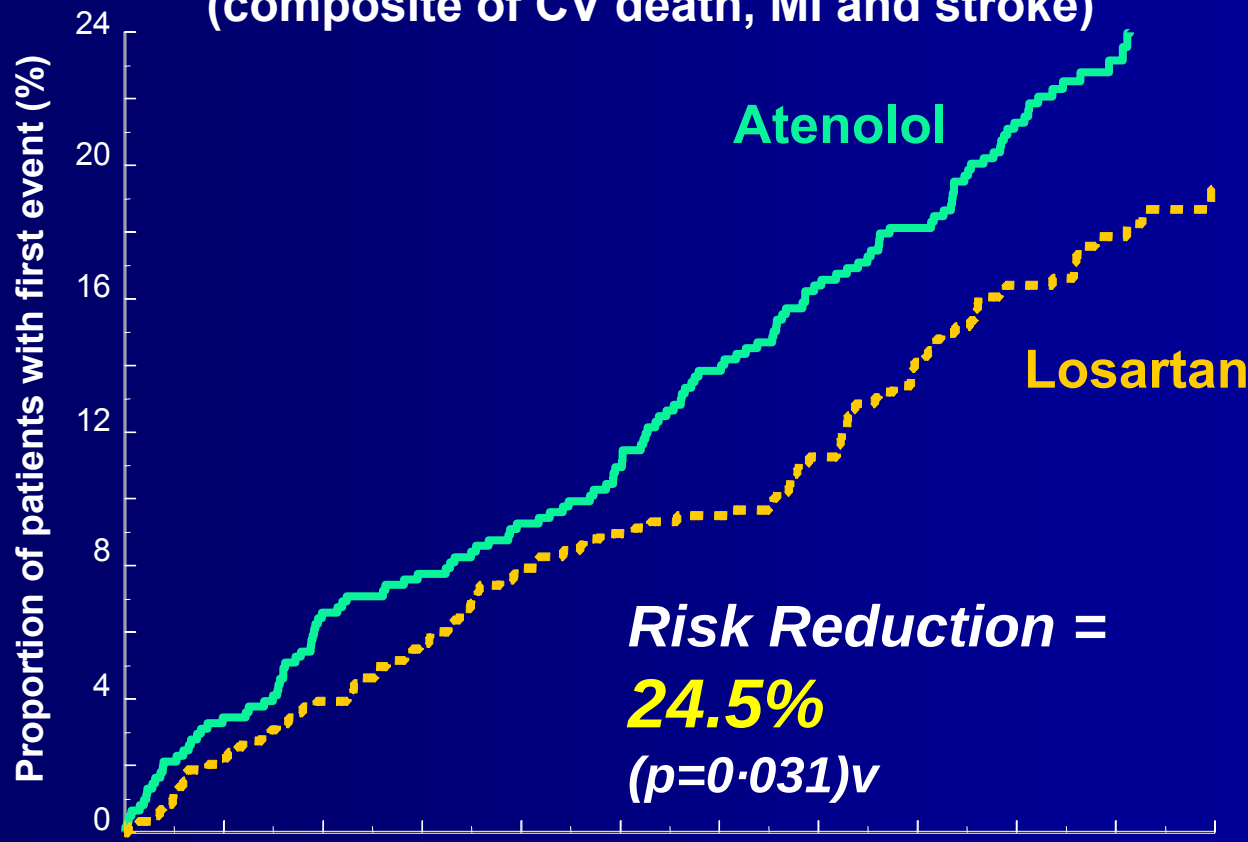
LIFE: *Primary Composite Endpoint*



Dahlöf B et al *Lancet* 2002;359:995–1003.

LIFE: Cardiovascular Benefits of Losartan Confirmed in Diabetic Subgroup

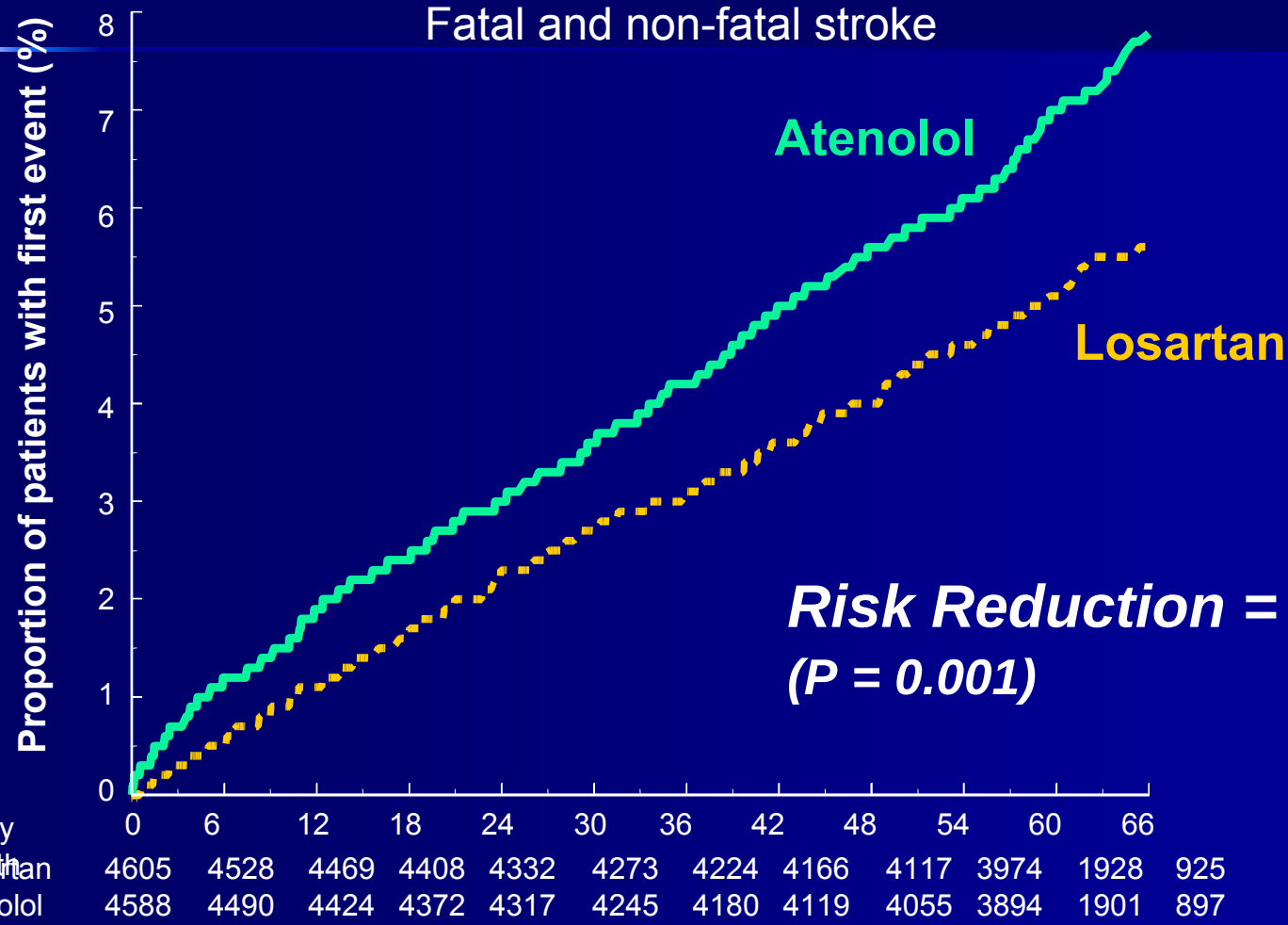
Primary composite endpoint
(composite of CV death, MI and stroke)



Study Month	0	6	12	18	24	30	36	42	48	54	60	66
Losartan (n)	586	569	558	548	532	520	513	501	484	459	237	127
Atenolol (n)	609	588	562	552	540	527	507	486	472	434	204	99

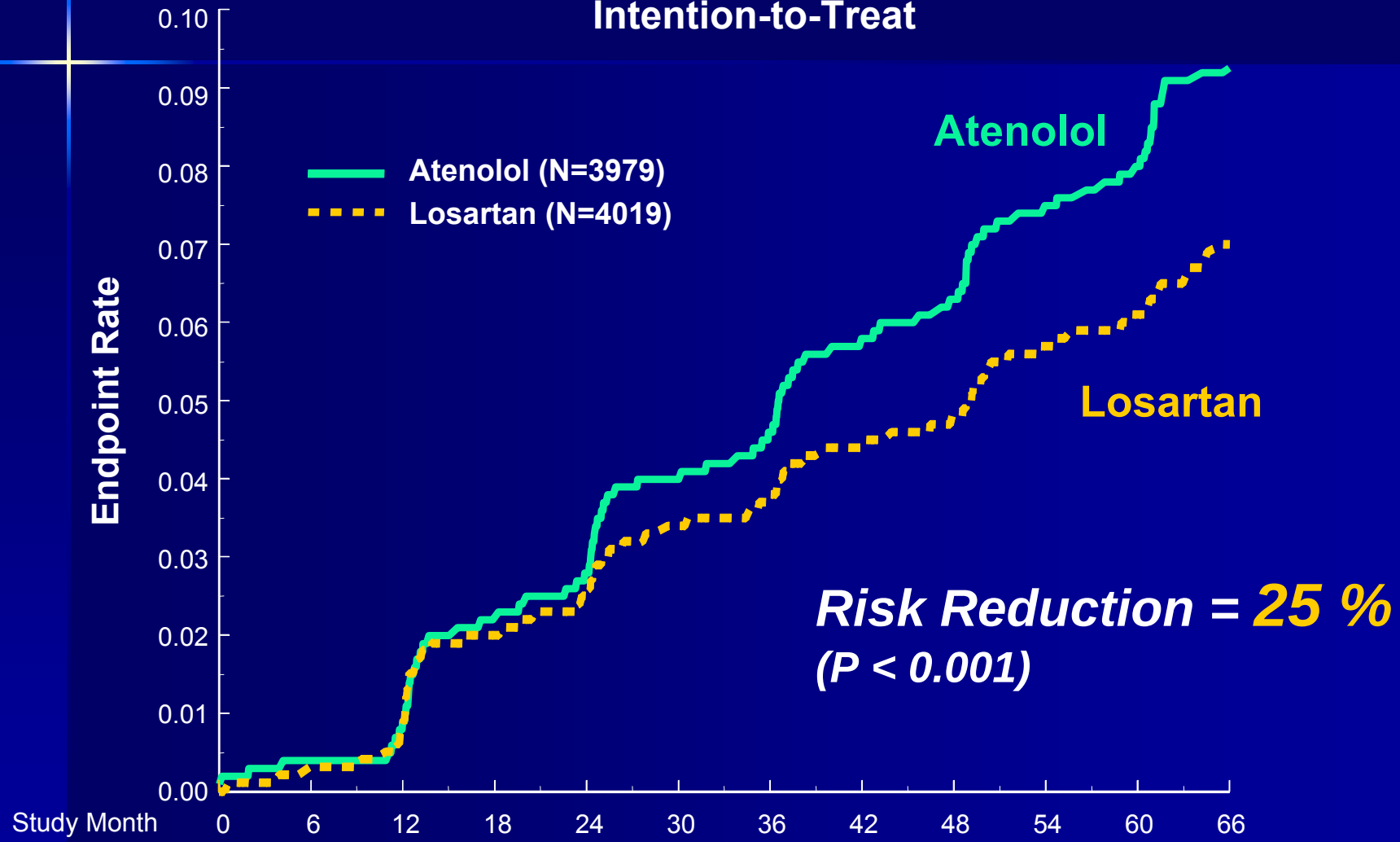
Lindholm LH et al *Lancet* 2002;359:1004 1010.

Stroke



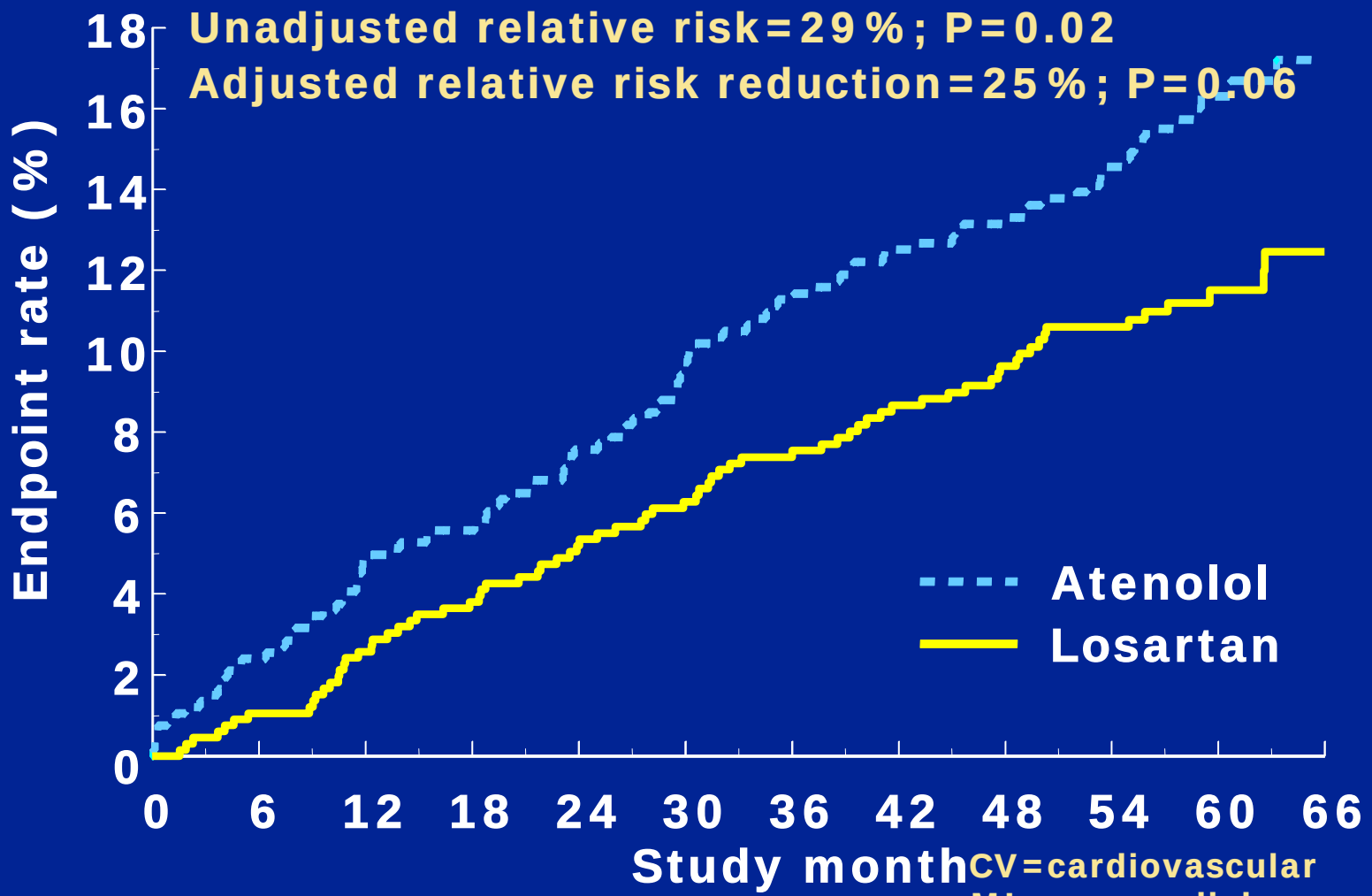
Dahlöf B et al *Lancet* 2002;359:995–1003.

LIFE: *New-Onset Diabetes*



B. Dahlöf at the American College of Cardiology, Atlanta, GA, March 17–20, 2002.

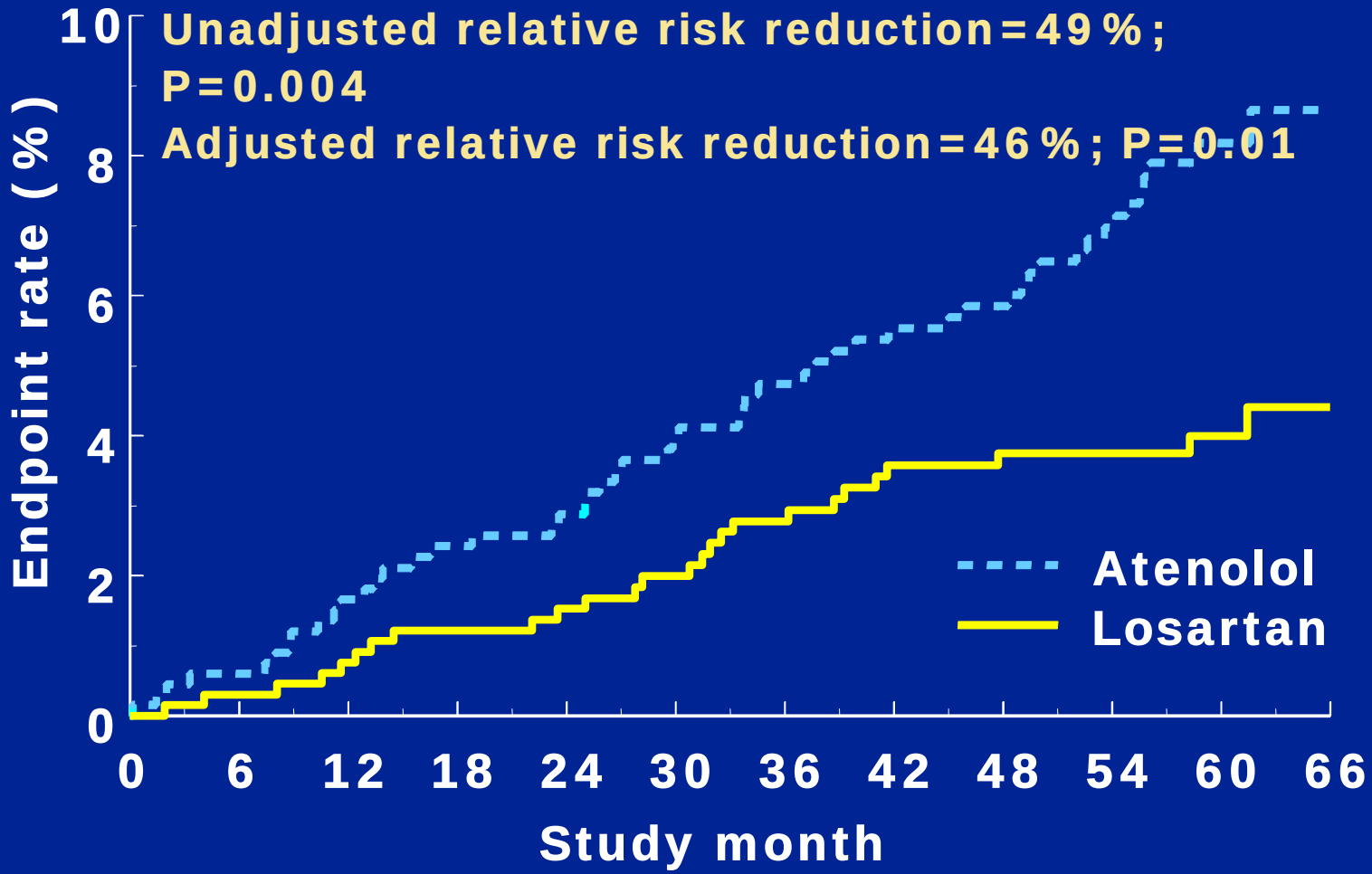
LIFE Study ISH Subgroup
Composite of CV Death, Stroke, and MI



CV=cardiovascular
MI=myocardial infarction

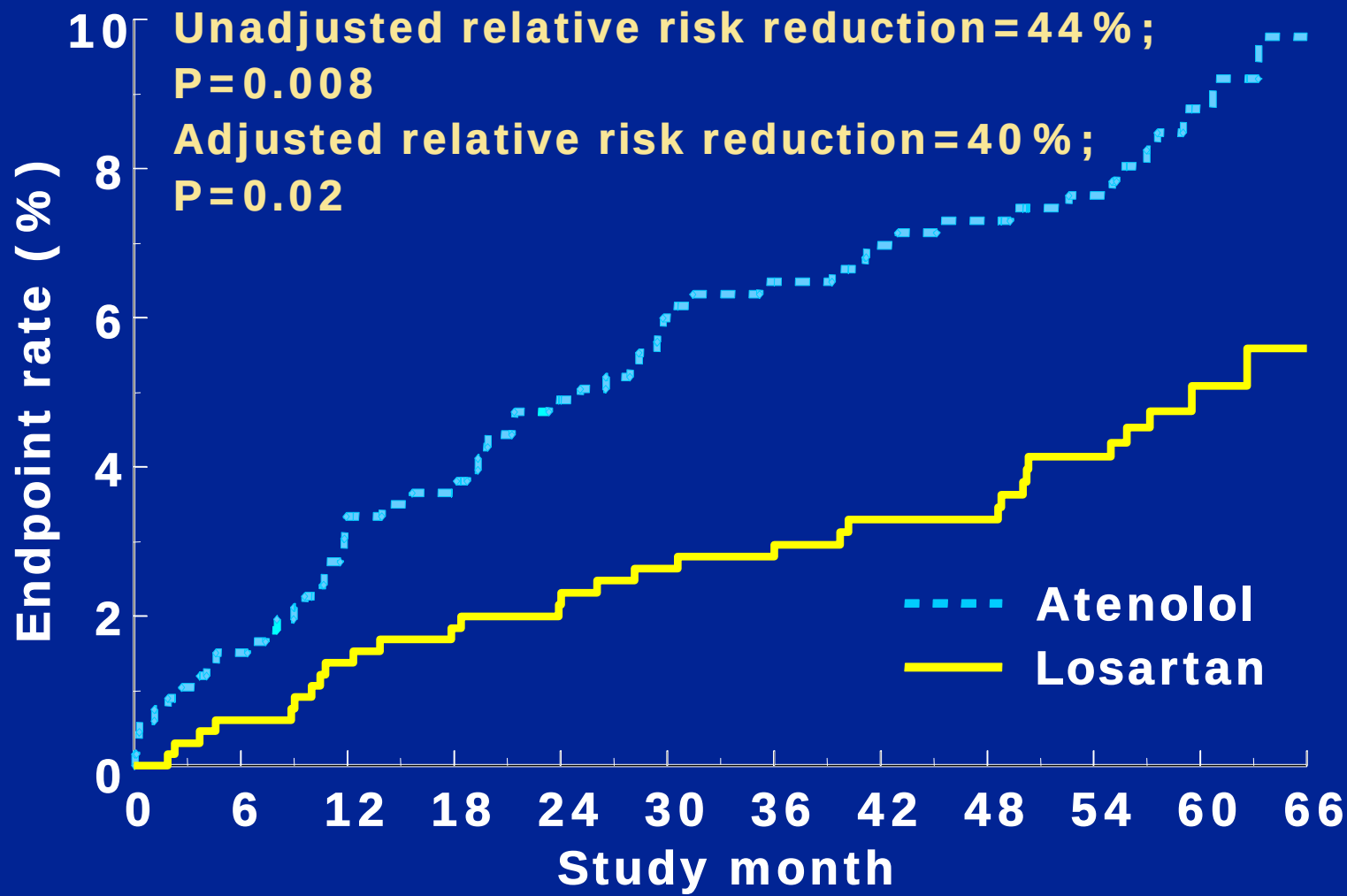
Kjeldsen SE, et al. JAMA. 2002;228:1491-1498.

LIFE Study ISH Subgroup Cardiovascular Mortality



Kjeldsen SE, et al. JAMA. 2002;228:1491-1498.

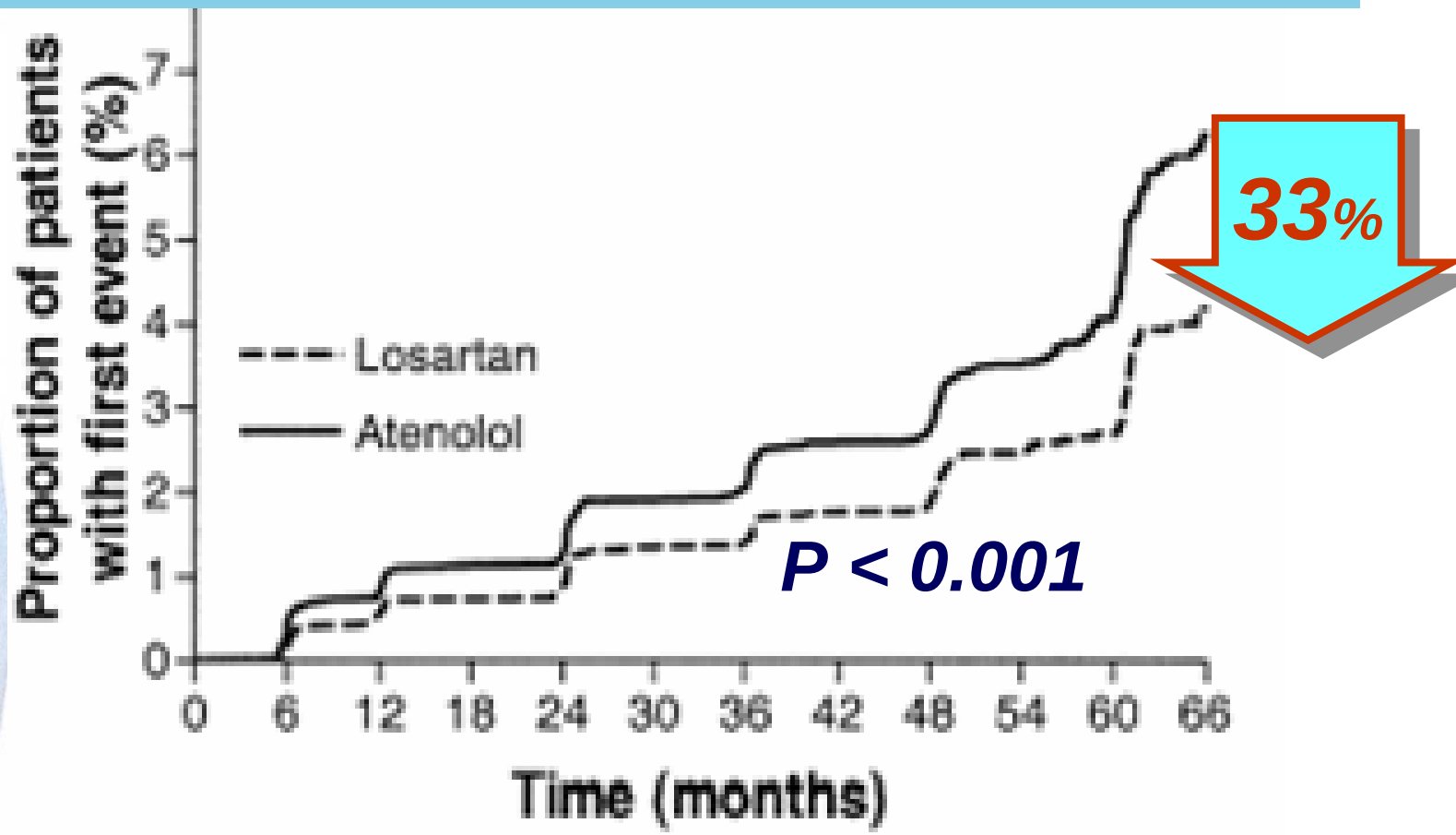
LIFE Study ISH Subgroup Fatal and Non-fatal Stroke



Kjeldsen SE, et al. JAMA. 2002;228:1491-1498.

The LIIFE Study: Losartan significantly ***reduced New-Onset Atrial Fibrillation*** Compared to Atenolol

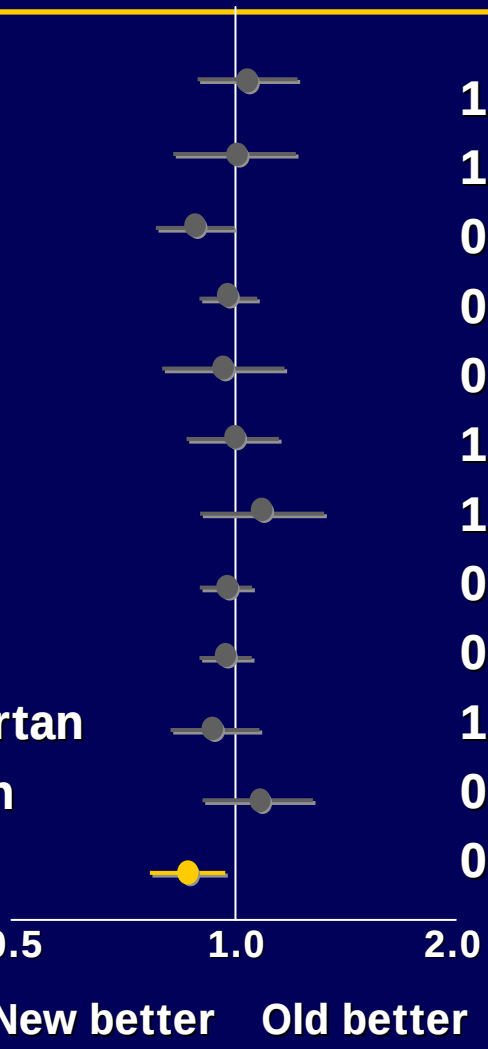
- ***FIRST study to show that one AHT treatment regimen - LOSARTAN - is more effective than another – Atenolol - in reducing new-onset AF.***



Wachtell et al. JACC Vol. 45, No.5, 2005. March 1, 2005:712–9.

Trials on "New" versus "Old" Treatments Primary Endpoints (RR + 95% CI)

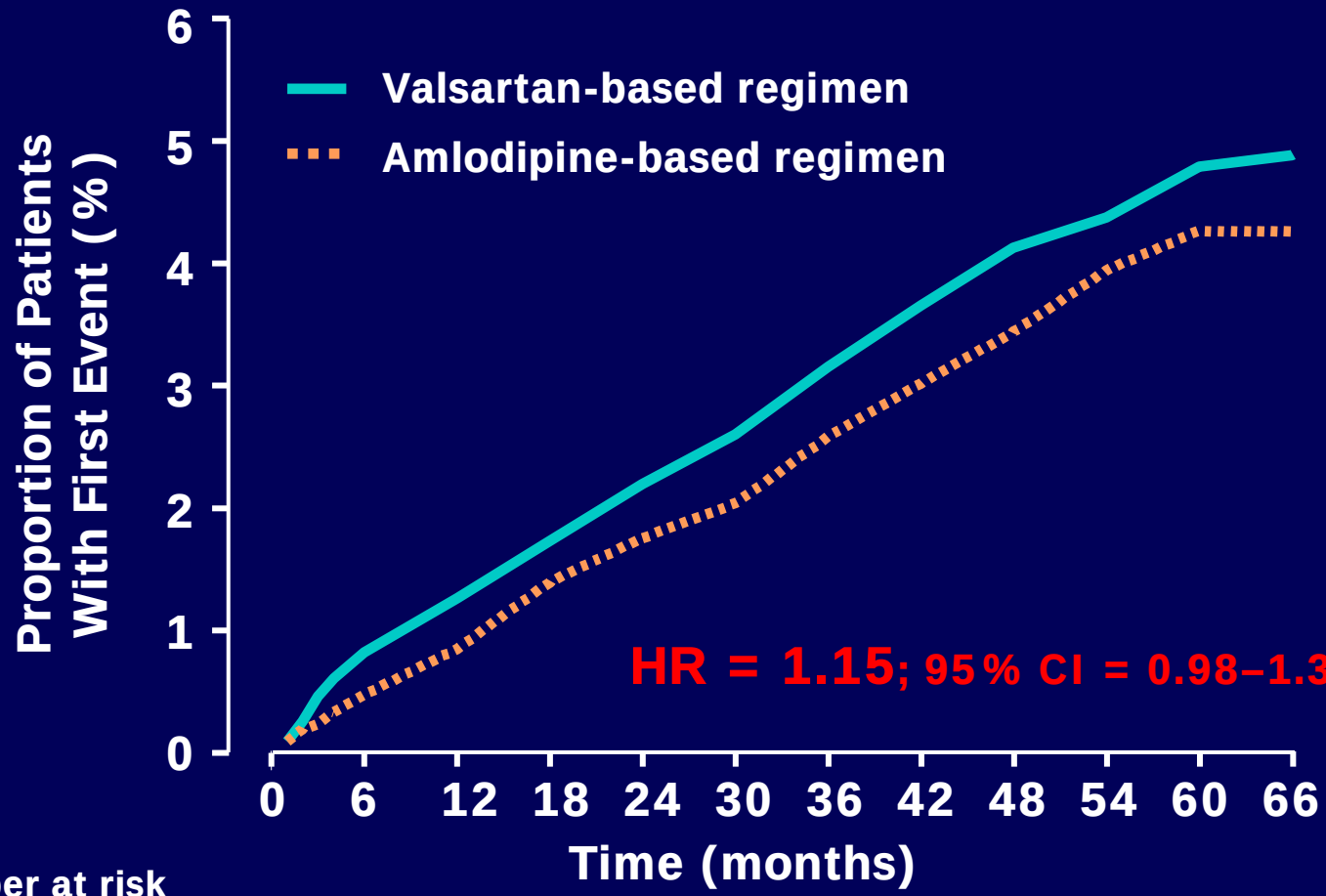
CAPPP*	ACE-I	1.05 (0.90-1.22)	n = 10985
STOP2*	ACE-I	1.01 (0.84-1.22)	n = 4418
ANBP2*	ACE-I	0.89 (0.79-1.00)	n = 6083
ALLHAT°	ACE-I	0.99 (0.91-1.08)	n = 9054
STOP2*	CCB	0.97 (0.80-1.17)	n = 4209
NORDIL*	CCB	1.00 (0.87-1.15)	n = 10881
INSIGHT*	CCB	1.10 (0.91-1.34)	n = 6321
ALLHAT°	CCB	0.98 (0.90-1.07)	n = 22599
INVEST*	CCB	0.98 (0.90-1.06)	n = 9048
SCOPE*	Candesartan	1.03 (0.90-1.17)	n = 4506
VALUE	Valsartan	0.89 (0.75-1.06)	n = 15319
LIFE*	Losartan	0.87 (0.77-0.98)	n = 9193



* CVD; ° CHD

Mancia G. et al., 2003

VALUE: Fatal and Non-fatal Stroke



Number at risk												
Valsartan	7649	7494	7448	7312	7170	7022	6877	6692	6515	6093	3859	1516
Amlodipine	7596	7499	7455	7334	7195	7055	6918	6744	6587	6163	3846	1532

Julius S et al. Lancet. June 2004;363.

VALUE

ARBs in CHF

ARB Trials in CHF:

	ELLITE 2	VAL HeFT	CHARM
No of Patients	3152	5010	7601
Entery CRITERIA	▪ age > 60y ▪ NYHA II-IV ▪ LVEF < 40 ▪ No ACE-I Or ARB within 3M	▪ Any age ▪ NYHA II-IV ▪ LVEF< 40 ▪ Background Therapy (ACE-I)	▪ Any age ▪ NYHA II-IV ▪ LVEF < 40
Treatment groups	Losartan Vs Captopril	Valsartan Vs placebo	Candesartan Vs placebo Candesartan+ACE-I
Results	No difference	No difference in all cause mortality Decrease morbidity	Significant decrease in CV mortality and composite end points

The Losartan Heart Failure Survival Study–ELITE II: Study Design

≥60 yrs; NYHA II–IV; EF ≤40%
Naïve to ACE inhibitors/A II antagonists*

Captopril
50 mg 3 times daily**
(n=1574)

Losartan
50 mg once daily**
(n=1578)

Clinical outcomes	**(event driven, target 510 deaths over ~2 years)**
Primary endpoint:	**All-cause mortality**
Secondary endpoint:	**Sudden cardiac death and/or resuscitated cardiac arrest**
Other endpoints:	**All-cause mortality/hospitalizations**
	Safety and tolerability

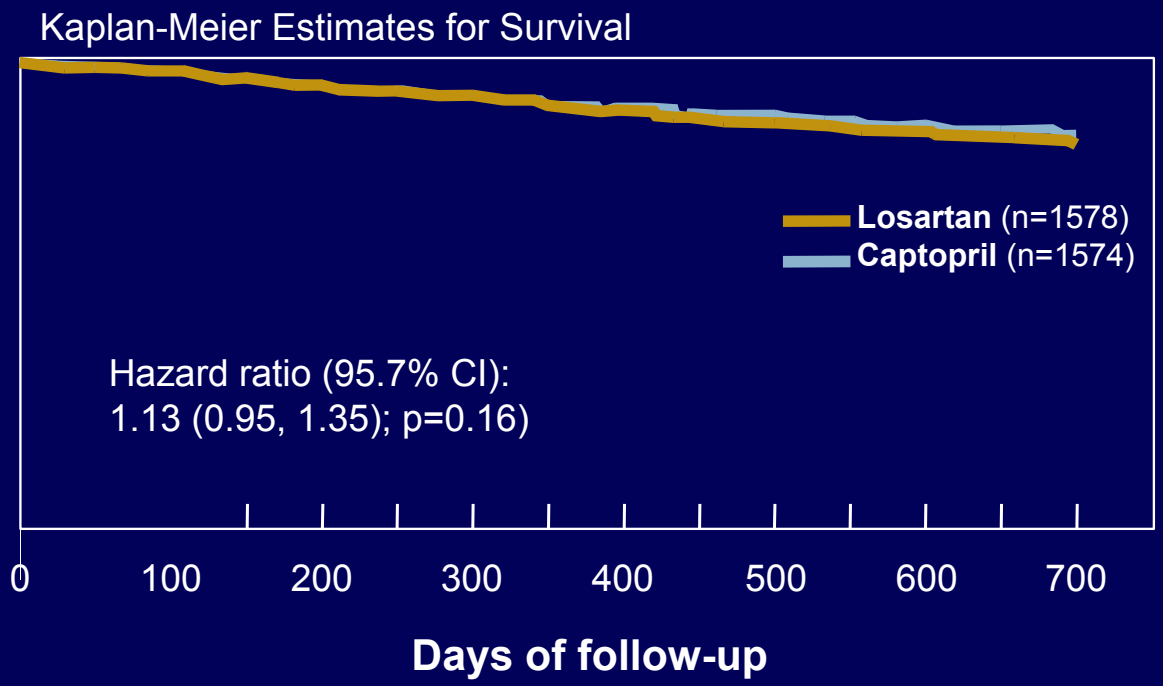
*Or exposure ≤7 days within three months prior to entry

**Concomitant treatments (diuretics, cardiac glycosides, aspirin or salicylates, calcium channel blockers) were allowed; beta blockers were limited to 25% of patients in the protocol. Randomization was stratified based on concurrent use of beta blockers.

Adapted from Pitt B et al *Lancet* 2000;355:1582–1587.

The Losartan Heart Failure Survival Study–ELITE II

Primary Endpoint: All-Cause Mortality



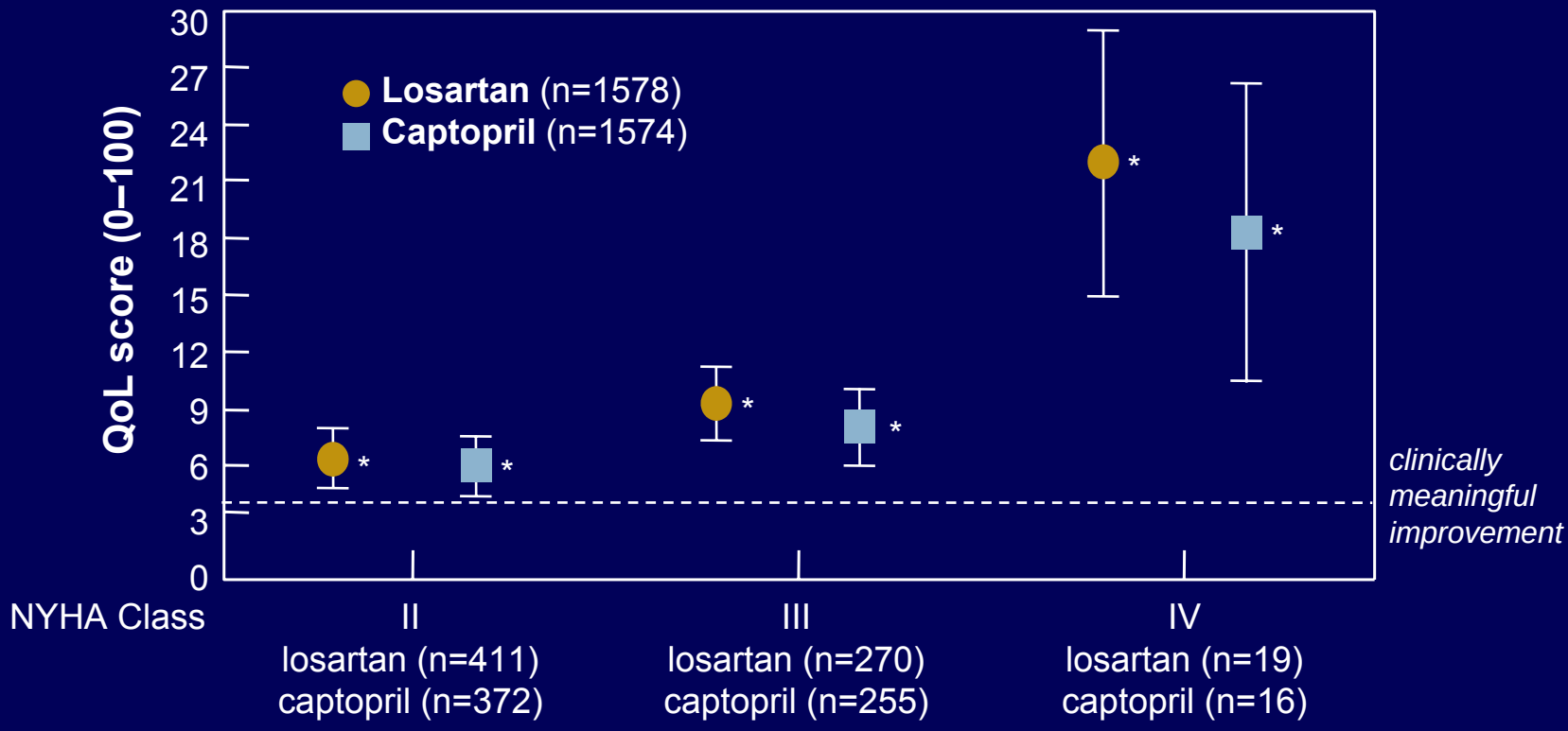
- No significant difference between losartan and captopril in reducing all-cause mortality in heart failure

"Despite evidence that ACE inhibitors are effective, many patients with heart failure who fulfil the criteria of the clinical trials do not receive this treatment, and when they do, it is usually given in inadequate doses."

CI = confidence interval. Adapted from Pitt B et al *Lancet* 2000;355:1582–1587. Adapted from Cleland JGF et al Lancet 1998;352(suppl):19–28 and Houghton AR, Cowley AJ Int J Cardiol 997;59:7–10

The Losartan Heart Failure Survival Study–ELITE II

Other Endpoints: Change from Baseline in Quality of Life among Survivors at Year 1 (n=1343)



*p<0.001 within group; p=NS between groups

Data on file, MSD.

Val-HeFT (Valsartan in Heart Failure Trial)

- **5010 patients (62% NYHA Class II, 36% NYHA Class III) randomized to valsartan or placebo, in addition to ACE inhibitors and followed for 1 year**
- **Valsartan showed no effect on mortality (Risk Reduction –2%, *P*=NS)**
- **Combined endpoint of all-cause mortality + morbidity* was lower in valsartan group (Risk Reduction 13%, *P*=.009), due primarily to reductions in hospitalizations for HF**
- **Use of valsartan adversely affected outcomes in patients taking ACE inhibitors and β-blockers**

*Morbidity was defined as hospitalization for HF, resuscitated sudden death, IV inotropes, or vasodilator use.

Cohn J. 2000 AHA Scientific Sessions, "Late Breaking Clinical Trials."

CHARM-Overall: Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity -TRIAL DESIGN -

Design

Combined data from three parallel MC, multinational, randomized, double-blind, placebo-controlled trials

Patients

7599 patients aged ≥18 years with symptomatic CHF (NYHA class II–IV) and:

- left ventricular ejection fraction (LVEF) ≤40%, receiving an ACE inhibitor (2548: CHARM-Added trial)
  or
- LVEF ≤40%, but not receiving an ACE inhibitor because of previous intolerance (2028: CHARM-Alternative trial)
  or
- LVEF >40% (3023: CHARM-Preserved trial)

CHARM-Overall: Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity -TRIAL DESIGN -

Follow up and primary endpoint

Primary endpoint: all-cause mortality. Mean 37.7 months follow up.

Treatment

Placebo or candesartan titrated to 32 mg once daily

CHARM-Overall:
Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity - Overall
- RESULTS -

- **All-cause mortality reduction in candesartan and placebo groups of borderline significance (23 vs. 25%, hazard ratio 0.91, 95% CI 0.83–1.00, P=0.055)**
- **Cardiovascular death significantly reduced (18.2 vs. 20.3%, P=0.012). Noncardiovascular death not significantly different (P=0.45)**

CHARM-Overall:

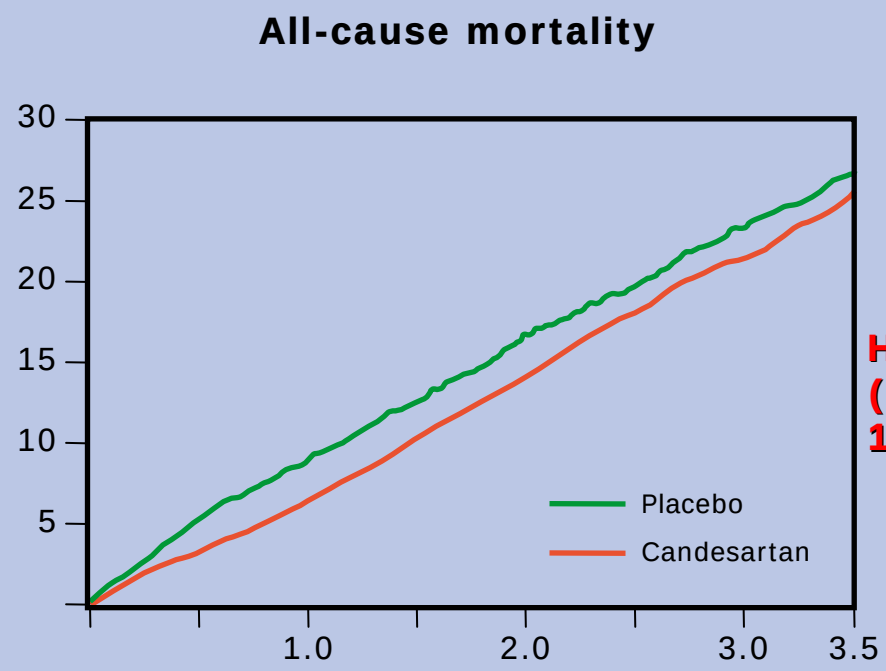
Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity - Overall

- RESULTS -

- **Combined endpoint of cardiovascular death or hospital admission for CHF significantly reduced (30.2 vs. 34.5%, P<0.0001)**
- **Hospital admission for CHF significantly reduced (19.9 vs. 24.2%, hazard ratio 0.79, 95% CI 0.72–0.087, P <0.0001)**
- **Permanent discontinuation due to adverse event or laboratory abnormality more frequent with candesartan (21 vs. 16.7%, P<0.0001)**

CHARM-Overall:

Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity - Overall



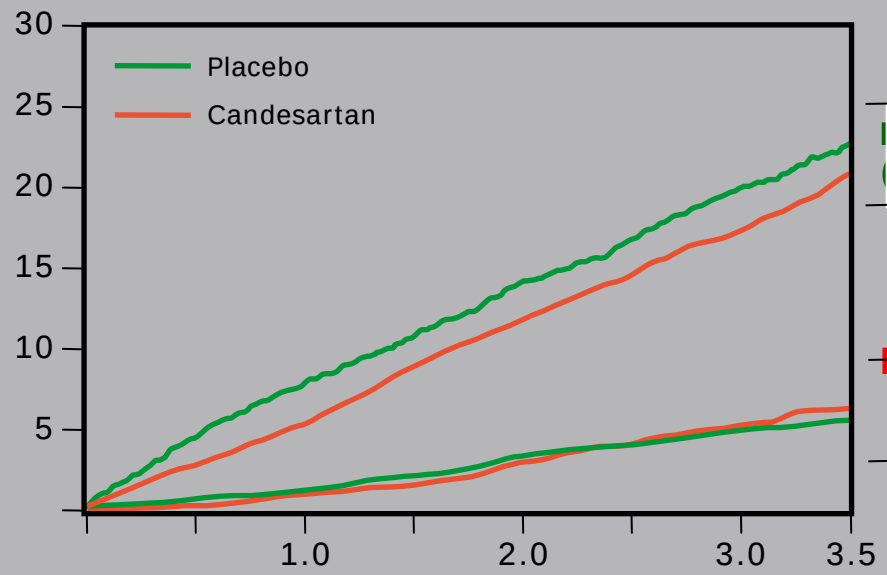
Hazard ratio 0.91 (95% CI 0.83–1.00)

P = 0.055

Pfeffer et al. Lancet 2003;362:759–66.

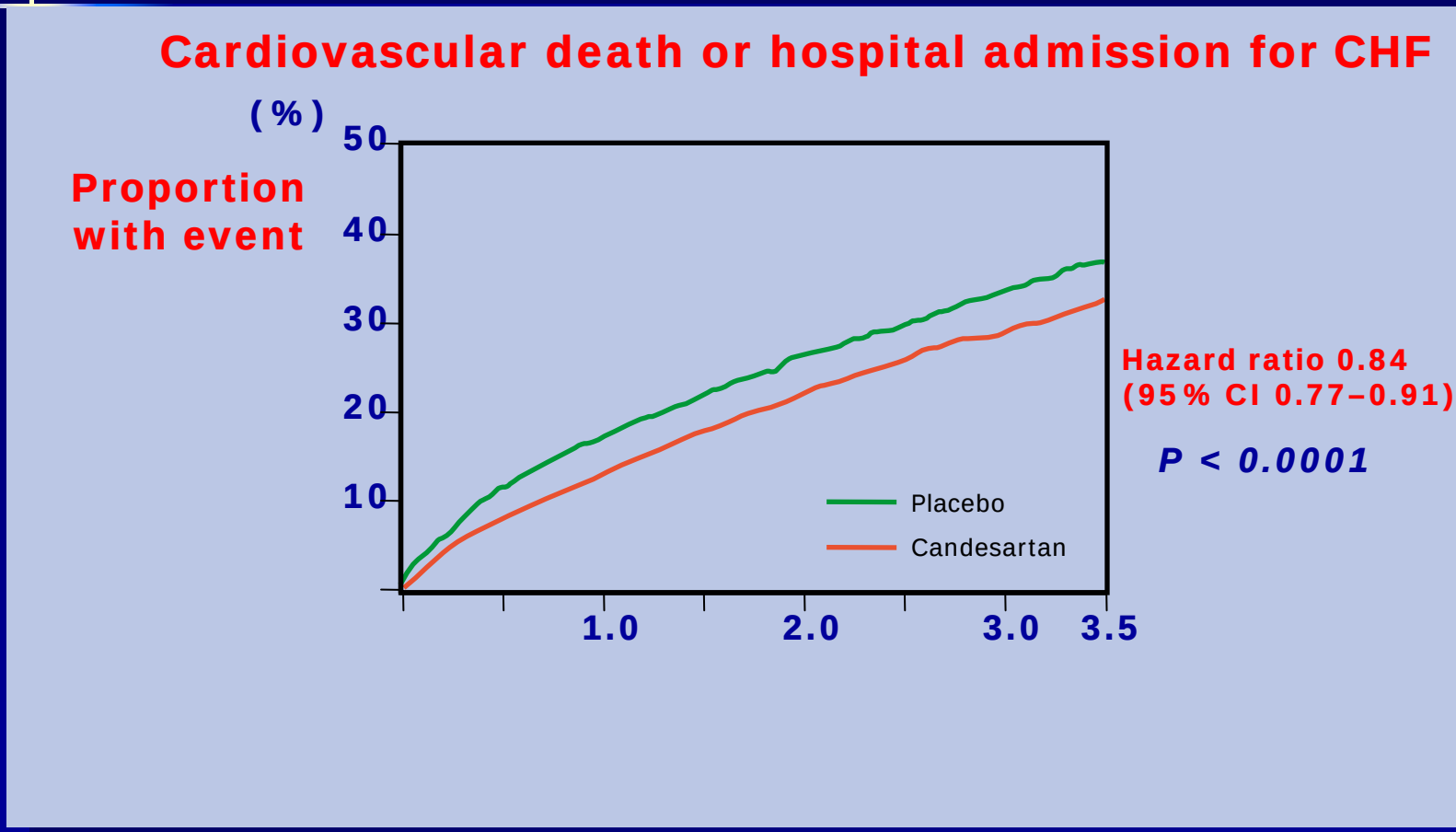
CHARM-Overall: Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity

Cardiovascular and noncardiovascular mortality



Pfeffer et al. Lancet 2003;362:759–66.

CHARM-Overall: Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity



Pfeffer et al. Lancet 2003;362:759–66.

ESC Guidelines of ARB in HF

- **Angiotensin II receptor antagonists (ARBs) could be considered in patients who do not tolerate ACE inhibitors for symptomatic treatment (level C).**
- **However, it is unclear whether ARBs are as effective as ACE inhibitors for mortality reduction (level B).**
- **In addition to ACE inhibition, ARBs may improve heart failure symptoms and reduce hospitalizations for worsening heart failure (level B).**
- **The addition of ARBs to ACE Inhibition or B-Blockade cannot be recommended at present and need further studies (level C)**

Eur Heart J, September 2001

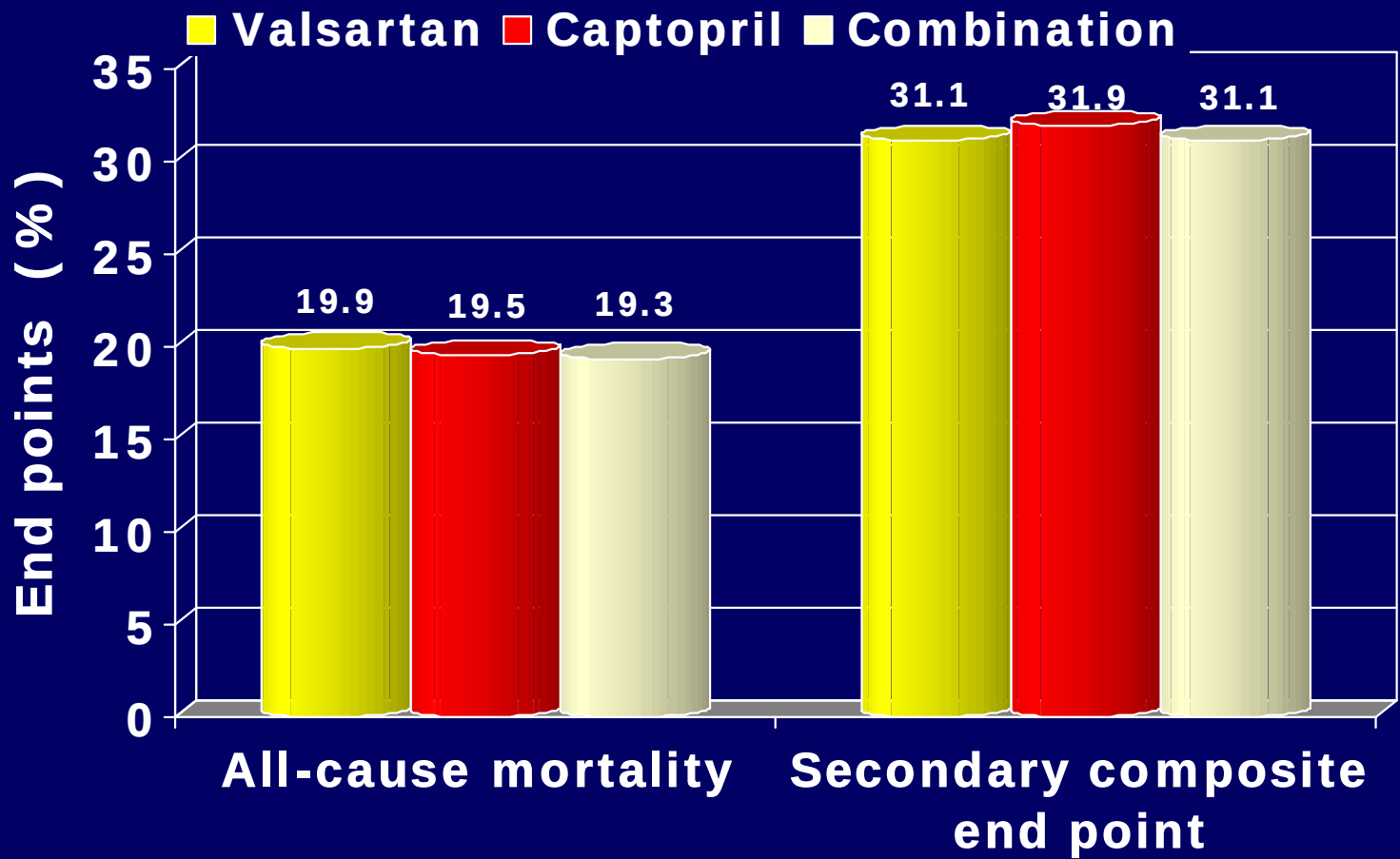
VALIANT: Design

Valsartan, captopril, or both in myocardial infarction complicated by heart failure, LV dysfunction, or both

- 14 703 patients with recent MI (<10 days)
- *Valsartan* (160 mg twice/day) vs *captopril* (50 mg three times/day) or *combination* (valsartan 80 mg twice/day + captopril 50 mg three times/day)
- Primary end point: all-cause mortality
- 2-year follow-up

(Pfeffer et al. *N Engl J Med* 2003; 349: 1893–1906)

VALIANT: Results



N Engl J Med 2003; 349: 1893–1906

VALIANT: Summary

- More side effects in the combination group
- Valsartan looks good compared to captopril
- Combination does not look as good as giving both agents alone

OPTIMAAL and ELITE-2

Better outcome with the ACE inhibitor captopril compared to losartan (50 mg/day) in OPTIMAAL and ELITE-II

Did losartan not do well because the dose was too low?

OPTIMAAL and ELITE-2 Dose issue

The low dose was definitely a problem

- **50 mg/day is a minimal antihypertensive dose**
- **100 mg to 150 mg twice/day would be far more appropriate**
- **New studies with higher losartan doses will confirm this**

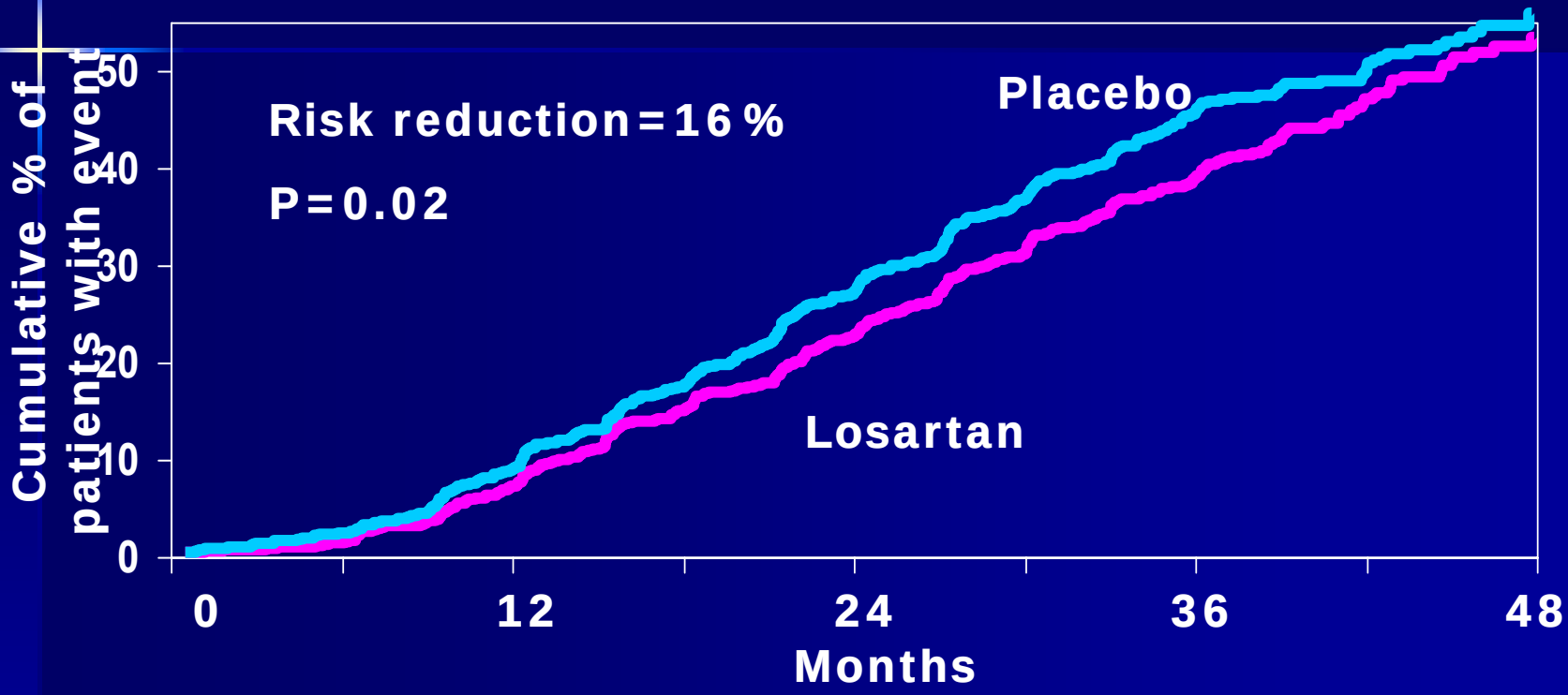
Weber

ARBs & DM

Benefit of Angiotensin Receptor Blockers in Diabetes:
Important Findings of 4 Major Clinical Trials

- **RENAAL (2001)**
  - **The angiotensin receptor blocker losartan compared to placebo reduced the risk of diabetic nephropathy developing to renal failure**
- **IRMA II (2001)**
  - **Higher doses of the angiotensin receptor blocker Irbesartan reduced the risk of progression of renal insufficiency**
- **IDNT (2001)**
  - **The angiotensin receptor blocker irbesartan compared to the calcium channel blocker amlodipine provided better renal protection in hypertensive type 2 diabetics, reducing the chance of diabetic nephropathy developing to renal failure**
- **MARVAL (2001)**
  - **Similar to IDNT with Valsartan**

RENAAL *Patients Reaching the Primary Composite Endpoint**



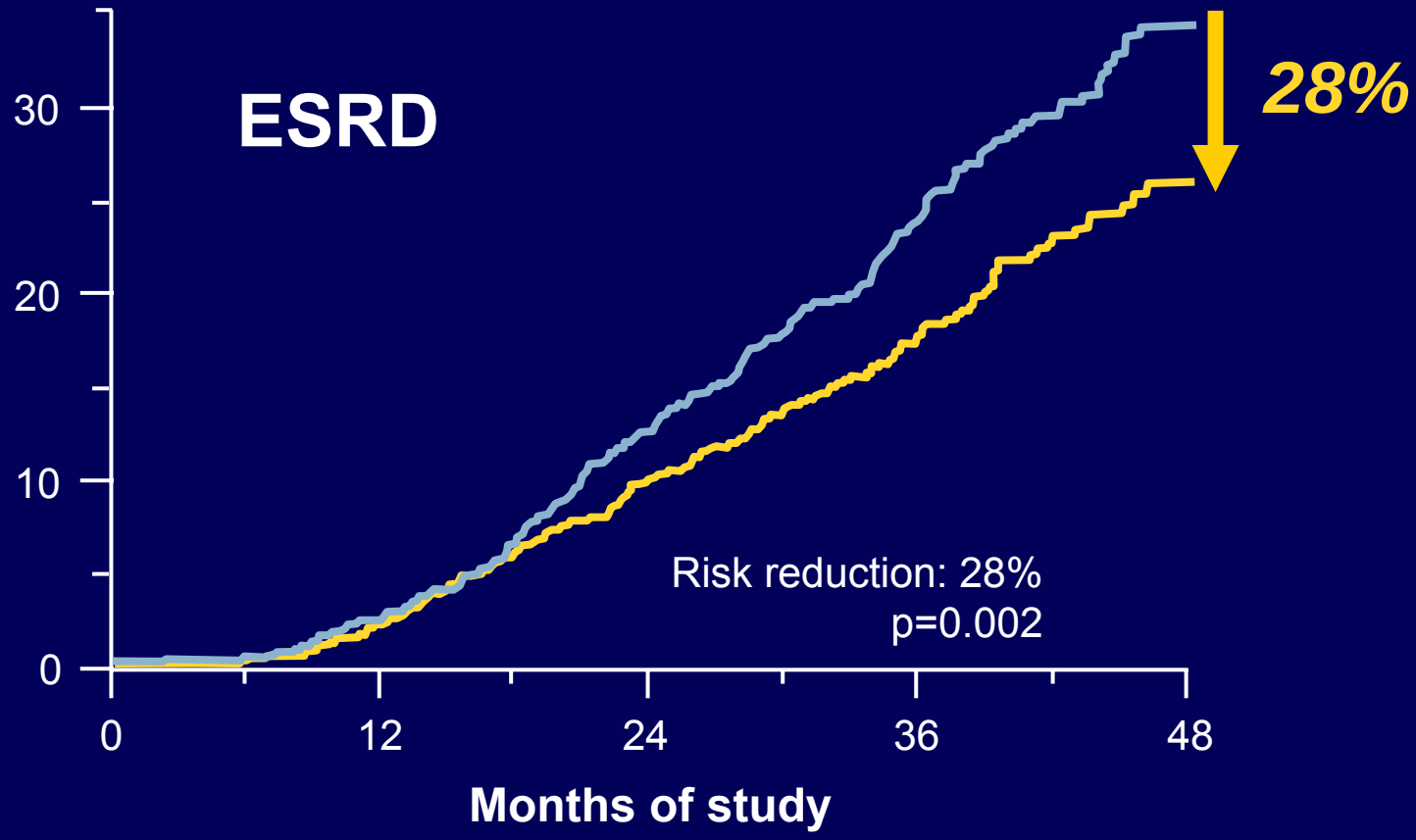
Placebo† (n)	762	689	554	295	36
Losartan† (n)	751	692	583	329	52

†In combination with open-label diuretic, calcium channel blocker, beta-blocker, alpha-blocker, and/or centrally acting agent

*doubling of serum creatinine, end stage renal disease, death

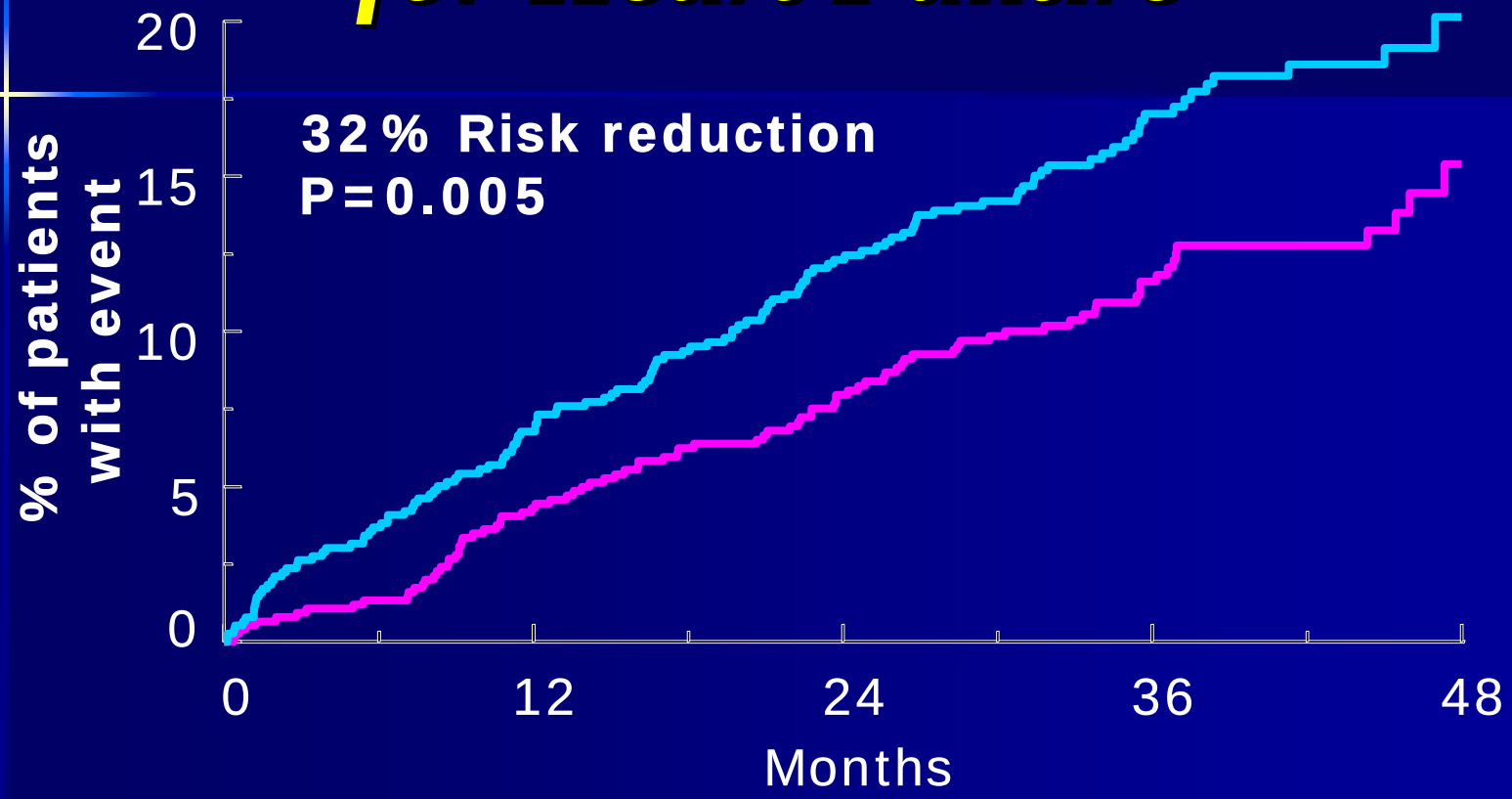
Brenner BM, et al. N Engl J Med. 2001;345(12):861-869.

Reduction of Endpoints in NIDDM with the A II Antagonist Losartan



Adapted from Brenner BM et al N Engl J Med 2001;345(12):861–869.

RENAAL *First Hospitalization for Heart Failure*

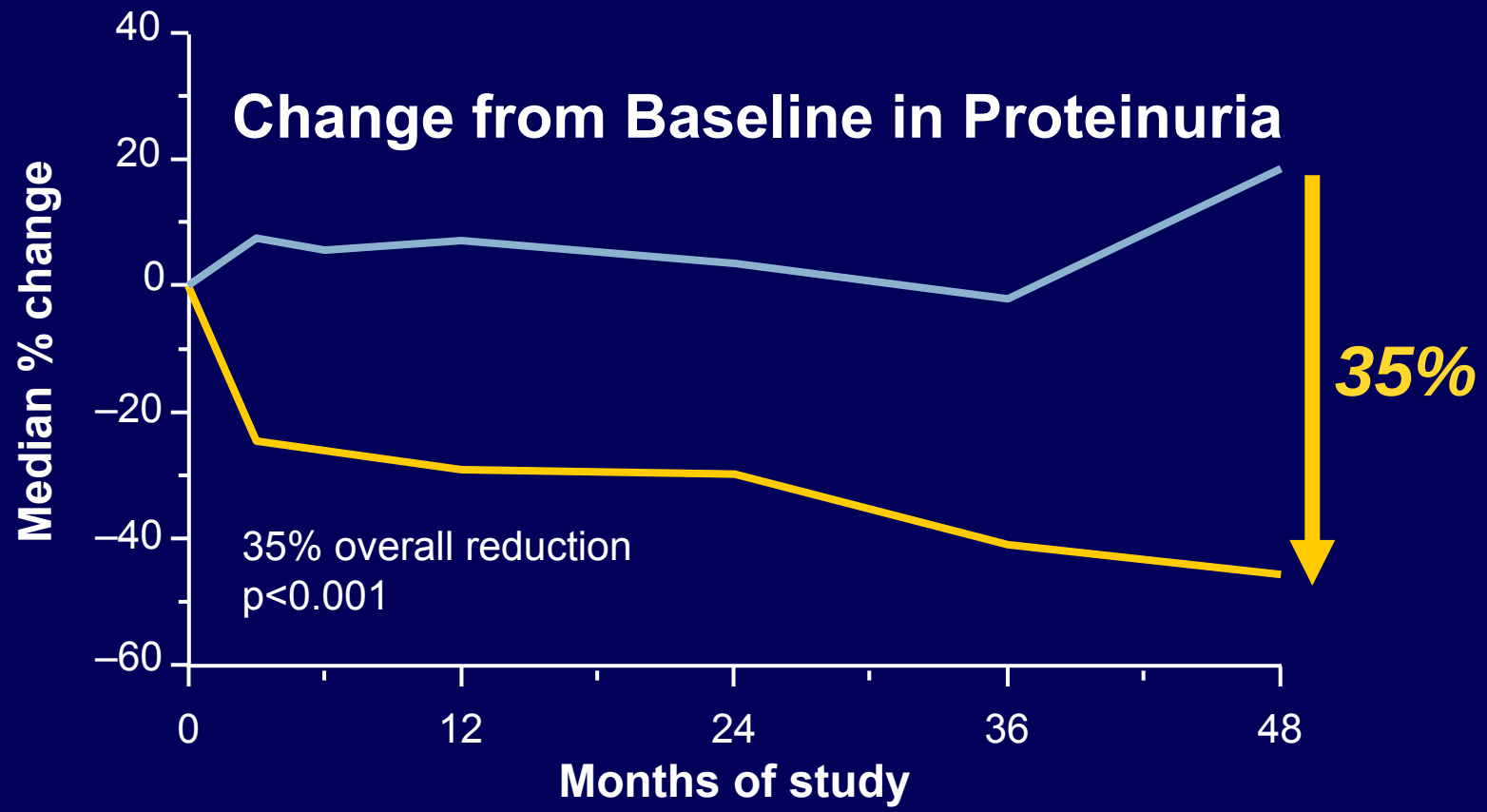


Placebo* (n)	762	685	616	375	53
Losartan* (n)	751	701	637	388	74

*In combination with open-label diuretic, calcium channel blocker, beta-blocker, alpha-blocker, and/or centrally acting agent

Brenner BM, et al. N Engl J Med. 2001;345(12):861-869.

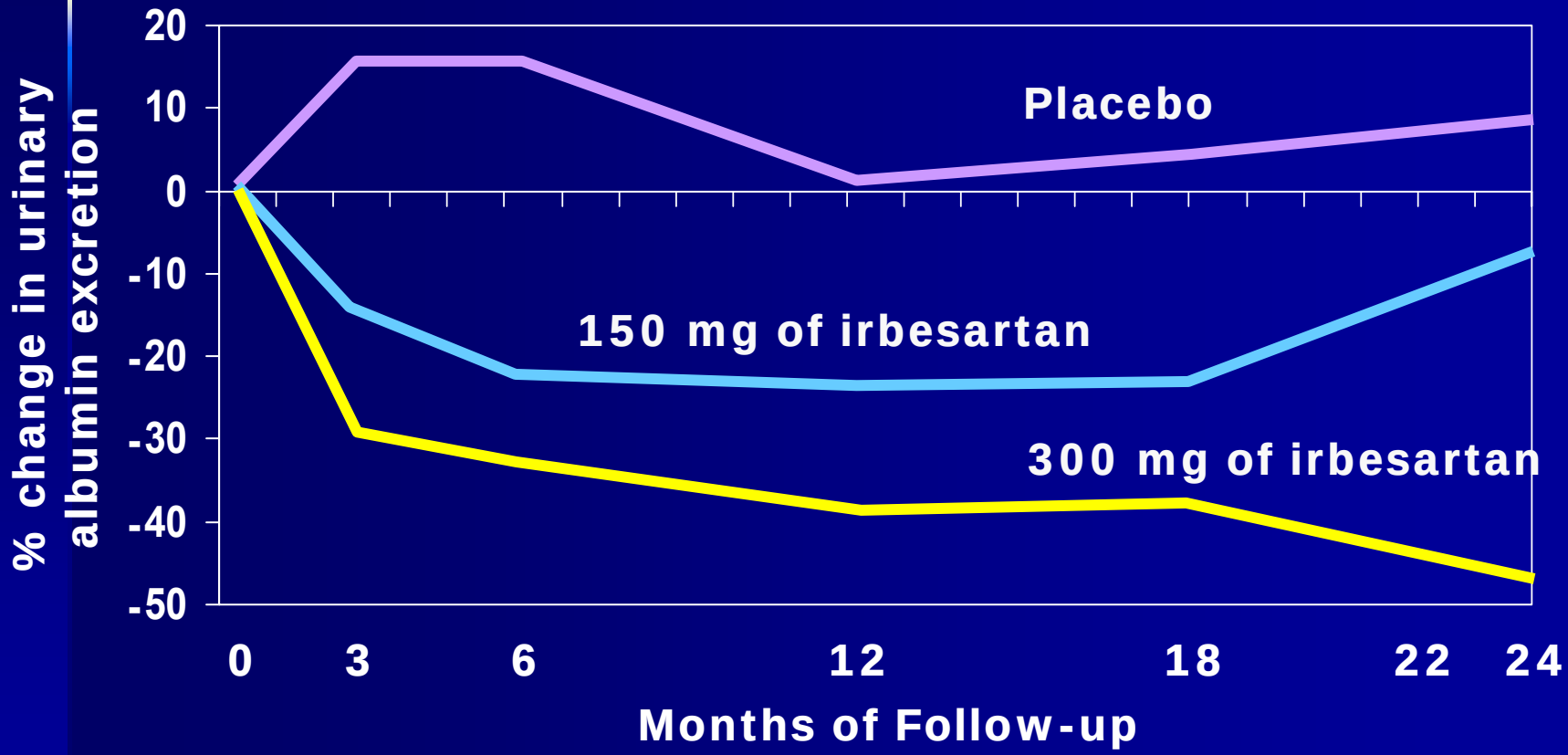
Reduction of Endpoints in NIDDM with the A II Antagonist Losartan



Proteinuria measured as the urinary albumin-to-creatinine ratio in a first morning specimen

Adapted from Brenner BM et al N Engl J Med 2001;345(12):861–869.

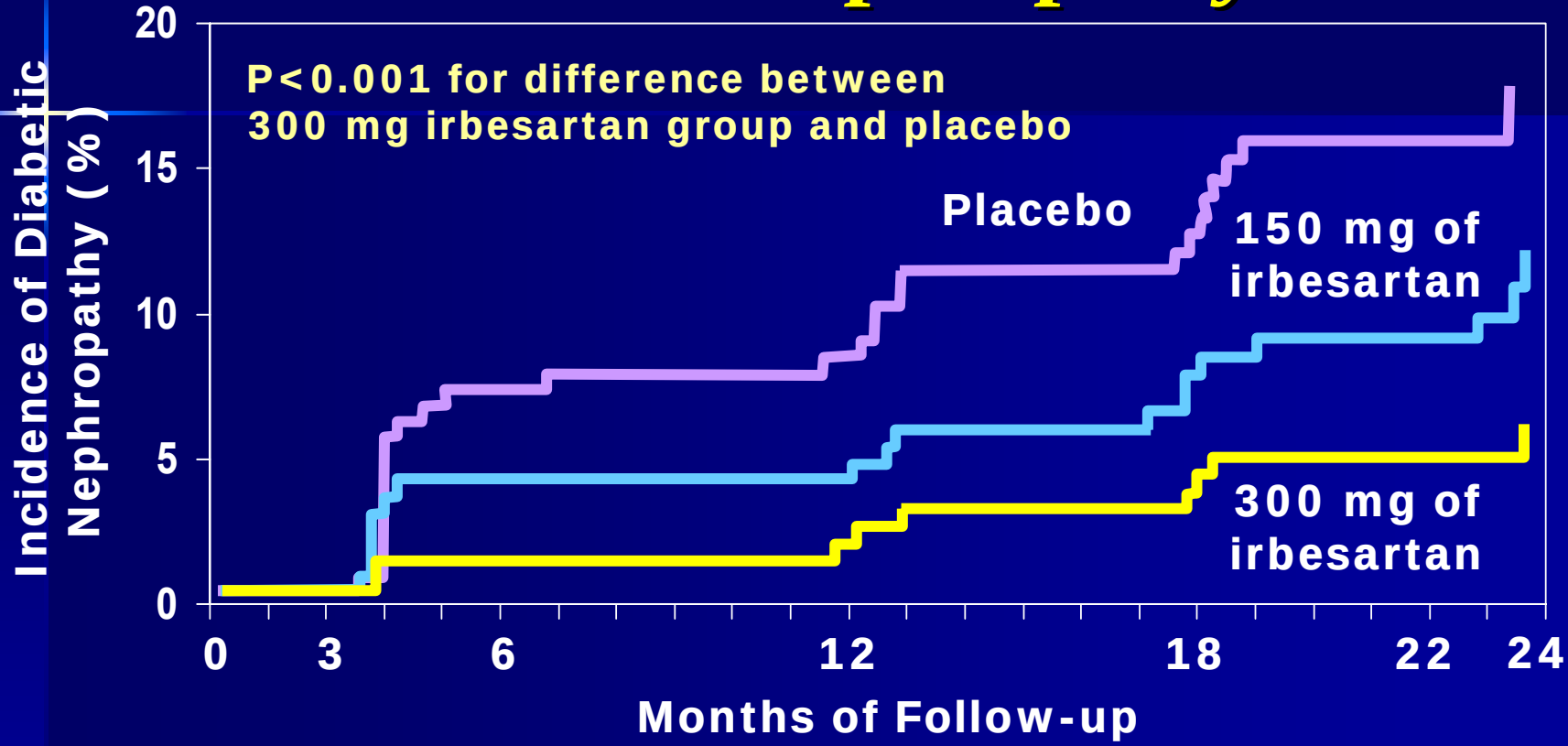
IRMA II *Change in Urinary Albumin Excretion**



*P<0.001 for difference between both irbesartan groups and placebo

Parving HH, et al. N Engl J Med. 2001;345(12):870-878.

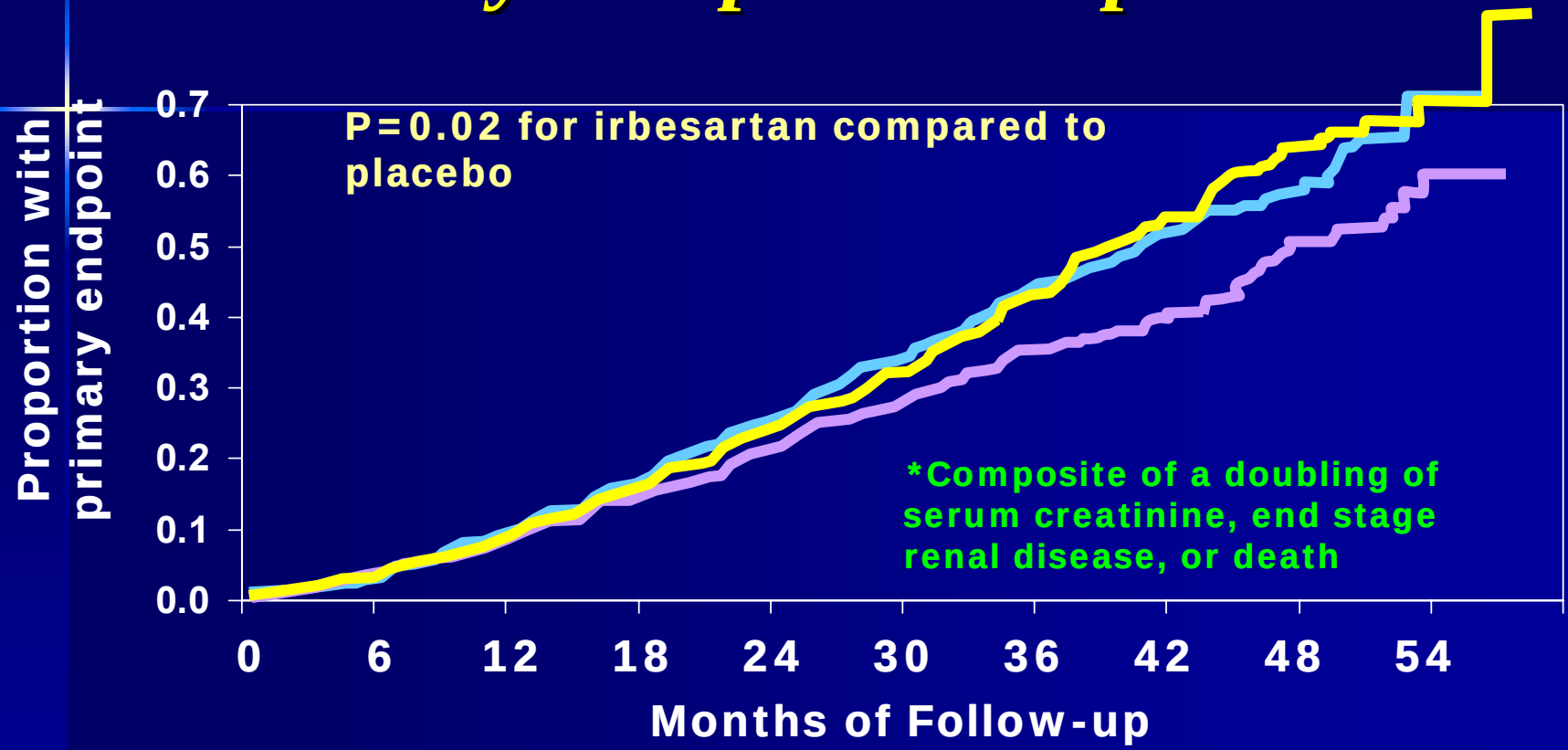
IRMA II *Incidence of Progression to Diabetic Nephropathy*



Placebo (n)	201	201	164	154	139	129	36
Irbesartan 150 mg (n)	195	195	167	161	148	142	45
Irbesartan 300 mg	194	194	180	172	159	150	49

Parving HH, et al. N Engl J Med. 2001;345(12):870-878.

IDNT *Proportion of Patients with the Primary Composite Endpoint**

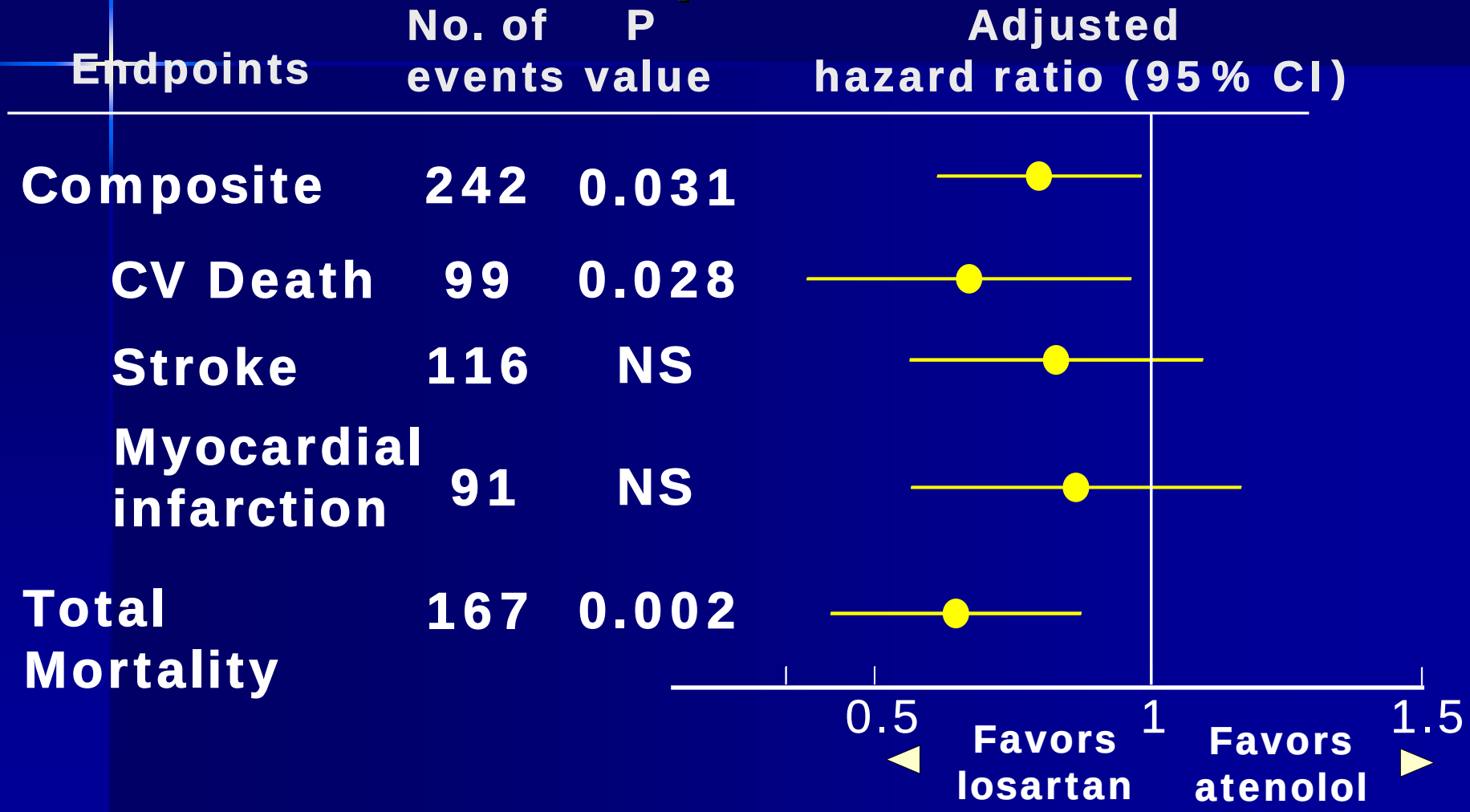


Irbesartan (n)	579	555	528	496	400	304	216	146	65
Amlodipine (n)	565	542	508	474	385	287	187	128	46
Placebo (n)	568	551	512	471	401	280	190	122	53

Lewis EJ, et al. N Engl J Med. 2001;345(12):851-860

LIFE Study Diabetes Subgroup

Primary Composite Endpoint and Components



Lindholm LH, et al. Lancet. 2002;359:1004-1010.

Summary & conclusions

- **RAAS plays a pivotal role in the pathogenesis of many CVD & its complications**
- **Drugs that antagonize this system have proved effective in prevention & treatment of many CVD**
- **ARBs represent a new group of RAAS antagonist that act at AT1 receptors thus blocking the harmful effects of AT**
- **They have been proved to be effective than ACEI in some of their indications**
  - **High risk hypertensive**
  - **Diabetics with renal disease**

Summary & conclusions

- Its use in HF has proved to be equal or even more beneficial than ACE-I in many large trials with more better quality of life but the guidelines still recommend their use in patients who do not tolerate ACE-I
- Its use in post MI patient is not better than ACE-I
- Their use in atherosclerosis prevention has some theoretical and experimental evidence but clinical evidence wait for the results of some undergoing trials


شكرا لحسن إستماعكم
مستشفى الباطنة التخصصى
Specialized Medical Hospital
Thank you
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